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Key Leaders' Opinions on Hot Issues of Cardiovasology

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Li Shen
Michael J. Lipinski

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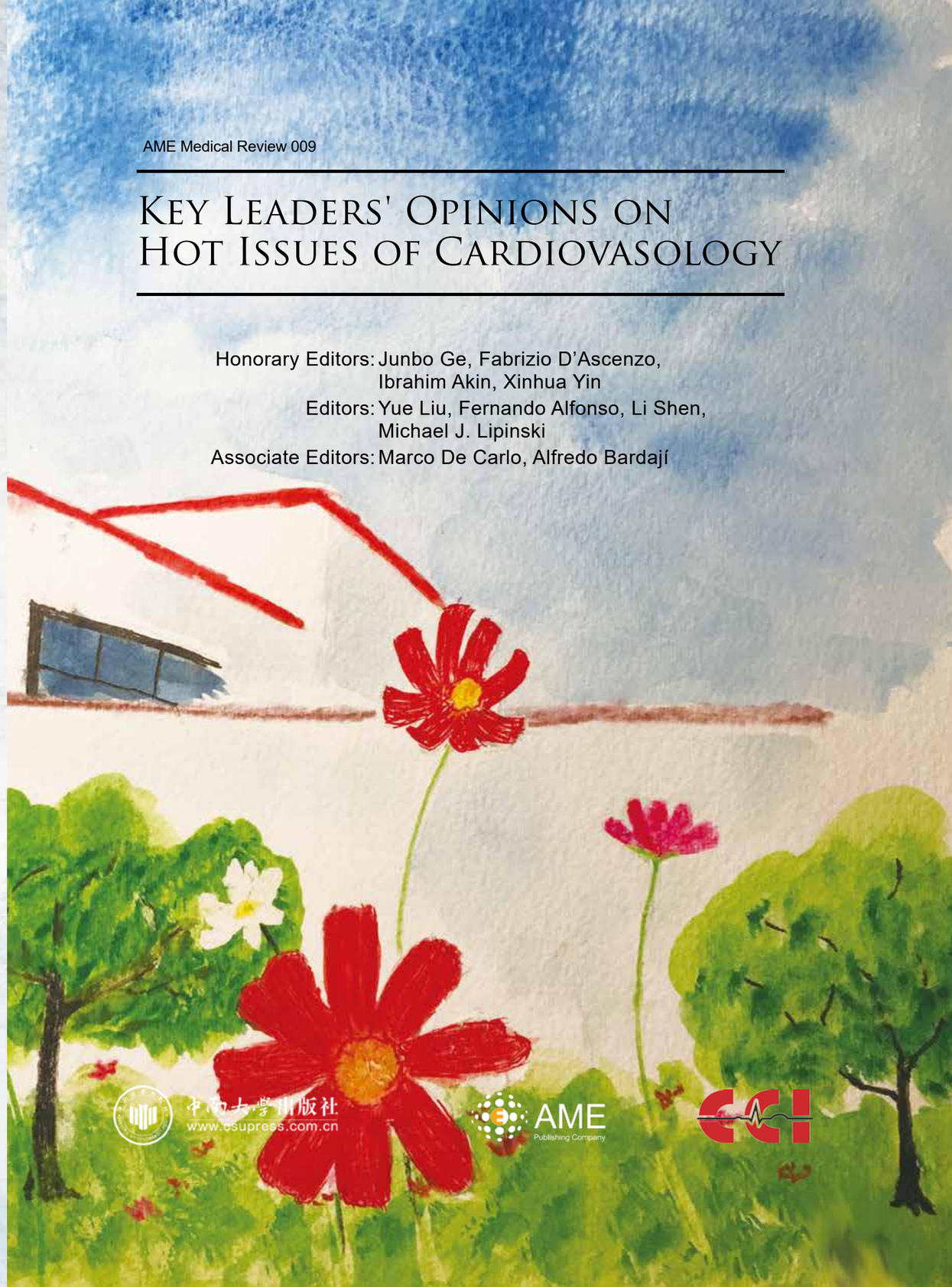

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Will scholarly journals perish?

Will scholarly journals perish? This is a question that has puzzled me for years.

The introduction of online journals results in the inevitable recession of print journals. The uprise of the open access journals has been changing the structure of scholarly journals ceaselessly. What keeps me thinking is the open access of clinical trials data. What would be the bigger picture if open access to clinical trials data becomes the mainstream?

It is interesting that with the primary bottleneck lying in the availability of open data, the Big-data Clinical Trial (BCT) seems to stay where it was in spite of the increasingly popularity of "Big Data" among scientists. It has to be the fact that without open data, a statistical analysis is restricted to a particular area (or several areas). Even with big enough data, the study can only be termed as "research with big data sets" rather than "big data research", which are totally different concepts. Big Data is constituted by a plurality of dimensions. On one hand, for an individual (e.g., a patient), the relevant data covering his/her disease course is big enough; on the other hand, for the entire population, as more as individuals (e.g., patients) are expected to be included, to contains all the elements just like the "universe set" in set theory; by doing so, scientists expect to carry out the so-called clinical studies in real-world settings.

Why do the real-world-based clinical trials so appealing? It is understandable that the results and conclusions are likely to be altered in studies targeting the same issue using the same research method with sample size changed. In addition, the probability of such a "likely" is quite high. In many top journals, it is a common phenomenon that some authors tend to validate the results of one study in another population using the same research method. However, if the results are "validated" in one population, it only means that they are "repeatable". Will the results also be repeatable in the second, third, and more populations? If the attempts are not continuing, which should be, the "validation" is equivalent to "self-deception" in a sense.

When clinical research data is open accessed, we can easily integrate data from multiple centers for statistical analysis and meanwhile "validate" the results in multiple populations. If this is the case, then another question arise: can everyone easily publish his/her results/papers in high-profile journals such as the *New England Journal of Medicine*? My answer is NO.

When the open access to clinical research data becomes mainstream, we can easily find the constant update of database on the Internet. Simply by clicking on a button, we obtain the statistical results of the most current data. A further button click would display the validation results based on a specific population. The database would be updated at a certain period of time (e.g., 1 month or 1 day), and the statistical results would "likely" also be changed accordingly. At that time, the questions may change to "would any researchers publish their findings in a journal?" Well, even if someone is still keen to write such articles, journals may be reluctant to publish them because of the indefiniteness of the findings with the risk of being overturned at anytime.

Eventually here it comes the serious question: will scholarly journals perish? My answer is still NO. Then in what way the scholarly journals would probably lead to?

During my Business Administration course, my teacher distributed to us an article from the Case Study column of the *Harvard Business Review*. In this highly respected journal, articles in this column often present one case first, followed by the comments from two experts. These comments could either support or oppose each other. My teacher asked us to study the case, read through the comments and then form our own point of views on the case. He encouraged us to interpret the case from different perspectives independently in what form that I found pretty practical.

The course brought a possible answer to me. When the open access to clinical research data becomes mainstream, the entire publishing industry, especially the publication of "scholarly journals", would eventually experience revolutionary change. It may no longer focus on the rigid and cold outcomes but it would definitely cares more about the reflection on the problems, update of insights, and integration of science and arts.

AME Medical Review Series is a production of the above thinking. As an attempt, we decided to invite experts internationally to provide their views on a specific topic to share their insights with more clinicians and thus benefit more patients. The first chosen topic for the series is the currently controversial one: conventional surgery versus stereotactic body radiotherapy for

the early stage lung cancer. As the first book to the series, we hope it would give you a glance at the coming changes.

The book series will be written by a group of individual experts who are willing to contribute medical reviews and comments to individuals who are interested in clinical research and medical reviews specifically. The book in your hand may possibly be on a heavy subject but we do hope it is presented in an easier way. It will be more than great if it brings you some thoughts and inspire you in some way.

Stephen D. Wang
Founder and CEO,
AME Publishing Company

I enjoyably read through the book *Key Leader' Opinions on Hot Issues of Cardiovasology*, and learn many insights on hot issues of cardiovasology from international renowned colleagues in this filed. These various opinions indeed drive researchers and clinicians forward and guides all of us to further scientific thinking on a particular medical issue. Especially for junior clinicians or researchers in the field of cardiovascular diseases, critical thoughts in this book are of great benefits in their future researches and practices.

All authors contributed in this edition are key opinion leaders in their specialties with extensive experience. They are encouraged to fully share their insightful comments on the most updated researches published on top-ranked journals, which covers the most important studies, understandings and updates on cardiovasology. Divided into different sections, this book covers a wide spectrum of current hot topics that are relevant to new techniques, methods and treatments in the field: ST-Segment Elevation Myocardial Infarction, Absorb Bioresorbable Vascular Scaffold, Percutaneous Coronary Interventions In Chronic Total Occlusion, Coronary In-Stent Restenosis, Atrial Fibrillation and Left Atrial Appendage Closure, Percutaneous Left Ventricular Assist Device, etc. These topics are thought-provoking, and worth being further discussed and addressed.

This book features profound interpretation and an easy-to-read format, providing valuable information in a perspective for those who have heavy clinical or research work and may have limited time to review vast publications.

I appreciate the Editors Drs. Yue Liu, Fernando Alfonso, Michael J. Lipinski, and Li Shen for their efforts on pooling together the prominent experts' opinions. I'm happy to see different insightful opinions written by experts from various countries, such as China, USA, UK, Italy, Australia, Germany, Spain, Japan, Switzerland, Republic of Korea, Turkey, India, etc. The hope is that insights derived from these key opinion leaders in the field of cardiovascular diseases will spur others to burst forth more ideas and inspiration, then lead the field of cardiovasology to further scientific development and finally benefit the patients. I also hope you will enjoy reading this book as much as I have had.

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The field of invasive cardiology, which encompasses interventional cardiology, invasive electrophysiology, interventions in structural heart disease as well as cardiac device therapy has undergone a mammoth transformation in the last 40 years. The advent of balloon angioplasty in the 1970's led to a breakthrough in the treatment of coronary heart disease, paving way to the several milestones we witness today. These include the development of the various techniques for balloon angioplasty, the use of bare-metal stents, drug-eluting stents and the recent bioresorbable scaffolds. In addition to the technological developments in implantable stents, there have also been significant advancements in the understanding of the pathophysiological and pharmacological processes governing coronary artery disease. The consistent refinements to periprocedural anticoagulation strategies as well as the adoption of thienopyridines to optimize post-procedural therapy by circumventing the risk of stent thrombosis have contributed to the increased use of such interventional techniques.

Procedural complications had always served as the Achilles heel of interventional cardiology, however, the greatly improved outcomes and minimal risks associated with these interventions today, have further augmented innovation of techniques, facilitating its use in different and difficult scenarios. These interventional practices have come to serve as the cornerstone in the treatment of coronary heart disease and are an established standard practice in all leading therapy guidelines. This book is an attempt to compile all relevant and current knowledge pertaining to the field of interventional cardiology.

The first chapter elaborates the use of thrombus aspiration in ST-elevation myocardial Infarction, recently classified as a Class III recommendation in the guidelines, while critically analyzing and dissecting the existing data. This chapter also includes a discussion on the three studies researching the practice of therapeutic hypothermia. An additional two chapters have been dedicated to highlight the use of anticoagulant therapy and duration of such treatments in light of the improved outcomes of patients with coronary artery disease.

The second chapter, briefly outlines milestones in the history of coronary stents including the use of bioresorbable scaffolds. Although, the sale of the first generation of these scaffolds have been stopped, it is pertinent to understand the technology leading to their development so as to optimize further innovation in stent engineering. An example of practical success demonstrated by the combined use of a stent, materials applied and techniques adopted can also be found in the treatment of chronic total occlusions. Although this pathology is seen in almost 15%-34% of all PCI-patients, technical limitations as well as a limited understanding of the patho-physiological processes and interventional methods has hindered possibilities for optimal treatment. Interestingly, recent technology has made it possible to re-canalize occluded vessels in either anterograde or retrograde fashion with a success rate of almost 90%.

The chapter describing in-stent restenosis discusses the current evidence and possible treatment strategies. In addition to the use of modern-day stents, specific attention has been drawn to the use of intravascular imaging and its potential in improving stent implantation techniques. Further chapters discuss non-coronary topics like therapeutic anticoagulation for prophylaxis against stroke in atrial fibrillation as well as cardiac support systems.

We hope that this compilation of topics in interventional cardiology, elucidating current data and evidence serves as an interesting viewpoint for the reader.

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I am very happy to know that the book *Key Leaders' Opinions on Hot Issues of Cardiovasology* is forthcoming. I have agreeably read through this book and then found that all the authors are very active experts and scholars in the international fields of cardiovasology in recent years, who provided their exclusive insights and deep thinking about cardiovascular hotspot issues in this book. I gladly accepted the invitation for foreword extended by Dr. Yue Liu, one of my students, who serviced as a member of editor-in-chief in this book.

Cardiovasology is rapidly developing today, and thus sets off a wave of innovation and development all over the world. With publication of large-scale clinical trials, meta-analyses of clinical trials, and basic researches in influential international conferences and journals in the past three years, multiple hot issues and heated debates are flourishing in the field of cardiovasology. At this time, this book co-edited by Drs. Fernando Alfonso, Li Shen, Michael J. Lipinski and Yue Liu presented critical comments on the hot issues of 144 famous cardiovascular specialists and scholars from 19 countries, such as the United States, Italy, Germany, France, Spain, Republic of Korea, Japan and China *et al*. It covered the updated concepts of emergency interventional therapy in acute myocardial infarction, the initiation and development of bioresorbable drug eluting scaffolds, the continuous change of antithrombotic scheme from drug usage to percutaneous left atrial appendage occlusion in patients with atrial fibrillation, the use of left ventricular assist device during the perioperative period of percutaneous coronary interventional therapy and new understanding of the influence of thyroid function change on coronary heart diseases. The book also further elucidated the confusing questions in the field of cardiovasology, including the mechanism of coronary stent restenosis, assessment and optimal revascularization strategy in treating coronary artery diseases such as coronary borderline lesions, left main lesions and multi-vessel lesions, and the questions whether anticoagulant therapy in pulmonary hypertension is effective and whether statins are suitable for the treatment of heart failure, and so on.

All the authors profoundly analyzed the hot topics of cardiovasology and expressed their key opinions and thinking from the point of view of uniqueness, novelty and guidingness, thus inspiring readers to think further. I believe this book will help clinicians and scientific researchers to better understand the development of cardiovascular disease and keep pace with the latest developments, and even more guide them to explore and move forward for innovation.

I also heard that the Chinese version is coming out in the near future, which can allow more domestic clinicians and scholars to quickly grasp the latest advances in cardiovascular research and gain benefits from them, thus promoting domestic clinical and scientific research. Therefore, I feel honor and great pleasure to write this preface.

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If we were to play a game of association of ideas and I said "study", many of you would reply "book". Since we learn to read as small children, books exert a fascination on our minds; as teenagers, we then regard books as a more or less heavy burden. Eventually, books become the cornerstone of our medical education; we have to study books in order to pass examinations and acquire specific skills, until we attain specialist/consultant status. Thereafter, books apparently lose their pivotal role in our life. However, the longest and most important phase of our medical education actually starts after the completion of our course of studies. In this phase, learning is generally left to individual interest and motivation, although professional/regulatory bodies are making continuing medical education (CME) programs compulsory in several countries. Sources for CME include attendance at conferences or meetings, attendance at master courses, reading of specialty journals, and self-assessment schemes and distance learning programmes.

Reading books is rarely included among CME sources, nevertheless it remains the easiest to reach source of knowledge for any specialist. A good book may be read at any time and for any time period, can be interrupted and resumed at our wish, and has no difficult web address or username/password combination to remember. Therefore, high-quality books remain a foundation of continuing medical education in its wider conception.

The present book "Opinions on Hot Issues of Cardiovasology" is a collection of expert reviews written by key opinion leaders in the fields of Cardiology and Vascular Medicine in general, and offers an in-depth assessment of many crucial issues we face in clinical practice. Topics include coronary artery disease (adjunctive treatments in ST-elevation myocardial infarction, bioresorbable vascular scaffolds, chronic total occlusions, in-stent restenosis, revascularization strategies for intermediate lesions and multivessel disease, left ventricular assist devices in high-risk coronary interventions), structural heart disease (left atrial appendage closure), valvular heart disease, heart failure, pulmonary arterial hypertension, and comorbidities (hyperglycaemia and hypothyroidism). All the contributions offer a critical appraisal of the issue they deal with, including the analysis of the most recent evidence and a thoughtful discussion of all the relevant aspects.

Updated knowledge of these topics is mandatory for our practice and we may obtain it by attending meetings and congresses; however, this book offers a convenient and effective manner to achieve this goal. Continuing our medical education through the reading of this book will certainly represent a benefit for us and for our patients.

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It is a great honor to participate in the foreword to the book *Key Leaders' Opinions on Hot Issues of Cardiovasology*, which introduces important developments in the diagnostic and therapeutic aspects of recent cardiology. The intense cardiovascular research that is ongoing around the world is bringing rapid advances in techniques and treatments that are progressively improving the quality and quantity of life in cardiac patients. This book includes important reviews in the fields of ischemic heart disease, cardiomyopathy and valvulopathy that all readers with an interest in cardiology will surely enjoy and appreciate.

Cardiovascular science is developing exponentially. Those of us who are old enough to have been working in this field for the last 30 or 40 years are well aware of the revolution that is currently taking place in the management of cardiovascular diseases. When I first began my career in cardiology, it was common to treat patients with acute myocardial infarction with antiarrhythmics and calcium antagonists, and techniques such as coronary angioplasty without the stent and ablation in cardiac arrhythmias were only in their infancy. When one looks back, the tremendous progress we have made is plain for all to see. In the pharmacological treatment of patients with acute coronary syndrome, new drugs such as antiaggregants and statins have completely changed the prognosis and have acquired a major role in improving the short and long-term prospects of these patients. In the field of percutaneous coronary intervention, procedures are now being performed on very complex lesions using coated stents with a high immediate success rate and a low rate of short and medium-term complications. Furthermore, percutaneous intervention is gradually becoming commonplace in structural cardiac pathology treatments that until recently had only surgical solutions, and although new solutions have started to be adopted for many valvulopathies, we can be certain that in the near future we will see many new procedures that until now were firmly in the realms of imagination. Similarly, in the treatment of cardiac arrhythmias, the use of navigators and new techniques such as cryoablation have completely revolutionized these procedures. No less important are the advances in the field of imaging; advanced echocardiography techniques, along with cardiovascular magnetic resonance and multi-CT scans, allow us to visualize the structure and cardiac function in ways that we could never have dreamt of in the past. In addition, we have come a long way in terms of research methodologies so that it is now commonplace to design studies aimed at producing evidence-based medicine.

The future is exciting and very close at hand. It is hard to imagine what cardiology will look like in 20 or 30 years' time but we will almost certainly be surprised when we recall how things were done in the first third of the 21st century. Moreover, as a clinical cardiologist, I hope that the inevitable advances will bring with them a more personalized and patient-centered medicine.

This book brings us up to date regarding many aspects of cardiovascular pathology and will be an invaluable aid in the process of lifelong and continuous training that is so vital to our specialty.

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Clinical perspective of optical coherence tomography and intravascular ultrasound in STEMI patients

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In the last years, the intravascular ultrasound study (IVUS) and further the optical coherence tomography (OCT) became two helpful tools to characterize of the atherosclerotic plaque.

These new technologies made possible to analyse *in vivo* the pathophysiologic mechanisms that previously were just speculated or observed post-mortem (1). Recently Dr. Higum and Prof. Jang published an interesting article named "*A combined OCT and IVUS on plaque rupture, plaque erosion and calcified nodule in patients with STEMI*", useful to describe the different presentation of culprit lesions in ST-elevation myocardial infarction (2).

In this paper the authors describe the findings about 112 STEMI patients who underwent to OCT and IVUS. Incidence of plaque rupture (PR) was 64.3%, plaque erosion (PE) 26.8% and calcified nodule (CN) 8%. The highlight hallmarks of PR were a higher lipid content inside the plaque, major thin-cap fibroatheroma (TCFA) and more numerous microchannels, with a trend toward a positive remodelling of plaque. PE showed less "vulnerable" morphology of plaque because of lower degree of TCFA, lipid content of plaque and microchannels. The structure of lesion with PE was more eccentric than PR and this was observed better through IVUS rather than OCT. CN lesions demonstrated higher amount of calcium compared to the other lesions, arranged like a "calcium sheet" along with negative remodelling of plaque. After primary Percutaneous Coronary Intervention (PCI) PR was associated with higher rate of myocardial blush grade ≤1 and consequently with a larger incidence of no reflow because of elevated thrombogenic burden enhancing *in situ*-thrombosis and distal embolization, confirmed by the higher creatinine kinase (CK) peak in PR lesions respect to the others kinds.

The population was rather homogeneous, apart from difference in ages. Patients with CN were of older age with a larger significative incidence of diabetes mellitus, that was a factor causing increased degree of vessel calcification as already shown in different setting of patients (3). Unfortunately, the incidence of another factor of progressive and widespread calcification like chronic kidney disease (CKD) wasn't reported.

Patients with culprit lesions characterized by PE were younger that those with PR, without relationship with gender. However, OCT and IVUS have showed some discrepancy due to its unclear definition and morphological criteria, so much that it in this study was just considered as a diagnosis of exclusion (4).

The results of this study confirmed the prevalence of PR in patients with STEMI and the elevated incidence of TCFA as risk factor of evolution toward myocardial infarction. A meta-analysis recently published by of our group (5) including 23 studies and 2,711 culprit lesions attested that at the observation through OCT the presence of PR and TCFA at 70.4% and 76.6% respectively, in STEMI patients (*Figure 1*). On the other side, in the others subsets of coronary artery disease the incidence of both these parameters resulted to be less important (NSTEMI 55.6% and 56.3%, UA 39.1% and 52.9%, and SAP 6.2% and 22.8%, respectively). Also in the evaluation of PR OCT and IVUS showed some discrepancy, a dated study with a lower number of patients (30 people) reported as cause of

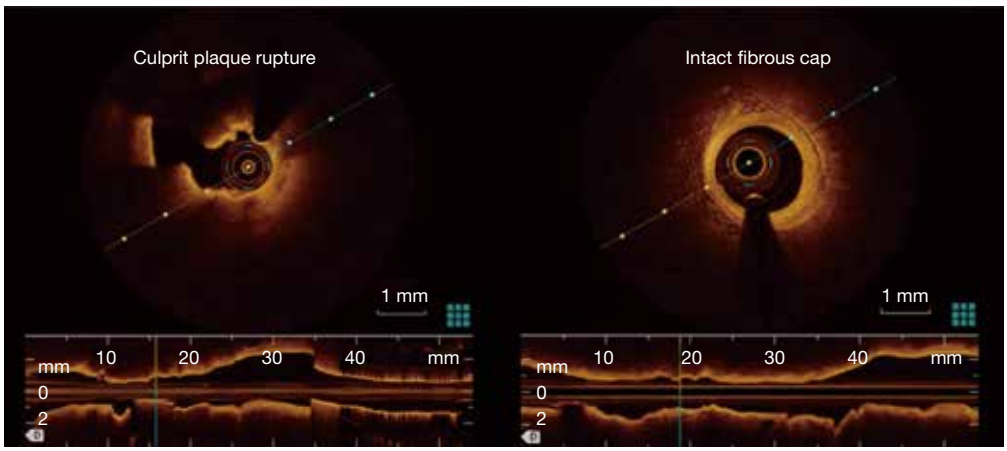

Figure 1 Two examples of OCT pull-back, on the right a culprit plaque rupture, on the left an intact fibrous cap atheroma. OCT, optical coherence tomography.

infarct in the 73% the disruption of fibrous cap evaluated by OCT, while 43% by IVUS.

An interesting finding in the report by Dr. Higuma *et al.*, and confirmed by our paper, is that clinical parameters seems not to be correlated with the presence of PR. This could be caused by limited sample size, limiting chances to reach statistical significance. Secondly classical cardiovascular risk factors such as hypertension, diabetes and age are surly correlated with atherosclerosis progression, so to the plaque burden, however plaque rupture itself mechanisms are not completely understood. It could be speculated that plaque rupture is a "stochastic" event determined by a "perfect storm" whom drops are the atherosclerotic burden, a vulnerable plaque, the sympathetic nervous system and the inflammation.

Surely this kind of study was very useful to describe pathological morphology of plaque, that just over a decade ago was a mirage. Despite both IVUS, and in particular OCT, raised interest in particular subsets of situations such as stent thrombosis (6), correct evaluation of stenosis diameter and stent's struts apposition (7) or differential diagnosis in underestimated cause of acute coronary syndrome (such as coronary embolisms) (8), an important restriction of their use remains the costs and the unclear clinical impact of these technologies in common practice.

Another interesting study about OCT in STEMI was OCTAVIA trial (9), which performed OCT on the culprit lesion during acute events and after follow-up of 9 months the coronary angiography was remade with the addition of evaluation through OCT. The population was divided according the presence of ruptured fibrous cap (RFC) and those with intact fibrous cap (IFC). They report similar ruptured cap rate compared with the study by Dr. Higuma.

Autoptical studies endorsed the plaque rupture incidence approximately at 75% (10,11). A higher prevalence of plaque rupture is comprehensible, as demonstrated by Dr. Higuma plaque rupture is correlated with an impaired myocardial blush and slow flow leading to a worse acute prognosis of these patients and probably more often to death.

The introduction of OCT made a remarkable contribution, because it improved the quality of plaque evaluation, performing the display *in vivo* intracoronary thrombus, plaque ruptures and erosion, mostly TCFA minor than 65 μm (12).

IVUS and mostly OCT demonstrated to be very close to the classic anatomicopathological description, certainly they corroborated the theories on autoptical field about the morphology of plaque; however the clinical impact of these data on treatment is unclear. A spot of controversy was concentred to differentiate the type of therapy in patients with STEMI on the basis of plaque's features, attempting a more custom intervention. Observing the pathophysiology knowledge's the presence of ruptured plaque should prompt for an aspiration procedure, followed by implantation of drug eluting stents and an aggressive medical therapy (in particular statins and antiplatelet therapy). While performing thrombus aspiration in case of plaque with IFC could be useless or even dangerous, while performing antiplatelet therapy beyond the time necessary for the stent

endothelialization could be not necessary.

Nevertheless, OCTAVIA trial showed similar healing response to follow-up of nine months for plaque with RFC or IFC, probably for local effect of aggressive antiplatelet therapy and also of stenting, shortening the hopes for a custom therapeutic address.

Indeed, the time to pass from the pure scientific speculation through the clinical application has come, further clinical trial in this sense are needed to reach a per-patients tailored therapy in order, as told by the Ulysses of Lord Tennyson "to strive, to seek, to find".

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Footnote

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Aspiration thrombectomy in 2015: a TOTAL defeat?

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Primary percutaneous coronary intervention (pPCI) is the treatment of choice for ST-elevation myocardial infarction (STEMI), but in a relevant proportion of cases it fails to achieve restoration of perfusion at the level of microcirculation, due to the "no reflow" phenomenon (1). Distal thrombotic embolization has a role among the mechanisms of no reflow, and intracoronary aspiration thrombectomy (AT) was conceived several years ago as an adjunct to pPCI to address this problem (2). Over the last 15 years, AT has been thoroughly investigated in clinical trials, but its clinical value is still debated. In fact, initial studies reported that routine use of AT impacted favourably on surrogate end points such as myocardial blush grade or ST-segment elevation resolution (STR) after pPCI; in addition, the randomized TAPAS trial (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study), although not powered for clinical endpoints, reported a benefit on 1-year mortality (3,4). Therefore, the 2012 guidelines on STEMI of the European Society of Cardiology (ESC) stated that "routine AT should be considered" (class IIa recommendation) (5). However, the larger TASTE trial (Thrombus Aspiration in STEMI in Scandinavia) failed to prove a significant advantage of routine AT in terms of early and medium-term mortality (6,7), leading to a downgrade of AT to class IIb in 2014 ESC guidelines on myocardial revascularization (8). Most recently, the TOTAL trial (Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI), enrolling 10,732 patients, confirmed the lack of mortality benefit with routine AT (9).

In this scenario, the updated meta-analysis by Elgendy and coworkers, involving 17 trials for a total of 20,960 patients, appears of particular interest (10). The main results of this meta-analysis confirm the lack of benefit with routine AT in terms of reduction of mortality and MACCE, while highlighting a non-significant increase in the incidence of stroke in the AT group. In particular, at a weighted mean follow-up of 3.7±2.7 months, routine AT was associated with a nonsignificant reduction in the incidence of all-cause mortality [2.8% *vs.* 3.2%; relative risk (RR) 0.89; 95% confidence interval (CI) 0.76–1.04; P=0.13] and of the composite of mortality or reinfarction (4.1% *vs.* 4.6%; RR 0.90; 95% CI, 0.79–1.02; P=0.11). In addition, AT was associated with a significantly higher incidence of complete STR (68% *vs.* 64%; RR 1.17; 95% CI 1.08–1.28; P<0.0001), and final myocardial blush grade ≥2 (59% *vs.* 43%; RR 1.39; 95% CI, 1.19–1.62; P<0.0001). The reverse of the coin was a nonsignificant increase in the risk of stroke (0.6% *vs.* 0.4%; RR 1.45; 95% CI, 0.96–2.21; P=0.08).

Importantly, the authors address through meta-regression analyses two additional issues, i.e., the effect of co-administration of intravenous glycoprotein IIb/IIIa inhibitors (GPIs), and the role of ischemic time. Thrombosis has a pivotal role in STEMI, and the anti-thrombotic regimen is therefore crucial. The only randomized trial designed to evaluate contemporarily the role of AT and of a potent anti-thrombotic agent, abciximab, was the INFUSE-Anterior Myocardial Infarction (INFUSE-AMI) trial, which randomized in 2×2 factorial design 452 patients with anterior STEMI to intracoronary abciximab *vs.* no abciximab and to AT *vs.* no AT (11). Although small, this trial was very well designed and relevant information has been derived from its results. Intralesional abciximab, but not AT, was associated with

a reduction in 30-day infarct size, as assessed by cardiac magnetic resonance imaging (MRI); 1-year results showed that intralesional abciximab, AT, or both compared with no active therapy resulted in lower mortality (4.5% *vs.* 10.4%; P=0.03), severe heart failure (4.2% *vs.* 10.3%; P=0.02), and stent thrombosis (0.9% *vs.* 3.8%; P=0.046) (12). In particular, AT was associated with significantly lower rates of new-onset severe heart failure (0.9% *vs.* 4.5%; P=0.02) and of rehospitalization for heart failure (0.9% *vs.* 5.4%; P=0.0008), and with numerically lower mortality between 30 days and 1 year (1.9% *vs.* 4.5%; P=0.12) (12). In the absence of a significant reduction in infarct size with AT, the pathophysiologic mechanisms of such potential clinical benefit remains unclear. The meta-analysis by Elgendy has the strength of the number of patients analyzed, but also the intrinsic weakness of pooling together markedly heterogeneous studies, notwithstanding the results of formal heterogeneity testing. In fact, anti-thrombotic drug treatment was quite different among trials, in terms of both GPI and ADP antagonists. Surprisingly, in the meta-regression GPI use did not influence any end point, both clinical and surrogate; the authors were not able to conduct separate meta-regression analysis using the difference in GPI use between AT versus no AT arm. Conversely, in another recent meta-regression analysis of AT trials, Bajaj and coworkers observed a marginal benefit on 30-day mortality with higher GPI use (P=0.047), being more evident in the AT arm compared with the control arm (P=0.01) (13). Regarding the effect of ischemic time, Elgendy and coworkers could not demonstrate a significant impact on any end point considered, an unreliable and contradictory finding that highlights the limits of meta-analyses when researchers try to extract information which go beyond the primary end point of the trials.

In our opinion, there are still a few issues to address, following the latest publications on AT: (I) is it reasonable to expect a reduction in mortality with routine AT in future trials? (II) is it reasonable to design future trials imposing routine use of AT, rather than selective use in patients with angiographic evidence of thrombus? (III) can we accept a benefit on "softer" end points, such as reduction in infarct size and hospitalizations due to heart failure, as a reasonable evidence to support the use of AT? (IV) is the increase in stroke rate a real issue with AT?

(I) Regarding the first question, we believe that a reduction in mortality by any adjunctive treatment will be extremely difficult to prove in randomized trials, given the dramatic improvement in the management of STEMI over the last 20 years. It is also evident that AT with currently available devices has a very limited potential to impact on mortality, if any. Other factors impact on mortality, as shown by the INFUSE-AMI trial, such as the location of the occlusion in the proximal vs mid left anterior descending artery (14), and a delay to reperfusion >3 hours (15);

(II) In randomized trials imposing routine AT in all STEMI patients, the potential benefit obtained in patients with high thrombotic burden is diluted among patients who may only get the risks of AT without any reasonable advantage. In the MUSTELA (MUltidevice Thrombectomy in Acute ST-Segment ELevation Acute Myocardial Infarction) randomized trial we previously failed to demonstrate that AT could reduce infarct size, even when used only in patients with high thrombotic burden (16). However, AT was associated with significantly higher rate of STR (57.4% *vs.* 37.3%; P=0.004), of final myocardial blush 3 (68.3% *vs.* 52.9%; P=0.03), and with lower rate of microvascular obstruction (11.4% *vs.* 26.7%; P=0.02). Although the benefit of AT on infarct size was smaller than expected, leading to the failure of the primary end point, we still believe that a larger patient population might have allowed for the detection of a significant benefit. In our opinion, future thrombectomy trials should focus exclusively on patients with high thrombotic burden, also reflecting the attitude of physicians in everyday practice, where AT is performed only in the presence of angiographically relevant thrombus;

(III) If AT cannot save lives, at least it can help saving muscle. In our opinion, the available evidence demonstrates that AT improves surrogate end points of successful myocardial reperfusion, such as higher STR, myocardial blush grade 3, and lower distal embolization (4,10,16,17). The INFUSE-AMI and MUSTELA trials failed to prove a reduction in infarct size at MRI with AT, showing that other factors (ischemic time, amount of jeopardized myocardium) have a prevalent effect. Nevertheless, the benefit of AT appears intuitive to whoever retrieved large amounts of thrombotic material from a coronary artery during pPCI; a tight similarity exist with the use of embolic protection

devices for carotid artery stenting, whose clinical benefit is still unproven, but whose necessity is self-evident to most interventionists;

(IV) No intervention is risk-free, and AT is no exception. The TOTAL trial reported for the first time a safety issue with AT, since stroke occurred more frequently (0.7% *vs.* 0.3%; hazard ratio 2.06; 95% CI 1.13–3.75; P=0.02) (17). However, if the mechanism of stroke were embolization of thrombus or air due to manipulation of the thrombectomy catheter, it is difficult to explain why stroke continued to occur more frequently in the AT arm between 30 and 180 days (1.0% *vs.* 0.5%; hazard ratio 2.08; 95% CI 1.29–3.35; P=0.002), possibly reflecting the play of chance. In the meta-analysis by Elgendy, the increase in the risk of stroke with AT was nonsignificant (0.6% *vs.* 0.4%; RR 1.45; 95% CI 0.96–2.21; P=0.08) (10). In our opinion, if a meta-analysis on >20,000 patients cannot rule out a chance finding, this question will hardly find a definitive answer. Nevertheless, AT requires expertise and its complexity should not be underestimated by the physician; in particular, extreme caution should be applied when performing AT in the left main trunk, and in the ostial segment of the left anterior descending, circumflex and right coronary artery, as thrombus may be dislodged in the aorta during advancement and retrieval of the thrombectomy catheter. Moreover, continuous suction should always be applied to the catheter during its retrieval from the coronary artery into the guiding catheter.

In conclusion, AT remains an important tool in the hands of the interventional cardiologist when dealing with extensive coronary thrombus during pPCI; if performed correctly, it can prevent distal embolization and the entailed myocardial damage, although it does not reduce mortality. Expertise is required in order to minimize the risk of brain embolization during maneuvering of the aspiration catheter.

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Footnote

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When clinical experiences clashes against evidence based medicine: the case of aspiration thrombectomy in primary percutaneous coronary intervention (PCI)

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Deciding when to apply a procedural technique, during a primary percutaneous coronary intervention (PCI) in the setting of a ST-elevation myocardial infarction (STEMI) is a matter of "know how" for the interventional cardiologist, from decision of correct antiaggregant/anticoagulation to choice of complete *vs.* not revascularization and, among the most debated, thrombus aspiration (1-3).

But deciding when to apply a technique on which efficacy is not clear is more than a matter of knowledge, it is what we usually call experience: it is the sixth sense that derives from the path you know because you walked it a lot of time. Finally, it is what differ the work of a craftsman made with the rule of the art from a simple and just technical approach to the problem. Obviously decision passes not only trough experience but always need deep knowledge of the problem: from this point of view meta-analysis help to extract strong message from published literature and to empower recommendations (4).

Deciding when to apply thrombectomy and the use of GpIIb-IIIa inhibitors directly mirror this situation. Both of them are well-known and widely diffused guns in the belt of the interventional cardiologists, that could bring to you a lot of satisfaction when correctly applied, but that nowadays have not reached a clear evidence-based verification.

Despite the first positive results of small single-centre studies such as the thrombus aspiration during percutaneous coronary intervention in acute myocardial infarction study (TAPAS) trial and subsequent meta-analyses (3,5), other studies adequately powered for clinical outcome including the trial of routine aspiration thrombectomy with PCI versus PCI alone (TOTAL) and the thrombus aspiration in ST-elevation myocardial infarction in Scandinavia (TASTE) trial observed no positive effect of aspiration thrombectomy on all-cause mortality (6,7). As a consequence of TASTE, current European guidelines downgraded the recommendation for thrombus aspiration in STEMI to a class IIb A indication (8).

The meta-analysis by Elgendy *et al.* (9) about the use of aspiration thrombectomy in patients undergoing primary PCI is the newest sum of published evidence. Its main strengths are the inclusion of a large larger number of patients and events, as well as a greater number of sites and operators, making the results more generalizable. They conclude that aspiration does not provide clinical benefit. However, a lot of experienced interventional cardiologists still consider useful this technique in selected patients.

The presence of thrombus is a phenomenon ubiquitously present in STEMI patients, but the benefits of aspiration of a small thrombus burden may not be sufficient to counterbalance the drawbacks of delivering bulky equipment. From the same point of view the benefits of its pharmacological treatment might not counterbalance the haemorrhagic risk. These reasons may explain the discordance between published studies and clinical practice. We also must remember that current management of STEMI patients has reduced hospital mortality to less than 5%, making it difficult to register mortality differences when randomizing new techniques.

The belief that aspiration thrombectomy or glycoprotein IIb/IIIa inhibitors would be useful in every STEMI patients is like sustaining that IABP would be useful for every patient in shock or parachute may be helpful for every kind of fall! Good sense—or as we like to call it when talking about patients—good clinical sense, should guide decision through different scenarios.

Starting from this assumption, the excellent work made by Elgendy *et al.* could be fully esteemed: in this analysis of 17 randomized trials, they demonstrated that aspiration thrombectomy did not significantly reduce the risk of all-cause mortality, reinfarction, the combined outcome of mortality or reinfarction, MACE, or stent thrombosis when compared with conventional PCI.

In addition, aspiration thrombectomy was associated with a nonsignificant increase in the risk of stroke. Moreover, the concomitant administration of intravenous glycoprotein IIb/IIIa inhibitors or ischemic time did not influence (i.e., reduce) the risk of mortality, reinfarction, the combined outcomes of mortality or reinfarction, MACE, or myocardial reperfusion markers in STEMI patients who underwent aspiration thrombectomy before primary PCI.

Regarding the glycoprotein IIb/IIIa inhibitors usage, the meta-analysis encloses the results from the intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction (INFUSE-AMI) trial and finally shares them (10). The use of this pharmacologic help is probably not a standardisable approach and remains to be evaluated in each situation. The trend toward a synergistic approach of the two strategies reflect the common pathophysiology on which they work, but again stress the need for a tailored strategy: aspiration thrombectomy and glycoprotein IIb/IIIa inhibitors are tricks of trade, that probably today just experienced cardiologist could appropriately prescribe.

There are some intrinsic limitations because of data derived from different trials with different inclusion criteria, designs and populations and variable follow-up durations. In particular follow up in these studies is important, because it was just 3.7±2.7 months.

Furthermore, due to the difficulty to obtain mortality differences because of the presence in studies of unselected STEMI populations and the difficulty to carry on trial with only higher risk patients (i.e., those with large thrombus), further analyses of additional end points such as left ventricular function, heart failure events, recurrent angina and long term mortality rates or procedural benefits such as ability to perform direct stenting or reduced stent length were not examined in the studies enclosed, and in future could be helpful to improve the understanding of the effects of aspiration thrombectomy and on myocardial perfusion and function in patients with STEMI.

In conclusion, we think that the message we could bring to home is that currently routine use of aspiration thrombectomy with or without the glycoprotein IIb/IIIa inhibitors usage is not supported by guidelines. It is not a routine technique but an ultra-specialistic approach to a particular subset of patients presenting with STEMI and a large thrombus burden, carrying not only potential benefits but also potential harms. Its use must be limited to patients in which could be useful, and this decision could be taken only after the angiography and not on a randomized fashion.

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Footnote

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Therapeutic hypothermia in ST elevation myocardial infarction (STEMI): a long way to go

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Post-ischemic reperfusion injury is mediated by infiltration and activation of circulating inflammatory cell subsets (i.e., neutrophils) that early entered the area-at-risk and release proteases and reactive oxygen species (ROS) (1-3). A recent study demonstrated that during recovery neutrophil infiltration might be protective, thus favoring a proper scar formation and potentially preventing negative left ventricle remodeling (4). Given this pathophysiological complexity, some selective drugs targeting these cells failed to induce a clear benefit on mortality and post-ischemic heart failure development in experimental models (2,5). Treatment schedule and safety (i.e., risk of immunosuppression) were suggested as the key limiting issues, potentially weakening the relevance of pre-clinical studies. However, despite a promising pilot study (6), patients with acute ST-segment elevation myocardial infarction (STEMI), did not benefit of the acute administration of cyclosporine (an immunosuppressive drug) on post-infarction clinical outcomes (7,8). Therefore, evidence from both basic and clinical research raised some concerns on therapeutic approaches inhibiting inflammation in all phases of post-ischemic reperfusion. A clear need of more selective treatments transiently abrogating inflammation might be more effective and safe.

Since decades, therapeutic hypothermia (TH) is empirically considered as a useful physical approach abrogating inflammation and reducing cellular metabolism of ischemic cells (9).

This approach was first supposed to be neuroprotective in survivors of cardiac arrest (10) and then, investigated to reduce cardiac injury (11). More recently, a systematic review and meta-analysis of randomized controlled trials (RCTs) investigated if TH might significantly reduce major adverse cardiovascular events (MACEs) as compared to controls in patients with STEMI.

Villablanca and co-workers evaluated the clinical efficacy of this approach not only on MACEs (primary end point), but also on secondary end points, such as all-cause mortality, new myocardial infarction, heart failure/pulmonary oedema and infarct size (12). Finally, safety endpoints (i.e., all-bleeding, ventricular tachycardia and bradycardias) were also assessed. In the meta-analysis, 819 patients from six RCTs that met criteria (the study was a RCT, age >18, diagnosis of STEMI, assessment of MACEs and TH administered in the setting of acute disease) were included.

The meta-analysis failed to show a clear clinical benefit of TH on post-STEMI outcomes. Only a sub-analysis of 4 RCTs that specified site of infarction (13-16) suggested that patients with anterior wall infarct had a reduction in infarct size when submitted to TH as compared to controls. Despite preliminary, since this minor result

came from only four RCTs, the article by Villablanca and co-workers suggests that TH might be useful in a selected population with cardiac arrest or some sub-groups of patients with STEMI. These results might be also explained by the fact that, differently from animal models of myocardial ischemia/reperfusion in which each 1 ℃ lowering of blood temperature cause a reduction in infarct size of 10% (17), the majority of STEMI patients in these RTCs did not reach the target temperature (12). These results were potentially influenced by the method to induce HT that was different in the RCTs [five RCTs used endovascular inferior vena cava (IVC) catheters and one a peritoneal catheter] (12). The use of an IVC catheter was previously associated with the induction of a slow HT as compared to the infusion of chilled intravenous fluid, thus unappropriated for the time PCI procedure (18). On the other hand, a more rapid heart cooling was reported by the peritoneal HT (19). However, the target temperature by standard TH protocol might be hard to be reached also when using this second device.

This meta-analysis did not apparently raise major concerns on safety. Although the safety end points were not recorded in all six RCTs at the same time, TH induced similar adverse events (i.e., all-bleeding, ventricular arrhythmias and bradycardia) as compared to controls. We might speculate that future TH RCTs in selected STEMI population might not risk to be limited by safety issues.

As partially acknowledged by the authors, the limited sample size for efficacy suggests that a meta-analysis in the next five years might be reasonable. We believe that such study should take into the account of standardized definitions of MACEs, hypothermia and target temperatures. The meta-analysis by Villablanca and colleagues has to be considered as preliminary result that requires additional confirmation. In fact, we believe that reduction in ischemia/reperfusion injury is critical to improve sequelae after effective revascularization in patients with STEMI. A better pathophysiological knowledge of inflammatory processes related to reperfusion injury might help to develop more efficient and timely treatments.

TH was already beneficial in animal models of ischemia/reperfusion (17). However, as it often happens, the translation of basic research results into human disease might have some difficulties. As identified by Bolli and co-workers, multiple barriers are interposed between the animal model and the patient (20). The most relevant clinical barriers are comorbidities, pharmacological ongoing treatments, population bias and the inability to identify and pre-treat patient with STEMI. TH remains a promising strategy in patients with STEMI. Additional RCTs are needed to conclude and potentially provide recommendations on its efficacy against STEMI.

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Footnote

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Therapeutic hypothermia in ST-elevation myocardial infarction (STEMI): targeting the appropriate STEMI

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We thank Drs. Liberale and Montecucco for their insightful commentary published in *Journal of Thoracic Disease*: "Therapeutic hypothermia in ST elevation myocardial infarction (STEMI): a long way to go".

We agree with their perspective, and in fact, their viewpoint incorporates many of the reasons for the limited success of therapeutic hypothermia (TH) shown in our meta-analysis.

Whilst timely myocardial reperfusion forms the cornerstone of therapy for STEMI patients, and prevention is by far the best strategy to limit the ravages of ischemic heart disease, novel strategies such as TH among others needs to be evaluated further. Paradoxically, although myocardial reperfusion is essential for myocardial salvage, it comes at a price, as it can in itself induce myocardial injury and cardiomyocyte death—a phenomenon termed 'myocardial reperfusion injury (MRI)'. There is currently no effective therapy for preventing MRI in reperfused-STEMI patients, making it an important residual target for cardioprotection.

Our study provides important information on the possible benefit in a subgroup of anterior MI. More importantly the Genova group point to the fact that adverse events were similar in the both groups.

Whilst TH has emerged as the standard of care in post-cardiac arrest patients (1), when we examine the evidence of TH specifically in STEMIs positive effects have been demonstrated in animal models of STEMI, but clinical application of TH has been extremely challenging in human studies.

In our meta-analysis (2), we provide an evidence-based review of TH in patients with STEMI and highlight potential therapeutic interventions of TH for preventing MRI, but these must be considered preliminary as pointed out by the Genova group, and the concept should not be abandoned based on prior studies and lack of efficacy in humans. As mentioned in their letter: (I) animal models may not fully reflect human studies; (II) smaller animals may achieve hypothermia more quickly; (III) animals may achieve target hypothermic temperature that is considered an "effective dose" to achieve a meaningful outcome, whereas the human studies thus far have a "sub-effective dose" to show therapeutic efficacy.

Given that the studies were underpowered to test for the effect of TH, we did a pooled analysis in order to arrive at more precise estimates of the efficacy and safety of the available evidence. What we found was no significant benefit from TH in preventing major adverse cardiac events, mortality, new myocardial infarction, heart failure and reduction of infarct size. However, we did find a significant reduction of infarct size TH utilization in anterior wall STEMIs. Our meta-analysis did analyze the safety concerns and found no harm with a TH strategy compared with standard of care, which is encouraging, however as further more robust studies are planned to a target lower TH, an

increase in adverse events may occur. In fact, TH seems to be safe and does not increase the risk of life-threatening arrhythmias and bleeding complications at the temperatures achieved in the completed (underpowered) studies, which may indeed be underpowered to assess adverse events.

So why the observed differences in animal models *vs.* human studies were not replicated in the RCTs and meta-analysis?

Animal models which are used to test potential cardioprotective strategies in the pre-clinical setting do not adequately represent the typical STEMI patient, in terms of patient age, co-morbidities, concomitant medication, and myocardial infarction pathophysiology, time to hypothermia: all factors which are known to attenuate the cardioprotective efficacy of many therapeutic interventions (3).

Another explanation for the lack of significant reduction in major adverse cardiovascular events was not only the small number of patients in the RCTs but also the design of the studies. The STEMI patients who are most likely to benefit from a therapeutic intervention targeting MRI are those with a complete occlusion in a large coronary artery territory, and in whom there is little coronary collateralization to the area at risk (4). By including patients without these characteristics, there is a risk of diluting any cardioprotective effect. The subgroup analysis of our paper indeed showed a significant trend in patients with anterior wall STEMI that at some point resembles the aforementioned characteristics of the patients that may benefit from novel therapeutics.

Furthermore, it is essential too, that the TH is applied prior to or at the onset of myocardial reperfusion and failure to do this may in part explain the negative findings of some RCTs. MRI occurs in the first few minutes of reflow, so delaying the implementation or failure to achieve target temperature could mitigate the effect of the intervention. Most of the trials showed that it is feasible to deliver efficient TH within the setting of a clinical trial to patients presenting with STEMI, without significant change of door-to-balloon time compared to standard control patient undergoing regular PCI. This can be achieved with a strict adherence to protocol, coordination of the team, and clearly defined roles. More importantly, this minor delay is well within the target 90-minute door-to-balloon time target that PCI centers are expected to meet. However, failure to achieve "effective" TH temperature remains an important goal. Multiple methods to establish hypothermia have been explored. To date only one RCT has compared different cooling methods (surface *vs.* endovascular), suggesting that endovascular cooling maintains target temperatures better than conventional surface cooling methods, with less temperature fluctuation and fewer complications, though no mortality difference (5). A small observational study reported that peritoneal hypothermia in patients with STEMI is feasible and results in rapid cooling too (6). There is a need to establish standardization in the future protocols to determine which is the best method to cool STEMI patients, as the correct rate to achieve TH and mechanism may also influence scar size.

We fully agree with the Genova group, that TH remains a promising strategy in patients with STEMI and that additional RCTs are needed to conclude and potentially provide recommendations on its efficacy against STEMI and MRI.

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Dual antiplatelet therapy duration after drug-eluting stents: how long?

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The implantation of drug-eluting stents (DES) has become a standard treatment for the management of patients with coronary artery disease (1). Millions of patients worldwide undergo coronary stenting each year. The use of dual antiplatelet therapy is critically important for the prevention of coronary stent thrombosis (2). Current clinical guidelines recommend at least 6- to 12-month treatment after DES implantation, but a longer duration of dual antiplatelet therapy (DAPT) may be beneficial. Interestingly, there is a slight but significant difference between the European and American guidelines, the European recommending 6 to 12 months, the American recommending at least 12 months after DES (3,4). Indeed, the recent guidelines of the European Society of Cardiology have suggested that 6-month DAPT is reasonable after second generation DES implantation in patients with stable CAD (3). The question of stopping DAPT is an important everyday problem for many clinicians. In everyday clinical practice, the decision on the optimum duration of DAPT for a given patient has to be determined. Several randomized trials comparing different durations of DAPT have been performed, and several meta-analyses have already been published demonstrating the importance of this topic in cardiology (5-9).

In this context, the report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines on Duration of Dual Antiplatelet Therapy in patients with Coronary Artery Disease is important and is asking three crucial questions about the optimal duration of DAPT after implantation of newer-generation DES (10). The first is the minimum duration of DAPT required after DES implantation, the second is about the clinical benefit of prolonging DAPT up to 18 to 48 months, the third is the clinical effect on DAPT in stable patients who are >1 year past a myocardial infarction.

About the minimum duration of DAPT required after DES implantation, the report has shown that DAPT of 12 months' duration, as compared with therapy of 3 to 6 months' duration was associated with no differences in death, major hemorrhage and stent thrombosis. It should be noted however that only two of the trials dealing with this question have compared a very short duration of 3 months compared to a longer duration (11,12). Moreover, in these two trials, patients were at low risk of thrombotic events. In the first one, the RESET Trial, 85% of the patients included had stable angina or unstable angina, in the second one, the OPTIMIZE trial, only 32% of the patients had a recent low-risk ACS. Therefore, there is still an uncertainty about safety of a very short duration (3 months) of DAPT after DES. Importantly, the context in which the stent is implanted is crucial.

Although the optimal DAPT duration in patients with ACS is controversial, there is general consensus that in

patients having an ACS, DAPT should be recommended for at least 1 year. Therefore it appears premature to recommend very short term duration of DAPT in patients with ACS and in patients with high thrombotic risk. It is however true that the evidence supporting the recommendation on DAPT duration after an ACS relies on a single randomized trial (the CURE trial) performed when ACS patients were treated conservatively, and with either balloon angioplasty or bare metal stents (13).

The second controversial point in the report is the possible clinical benefit effect of prolonging DAPT up to 18 to 48 months. In fact, only four randomized trial have prospectively compared 12 months of DAPT with a longer duration after DES placement (14-17). The DAPT trial has included the largest number of patients. The analysis has shown that prolonged DAPT significantly reduces the risks of myocardial infarction and stent thrombosis but increases the risk of major hemorrhage. There is indeed a difficult balance between the reduction in thrombotic events and the increase of bleedings. The authors of the present report performed a risk-benefit analysis and found with a longer DAPT duration no significant difference in the incidence of all-cause death, three fewer stent thrombosis (95% CI: 2–5) and six fewer myocardial infarctions (95% CI: 2–11) but five more major bleeds (95% CI: 3–9) per 1,000 patients per year. Therefore, it is not surprising that efforts have been done in identifying factors predicting whether the expected benefits of prolonging DAPT outweigh the feared increase in bleeding. Recently, Yeh *et al.* have developed a clinical decision tool to identify such patients (18). Using the large DAPT study, a prediction rule was derived stratifying patients according to their ischemic and bleeding risks. The validation was both internal and external. Because the DAPT study has randomized patients without thrombotic or bleeding events the first year after stenting, the DAPT score they derived applies only to these relatively low risk patients. Also, the authors acknowledged that their prediction rule assessing risks about DAPT continuation showed only modest accuracy. Nevertheless, it is interesting to note that among the different variables of the DAPT score, age is an important factor, and particularly an age >75 years is affected by a coefficient of –2. In other words, the older your patient is, the more cautious you have to be if you think to prolong DAPT. It seems that a prolonged duration of DAPT may be possible in patients at low bleeding risk who have tolerated DAPT the first year after stenting.

The third question is related to the clinical effect of DAPT in stable patients, more than 1 year after an acute myocardial infarction. The authors of the review conclude that the use of DAPT more than 1 year after a myocardial infarction reduces the composite risk of cardiovascular death, myocardial infarction or stroke but increases the risk of major bleeding. Once again, the equipoise is difficult but in the DAPT trial, the benefit of prolonged DAPT was accentuated in patients with MI at presentation (19). This is also reflected by the DAPT score in which myocardial at presentation at the time of PCI and prior myocardial infarction are taken into account. But in this situation also, the use of extended DAPT requires caution given the increased bleeding risk.

It has to be noted that the different trials analyzed in the report of Bittl *et al.* have included patients with implantation of predominantly newer-generation DES. The rationale for a prolonged duration of DAPT is only partially the prevention of stent thrombosis that is remarkably rare with the latest-generation stent, but also the prevention of ischemic events unrelated to the index coronary lesion (17). Newer-generation DES are associated with a risk of stent thrombosis approximately one half that of the first-generation DES, as it is reported by Bittl *et al.* (10).

In conclusion, the decision to continue or discontinue DAPT is still difficult. It depends on the bleeding and ischemic risks that are also evolving during time. The duration of DAPT has not always to be recommended at the time of the stent implantation. The rule of 1 year DAPT treatment after stenting does no more apply to each patient. In patients treated with new-generation DES for stable coronary disease, 6 months (and perhaps 3) of DAPT is an option. On the other hand, in patients at low bleeding risk, after 1 year without a cardiovascular event after DES, extension of DAPT beyond 12 months to prevent myocardial infarction may be optimal. However, there is room for better risk stratification strategies.

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Footnote

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Prolonged dual antiplatelet therapy in renal failure: a challenging trade-off

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Patients with renal failure and coronary artery disease (CAD) represent a complex and delicate cohort. Obviously, their management can be challenging and requires attention and expertise. Globally, the prevalence of chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 and/or the presence of albuminuria, seems to constantly increase with CKD now having evolved as a global public health issue (1,2). Nowadays, the most important factors promoting the development of CKD worldwide include aging, obesity, diabetes, hypertension and atherosclerotic disease (1-3). Renal failure is not only the consequence of manifold systemic diseases, but also has systemic adverse effects and is related to high morbidity and mortality, even at an early stage (4,5). Among patients with established cardiovascular disease, CKD is related to a higher rate of adverse events, including atherothrombotic manifestations and hemorrhagic events (3). Taken together, those factors contribute to the massive increase in mortality in patients with both CAD and CKD (6).

With this background, Siddiqi *et al.* aimed to shed some light on this field. By analyzing administrative data from the Veterans Affairs Healthcare System, they assessed the role of prolonged clopidogrel therapy among an all-comer cohort with CKD undergoing percutaneous coronary intervention (PCI) and stenting. According to their findings, extended dual antiplatelet therapy (DAPT) after stenting might reduce risk for myocardial infarction (MI) or death in certain patients with renal failure. Moreover, the authors found no difference in rates of relevant bleedings between those patients with normal and those with impaired renal function.

Pursuant to a recent analysis from the U.S. EVENT Registry, approximately 40% of all patients undergoing PCI have an impaired renal function (7). In comparison to those with normal renal function, PCI among individuals with CKD is related to higher rates of procedural and other complications, including restenosis and future ischemic events (3,7). CKD additionally represents an important predictor for bleedings, both in the specific case of PCI as well as in general (7,8).

However, DAPT after PCI is supposed to prevent stent thrombosis during the healing phase and atherothrombotic events stemming from lesions beyond the stented segment (9,10). Recently, prolonged DAPT after PCI gained much attention as several landmark studies have been published in that field (9-11). In summary, they reported that DAPT beyond one year after MI with or without stenting, reduced the risk of cardiovascular events in comparison to aspirin alone, but increased the risk for bleedings (9,11). Since patients with CKD were underrepresented among those trials, more robust data is needed. Hence, the study by Siddiqi *et al.* addresses an important and incompletely covered subject.

While the *Dual Antiplatelet Therapy (DAPT) Trial* did not provide any information about the number

of individuals with CKD, about one fourth of all patients included in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS-TIMI 54) trial had an eGFR <60 mL/min/1.73 m^2 (11). Additionally, a subgroup analysis of PEGASUS-TIMI 54 trial showed that patients with non-end stage renal dysfunction on either 60 mg or 90 mg ticagrelor twice daily had a better outcome in comparison to those on placebo (11). Nevertheless, DAPT with ticagrelor was related to higher bleeding risk, irrespective of underlying renal function (11). Although these data must be interpreted cautiously, it may highlight the fact that patients with renal dysfunction represent a vulnerable cohort that has a further benefit from a more intensive antiplatelet management. In addition, one of the main findings of the DAPT study was that recipients of paclitaxel-eluting stents, i.e., a first generation drug eluting stent, had the greatest benefits from extended thienopyridine therapy with regards to the reduction of atherothrombotic events (9). That finding implied that the suggested advantages of prolonged DAPT might partially rely on the implanted stent-type. Since Siddiqi *et al.* analyzed only patients with first generation drug eluting stents, their findings point toward the same direction. Taken together, a growing body of evidence indicates that prolonged DAPT may be beneficial in selected patients. However, establishing DAPT reflects a challenging trade-off, in particular among those with renal failure.

Regarding the interaction between CKD and antiplatelet therapy, it is important to note that renal disease can be related to complex enzymatic coagulation, platelet dysfunction and endothelial abnormalities (12,13). In renal failure, coagulopathies with decreased levels of protein C and elevated levels of plasminogen activator inhibitor-1, fibrinogen, thrombin–antithrombin complexes, and von Willebrand factor (vWF) multimers are found. Furthermore, platelet dysfunction with a decreased production of thromboxane A2 and other platelet transmitters, abnormal intracellular calcium handling, and activation-dependent binding of glycoprotein llb/llla to vWF represent important issues. Finally, enhanced endothelial dysfunction itself promotes atherosclerosis and atherothrombosis (13). This background may partially emphasize the changes and mechanisms contributing to the clash of atherothrombotic and bleeding events in patients with CAD and impaired renal function (3).

The handling of antiplatelet therapies is complicated not only by altered thrombocyte function and plasmatic coagulation, but also by changed pharmacokinetics of drugs when used in CKD (3). Of note, patients with severe or end stage renal failure are either underrepresented or excluded in major cardiovascular trials studying the P2Y12 receptor antagonists (12). Therefore, data analyzing the role of P2Y12 receptor antagonists are limited and their prolonged administration in CKD conflicting (3,14). The Clopidogrel for the Reduction of Events during Observation (CREDO) and the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trials have implied that renal function may affect the clinical efficacy of clopidogrel and therefore outcomes (15,16). In those studies, patients with CKD treated with clopidogrel had worse outcomes in comparison to those with normal renal function (15,16). The use of clopidogrel significantly reduced the rate of major cardiovascular adverse events in patients with preserved renal function, but this benefit was less obvious among individuals with mild CKD and even vanished in moderate CKD (16).

Due to the nature of the data and the analyses performed, some questions and limitations remain unmet by Siddiqi *et al*. and may establish the fundament for future research. First, it is not possible to draw definitive conclusions based on the nature of that analysis. Second, the applied exclusion criteria may have resulted in a selection bias. Third, bleedings in CKD patients with PCI seem to be more common than reported here (7,8). In the DAPT study, BARC type 2, 3, or 5 bleedings were met in roughly 5% in the intervention arm (9). Thus, this retrospective analysis with less reported bleedings should be interpreted with caution—it may not reflect the real world, and more prospective data are warranted. Fourth, within the last decade, there were tremendous advances in PCI and stent technology. From this perspective, it would therefore be of interest to know how the use of the latest stent generations (e.g., coated with mTOR inhibitors or biodegradable polymers) impacts the outcome of CKD patients. Fifth, the association between eGFR and cardiovascular events is not linear but rather exponential. Hence, the dichotomized classification applied by the authors, which groups individuals either to an eGFR value of below <60 mL/min per 1.73 m^2 or beyond and normal, may oversimplify that relationship and excludes potentially relevant subgroups.

Sixth, since the analyzed data stem from administrative data including almost only male individuals, the gender aspect had inevitably to be excluded by the authors. Nonetheless, one needs to take in account that the underlying gender influences the outcome of cardiovascular diseases and sex-specific disparities in thrombotic and bleeding risks may play a fundamental role (17).

What should we learn and take along from that study?—patients with CKD have a markedly higher risk for recurrent ischemic events and death. Among those patients, the trade-off between benefits and risks of prolonged DAPT will remain challenging, since an adequately powered randomized trial is still missing. In patients with CKD undergoing PCI, a thorough assessment and balancing of bleeding and ischemic risks is mandatory. Prolonging DAPT among renal failure patients that received a first generation drug eluting stent seems to be reasonable with regards to the beneficial long-term outcomes with those stents. This is of special interest, since the number of patients treated with those stents and returning for recurrent ischemic events is growing in the near future, specifically in patients with CKD.

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Footnote

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Time for science to catch up with clinical practice?

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Siddiqi *et al.* performed a retrospective analysis of the large Veterans database to explore the effect of clopidogrel prolongation beyond 12 months compared with 12 months or less after coronary stenting (1). Patients treated between 2002 and 2006 were divided in two groups: normal renal function (n=18,162) or chronic kidney disease (CKD, n=4,880) based on an estimated glomerular filtration rate (eGFR) cut-off of ≥ or <60 mL/min, respectively. A further stratification was made to compare patients treated with bare metal stents (BMS) and those treated with drug-eluting stents (DES). Outcomes were evaluated in patients free from ischemic or bleeding events within the first 12 months after percutaneous coronary intervention (PCI), at a follow-up ranging from 1 to 4 years after PCI. The primary endpoint was the combined outcome of death or acute myocardial infarction (MI), which was significantly increased in patients with CKD in both DES and BMS subgroups. However, CKD was also associated with an increased risk of disabling or life-threatening bleeding after DES and BMS implantation.

The authors reported that clopidogrel use of more than 12 months after PCI in patients with CKD receiving DES was associated with lower risk of death or MI (18% *vs.* 24%, HR=0.74; 95% CI, 0.58 to 0.95), and death (15% *vs.* 23%, HR=0.61; 95% CI, 0.47 to 0.80). At multivariate and propensity-score adjusted analyses, however, results were confirmed for death but not for the composite of death or MI. Furthermore, the potential benefits of prolonged dual antiplatelet therapy (DAPT) on the primary endpoint did not apply to patients treated with BMS. No significant increase of life-threatening bleeding was observed by prolonging DAPT administration after both DES or BMS implantation in patients with CKD at multivariate or propensity analyses, however: (I) a trend of increased risk was present (significant at univariate analysis in DES subgroup); (II) the rates of major bleeding were not reported and (III) the number of life-threatening bleeding events was probably too low to detect a significant difference between subgroups.

Finally, in patients with normal renal function, the authors observed consistent findings but the magnitude of ischemic risk reduction was lower than that observed in CKD patients treated with DES.

Although affected by some inherent critical limitations, this large retrospective study is well conducted and of interest to the community because it deals with a specific patient population (i.e., patients affected by CKD) in whom few data from randomized trials are available.

DAPT administration aims to reduce the risk of stent thrombosis (ST) after coronary stent implantation and prevent coronary atherothrombotic events at sites outside of the stented segment. However, the optimal duration of DAPT after stent implantation in general, and following DES implantation in particular, is matter of ongoing debate (2,3).

Does this study help in identifying the target population in which DAPT should be prolonged well beyond 12 months? We believe the reader should apply caution while interpreting study results. Beyond the obvious limitations carried by a retrospective and non-randomized analysis, these findings should be critically contrasted with the results of randomized controlled studies, which showed a clear effect of DAPT prolongation on non-fatal ischemic endpoints, i.e., MI and very late ST, in the absence of a

mortality benefit. How can we reconcile those with the observed reduction in mortality but not mortality or MI risk in the current analysis? A plausible interpretation is that in clinical practice clinicians are able to identify patients who benefit from prolonged DAPT duration and using sophisticated statistical tools, no adjustment can be made for baseline or updated covariates that are not routinely captured, and perhaps not even capturable, in registries.

Drug eluting stents have consistently reduced in-stent restenosis as compared with BMS but at the expense of safety concerns duo to an increase in late and very late ST. In particular, first-generation DES were associated with a four- to five-fold higher risk of very late ST as compared with BMS, which fueled "the longer the better" recommendation for DAPT duration in patients treated with DES (4). Conversely, second-generation devices were shown to be safer in terms of ST as compared with both first-generation DES and BMS (5).

Recent trials, reviews and meta-analyses (2,6-12) compared efficacy and safety of short (<12 months) and long term (≥12 months) DAPT after first- and second-generation DES implantation with respect to the currently recommended 12-month therapy (13,14). A short course of DAPT was associated with a significant reduction in major bleeding without significant differences in ischemic or thrombotic outcomes. Moreover, patients associated with high risk of bleeding events were recently evaluated in two different trials (15,16) in which DAPT was stopped very early (1 month) after second-generation DES implantation without safety concerns in terms of ischemic events. In particular, the ZEUS trial (15) compared Zotarolimus-eluting Endeavor sprint stent followed by 30-day DAPT with BMS followed by the same DAPT regimen, while the LEADERS FREE trial (16) compared a polymer-free Biolimus-eluting stent with a very similar BMS platform followed by 1-month DAPT. Both studies demonstrated that a treatment strategy consisting of second-generation DES implantation followed by a shorter than currently recommended DAPT regimen (30 days) resulted in a lower risk of MACE as compared with BMS in high-bleeding risk patients.

Conversely, prolonging DAPT over 12 months yielded a significant reduction in terms of MI and ST, in particular in trials including first-generation DES use (10,17), but at the price of a substantial increasing in major bleeding. Moreover, all-cause mortality was also significantly increased in the long-term DAPT population (10,11,18). Actually, bleeding and ST may have a different impact on mortality as highlighted in a recent meta-analysis reporting a significant association between bleeding and non-cardiovascular death but not between ST and cardiovascular death (19).

As a result, a personalized DAPT duration based on patient's bleeding and ischemic risk seems to be a more logical strategy in order to reach maximum benefits with limited side effects.

Patients with CKD represent a sizable proportion of patients (between 33% and 50%) with myocardial ischemia undergoing percutaneous coronary stent implantation (20), although frequently excluded or marginally represented in major randomized trials evaluating clopidogrel duration after coronary stenting. Siddiqi *et al.* included a high number of patients with eGFR <60 mL/min in whom primary and secondary outcomes were evaluated with multivariate and propensity analyses (1). The sensitivity analyses using the CKD-Epi equation, which seems to be more precise in estimating renal function, supported the consistency of their results. Unfortunately, due to the small number of subjects with eGFR <30 mL/min, the differences across different degrees of CKD have not been evaluated in this study (1).

In early-stage CKD population the risk for premature cardiovascular disease is increased by 25% to 30% while in end-stage CKD patients it is more than 30- to 50-fold higher. On the other hand, also the bleeding risk is increased in patients with renal dysfunction (1,20). Indeed, renal disease was identified to be commonly used in the clinical practice to weigh the bleeding risk after DES implantation in a recent survey (3), and it is also included in the most relevant available bleeding risk scores (i.e., CRUSADE and HAS-BLEED).

Siddiqi *et al.* concluded that: "in patients with CKD, prolonging clopidogrel beyond 12 months after PCI may decrease the risk of death or MI only in patients receiving first-generation DES as compared with BMS". Key questions remains with respect to whether and how much these results may be applicable to patients with more severely reduced renal function (i.e., eGFR <30 mL/min) or to patients treated with contemporary devices, such as newer generation DES.

The observation that prolonged DAPT did not increase bleeding risk, a finding which has been remarkably consistent across all randomized controlled studies and meta-analyses, further raising concerns on the adequacy of

adjustment for biases in the current analysis.

Conclusions

Prolongation of DAPT still remains highly debated, irrespective of specific subgroups of patients, because it is associated with ischemic benefits, but also with a time-dependent risk of major and clinically relevant bleeding complications, which in turn significantly affect morbidity and mortality.

The present study offers data for additional debate as it focuses on a large sub-population of patients with high ischemic and bleeding risks, who are frequently under-represented in randomized trials on DAPT duration and/or stent types. The key lesson here is that perhaps clinicians seem to be able to select the ideal CKD population in whom DAPT may and should be prolonged, better than conventional inclusion or exclusion criteria so far employed in clinical trials. Hence, once more trialists and device or drug manufacturing companies need to learn from clinicians more than vice versa.

Randomized trials of new generation DES and reliable $P2Y_{12}$ inhibitors (ticagrelor or prasugrel) are needed to help clinicians to perform even better.

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Footnote

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Bioresorbable drug eluting scaffolds—are bioresorbable stents ready for today's clinical practice?

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During the course of stent development, a novel concept has recently been introduced, which is based on transient scaffolding of the coronary artery with the help of fully bioresorbable stents eventually allowing vascular restoration over time. Bioresorbable vascular scaffolds represent a landmark innovation and are designed to fully disappear from the coronary artery once their function is no longer needed. This new approach in the treatment of coronary artery disease is widely believed to be beneficial as compared to current metallic devices, especially in younger patients. In this context, recent studies have indicated potential advantages of bioresorbable scaffolds, as treated vessels seem to regain vasomotor functionality during degradation of the device (1).

Different materials and components have been investigated, where two concepts have reached the stage of clinical investigation: Magnesium-based bioresorbable stents and scaffolds consisting of lactic acid co-polymers. The development of the latter material is further advanced to date and by now two bioresorbable scaffolds based on a lactic acid polymer have received CE approval at the European market (ABSORB—Abbott Vascular, Santa Clara, California and DESolve—Elixir Medical Corporation, Sunnyvale, California).

Despite the rapid adoption of this novel technology in clinical practice soon after CE-mark approval, comparative clinical data on patient outcomes relative to current standards have been missing. Recent randomized studies and registries helped to improve our understanding of the benefits and drawbacks of this novel technology. In this regard, the most important requirement for innovative techniques or technologies is the proof of non-inferiority regarding both safety and efficacy versus the existing standards, especially in the initial phase after treatment (2). Apart from the results of the first clinical trials, the available literature on clinical outcome data after bioresorbable stent implantation has increased significantly within the last year. Although the overall clinical results reported so far look promising, a slightly higher risk of early device thrombosis seems to dampen the widespread optimism derived from bioresorbable scaffold implantation (3). One of the key pathological explanations seems to be the substantially increased thrombogenicity of current generation BRS, where strut thickness and width exceeds by far what we have been accustomed to with the use of contemporary metallic DES. It has been demonstrated in a preclinical porcine arterio-venous shunt model that bioabsorbable scaffolds reveal a significantly higher acute thrombogenicity compared with second generation DES; besides that, metallic DES showed greater re-endothelialization after 28 days and reduced inflammatory reactions after 14 days as compared with bioabsorbable scaffolds (4).

Since the introduction of BRS in clinical practice, there has been continued debate about their practical implementation, where one of the suggested indications was in the setting of acute myocardial infarction. The proposed benefit of BRS in this specific setting is thought to derive from their temporary presence since malapposition of stent struts is a frequent finding when stents are implanted in occluded vessels where appropriate sizing represents a major

challenge. Furthermore, it is believed that BRS enable vascular restoration over time, which may be especially important in the healing phase of acute plaque rupture, where vascular remodeling plays an important role. Another argument favoring the implantation of BRS in the setting of acute ST-elevation myocardial infarction is that patients are often younger than patients presenting with chronic stable CAD, where the capacity of vascular restoration might be preserved. In this respect, an interesting study which was published in *JACC Cardiovasc Interv* in 2015 has to be highlighted, in which the authors focused on the performance of fully bioresorbable scaffolds in the setting of acute myocardial infarction (5).

For their observational study, Brugaletta and colleagues combined the data from two independent studies in order to analyze differences between everolimus eluting bioresorbable scaffolds and contemporary DES and bare metal stents, respectively (5). Although the rate of stent thrombosis was higher in the biodegradable scaffold group as compared with DES within 30 days (1.4% *vs*. 0.3%) and 12 months (1.7% *vs*. 0.7%), the authors describe no statistical significant differences among the groups. To reduce the strong influence of baseline patient risk differences among the two datasets, the authors performed propensity-score matching. However, this correction cannot fully compensate differences in patient baseline characteristics and, although the propensity score matching was overall well performed and described, the customized model might have had some downsides. The main goal of this statistical matching technique is to gauge the effects of pre-treatment factors that predict receiving one treatment or the other. For this reason, only pre-treatment factors that potentially can influence the treatment should be considered for this matching whereas e.g., procedural circumstances should be disregarded (6). Furthermore, as the presented study was not randomized, other influences than the chosen stent type might affect the outcome results. Especially the fact that patients treated with biodegradable implants were enrolled in the setting of a registry study whereas the patients of the DES and BMS groups were selected from the dataset of a prospective clinical trial has to be considered critically. Furthermore, the comparison of bioresorbable stents *vs*. bare metal stents seems to be pointless, as bare metal stents are nowadays not recommended for the setting of primary angioplasty. Last but not least, the study appears to be underpowered in order to compare rarely-occurring clinical endpoints like stent-thrombosis.

Nevertheless, the study highlights promising and potentially pioneering results in regard to daily clinical use of fully biodegradable drug eluting stents in the setting of primary angioplasty. The most notable finding is the similar performance of the degradable devices as compared to the standard metallic drug eluting stents at 12 months follow-up. These findings were recently confirmed in the Absorb III trial which showed a non-inferiority of BRS compared with metallic DES in regards of target lesion failure at one year follow up (7). Furthermore, fully biodegradable scaffolds were recently investigated in the setting of acute ST-elevation myocardial infarction and compared against 2nd generation DES with regards to their performance on a multicomponent ordinal healing score (8). In this respect, the absorbable vascular scaffold was non-inferior and compared favorable to the metallic DES in the percentage of malapposed stent struts. However, this innovative imaging endpoint, even though it is promising, has important limitations since established and validated evidence for this score is missing. For that reason, skepticism regarding the safety profile of fully absorbable scaffolds in the setting of acute myocardial infarction is still indicated.

In their meta-analysis of all available randomized controlled trials, Cassese and colleagues recently highlighted the increased risk of stent thrombosis, especially within the first 30 days, as well as a greater in-device late lumen loss in BRS as compared with metallic DES (3). Therefore, we should not become too euphoric in this respect as long-term results (>1 year) are still pending. These long term results might also answer the questions whether or not the new generation of devices is capable to re-establish vasomotion and to provide a positive remodeling effect within the treated artery or whether the degradation process triggers inflammatory reactions after drug elution. The finding of slightly higher thrombosis rates, especially within the first 30 days of implantation, seems to be mainly related to the procedural results more than to the shape or chemical composition of the stent. Additional information from intravascular imaging techniques should be gathered whenever necessary to guarantee satisfying stent positioning and deployment. Further development of the bioresorbable scaffolds might solve current disadvantages with regard to radial strength.

To summarize: the available data, as well as our own experience, furnishes us with optimism that this latest technology can deliver benefits to many patients. The essential point behind the successful use of fully biodegradable stents seems to be a careful patient—as well

as lesion selection combined with an optimization of the procedural results.

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Footnote

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Bioresorbable vascular scaffolds in patients with acute myocardial infarction: a new step forward to optimized reperfusion?

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Abstract: Bioresorbable vascular scaffolds (BVS) represent a disruptive technology that has caused a new revolution in interventional cardiology. BVS appear to be particularly appealing in patients presenting with an acute myocardial infarction (MI). The available evidence on the value of BVS implantation in this challenging scenario is very promising but still limited. Results come from preliminary small observational studies, prospective registries that include a control group, and from scarce randomized clinical trials with surrogate mechanistic or angiographic primary end-points. Further studies, powered for clinical endpoints, are required to establish the relative safety and efficacy of BVS *vs.* new-generation metallic drug-eluting stents (DES) in patients with ST-segment elevation acute MI.

Keywords: Acute myocardial infarction; bioresorbable vascular scaffolds (BVS); drug-eluting stents (DES); myocardial infarction (MI)

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Introduction

Major advances have occurred during the last decade in the treatment of patients presenting with acute myocardial infarction (MI) (1). These include logistic improvements leading to the organization of efficient network programs that enable timely and optimal primary angioplasty procedures, the advent of novel antithrombotic regimens and the use of new-generation drug-eluting stents (DES) (1,2). Patients with ST-segment elevation MI (STEMI) are associated with a complex underlying coronary substrate leading to a higher rate of restenosis but also to a higher risk for stent thrombosis. The controversy on the value of first-generation DES versus conventional bare-metal stents (BMS) in these patients was maintained for some years (1). Although DES were able to significantly reduce the restenosis rate the possibility of increasing the risk of late and very late stent thrombosis was a cause of concern (1). Suboptimal stent implantation (mainly undersizing) secondary to difficulties to accurately ascertain the true vessel size in the presence of vasospasm secondary to sympathetic activation and to the existence of a large residual thrombus burden, were implicated in the appearance of adverse long-term clinical events. Accordingly, careful thromboaspiration was advocated to optimize acute procedural results and to prevent the occurrence of late acquired malapposition resulting from the disappearance of the residual thrombus entrapped behind the stent (1,2). However, the widespread systematic utilization of manual thrombus aspiration during routine primary angioplasty procedures has been recently halted in the light of the negative results of 2 large controlled trials of routine thromboaspiration in STEMI powered for major

clinical events (1,3). Moreover, the delayed healing and the potential toxic effects on the vessel wall leading to positive remodeling and late acquired malapposition occasionally seen with first generation DES (4), were additional issues of concern explaining the delayed widespread adoption of DES in STEMI patients (1). Nevertheless, novel generation DES have proved to be not only more effective but also safer than first generation DES (5). Indeed, studies demonstrated that rates of stent thrombosis were even lower with second-generation DES than with BMS (6). Importantly, in patients with STEMI, the EXAMINATION randomized clinical trial demonstrated that everolimus-DES (EES) were associated with a reduced rate of stent thrombosis compared with BMS (7). In this study EES also significantly reduced the rates of target-lesion revascularization (7). Moreover, the 5-year results of this randomized trial (8) confirmed that the sustained clinical efficacy of EES in STEMI patients may translate into a survival improvement.

Attractiveness of bioresorbable vascular scaffolds (BVS) in STEMI

BVS represent a disruptive technology leading to a new revolution in interventional cardiology (1,9,10). Current generation BVS provide nearly the same scaffolding properties than metallic stents ensuring optimal acute anatomic results. However, to obtain a similar radial force and prevent acute recoil currently available BVS have thicker struts (150 μm). Actually, BVS maintain better conformability than new-generation metallic DES. However, the crossing profile and device pushability and deliverability remain a limitation of these devices specially in tortuous and calcified vessels (9,10). Likewise, as the dilation range is rather narrow optimal scaffold sizing remains of paramount importance to avoid fracture due to over-dilation. BVS elute the antiproliferative drug with a similar efficacy to metallic DES (9,10). In fact, the amount of everolimus eluded is larger from BVS than from EES. In favourable clinical and anatomic scenarios the long-term clinical and angiographic results of BVS appear to be comparable to those obtained with DES (9,10). Accumulating evidence also suggest the long-term clinical safety and efficacy of BVS used in more complex clinical and anatomic settings (11). Nevertheless, in a "real world" routine clinical practice some studies with an "all-comers" design have suggested the possibility of increased risk of acute and subacute thrombosis associated with the use of BVS (12). The technical subtleties and nuances associated with the delivery and implantation of these early generation scaffolds (thicker struts and less flexible devices) have been implicated. Attention to adequate predilation, accurate sizing and optimal postdilation have been suggested to prevent these potential problems, especially in patients with complex lesions. The "soft" lesions that characterize STEMI patients (ruptured thin-cap fibroatheromas with a large necrotic core, positive vessel remodelling and large intraluminal thrombus) may provide an ideal substrate for BVS implantation. Some investigators suggest a potential benefit of slight scaffold oversizing in these patients. However, the risk of no reflow phenomenon could be higher when aggressive post-dilation is systematically performed. The higher strut-to-vessel ratio that characterizes current BVS as compared with second-generation DES might facilitate the entrapment of the residual thrombus ("snow racket effect") and prevent silent distal embolization or clinically evident no reflow phenomena. However, the potential risks of BVS implantation in a highly thrombogenic milieu, as in STEMI patients, should be critically assessed. In these patients, the use of thromboaspiration and novel potent antiplatelet agents (prasugrel or ticagrelor) before BVS implantation is, therefore, particularly appealing.

The beauty of BVS is simply that they eventually completely disappear from the vessel wall after serving their function (9,10). Polymeric scaffolds consist of polylactide (a mixture of crystalline and amorphous poly-L-lactic acid) that is degraded to lactic acid that, in turn, is hydrolyzed to CO_2 and H_2O via the Krebs cycle (9,10). The absence of a permanent metallic cage and durable polymer coatings on the vessel wall is very attractive indeed. BVS may overcome some shortcomings associated with permanent metallic jailing of side-branches and the "freezing" of the vessel wall preventing remodelling phenomena able to compensate for plaque growth or even promote lumen enlargement. Furthermore, BVS dissipate concerns on the risks associated with delayed healing and endothelialization of the stent struts and those related with very late malapposition (5). Preliminary studies already suggest that coronary vasomotion and normal vessel wall physiology are restored at long-term follow-up after BVS implantation (13). In addition, the possibility of a significant reduction in the underlying plaque burden associated with late lumen enlargement has been recently suggested (14). Finally, in patients with acute coronary syndrome treated with BVS the late healing process appears to be associated with the development of a novel neointimal layer or "thick cap"

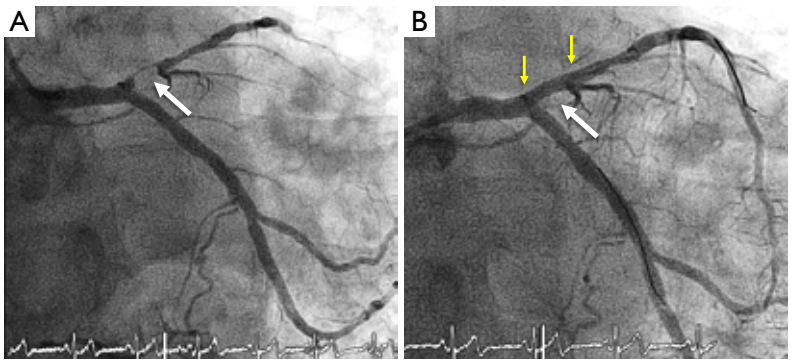

Figure 1 Angiographic results of BVS in STEMI. A 61-year-old patient presented with an anterior STEMI. (A) Urgent coronary angiography revealed a very tight stenosis in the most proximal segment of the left anterior descending coronary artery (arrow). The angiographic image was suggestive of a large thrombus burden; (B) following thromboaspiration a BVS (3.5 mm × 18 mm) was implanted with an excellent angiographic result (yellow arrows indicate the edges of the BVS). BVS, bioresorbable vascular scaffolds; STEMI, ST-segment elevation myocardial infarction.

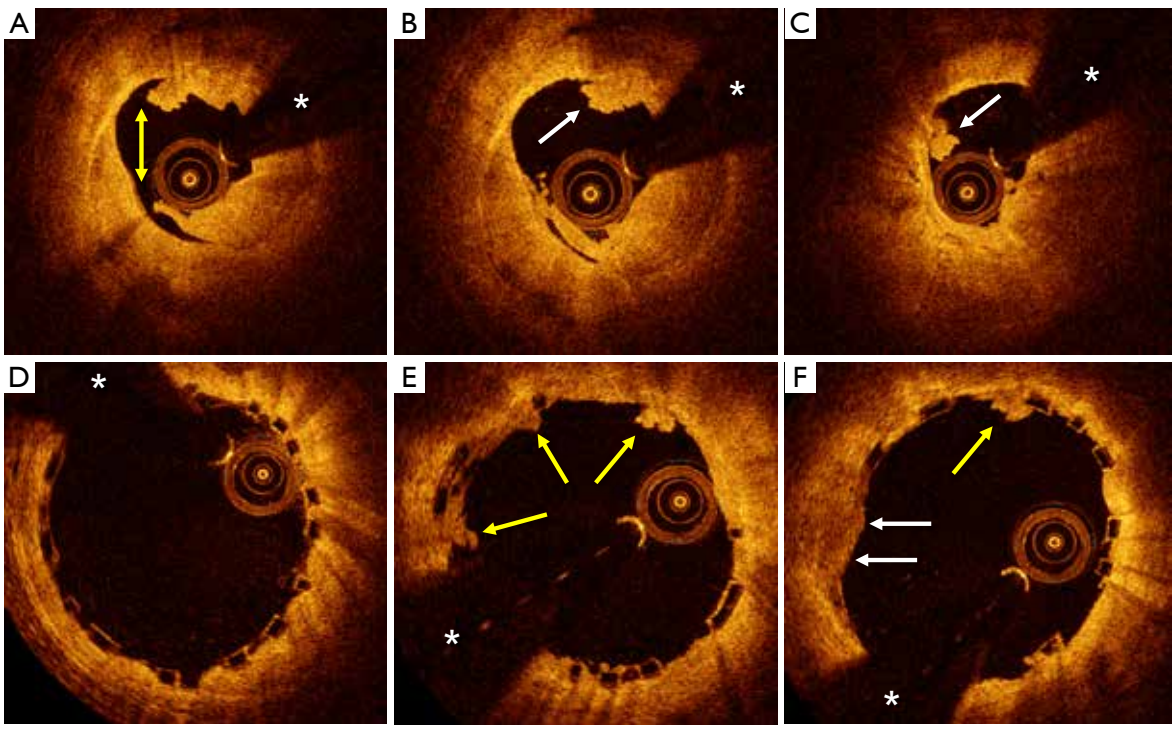

Figure 2 Optical coherence tomography images of the same patient as in *Figure 1*. (A-C) Images preintervention. (A) Plaque rupture (double-headed arrow); (B,C) culprit plaque with intraluminal protruding thrombus (white arrows); (D-F) images after intervention. The characteristic black-box images of the fully expanded and well apposed BVS struts are readily depicted. Images suggestive of residual protruding thrombus (yellow arrows) and lipid plaque prolapse (white arrows) are also detected. *, wire artefact. BVS, bioresorbable vascular scaffolds.

that covers, seals and potentially "stabilizes" the underlying guilty pathologic substrate (15). All the advantages associated with this phenomenon known as late "vessel restoration" could be of particular value in STEMI patients. In addition, STEMI patients tend to be younger and have proximal non-calcified culprit plaques with less extensive disease and, theoretically speaking, may particularly benefit from not having a long-life permanent rigid metallic

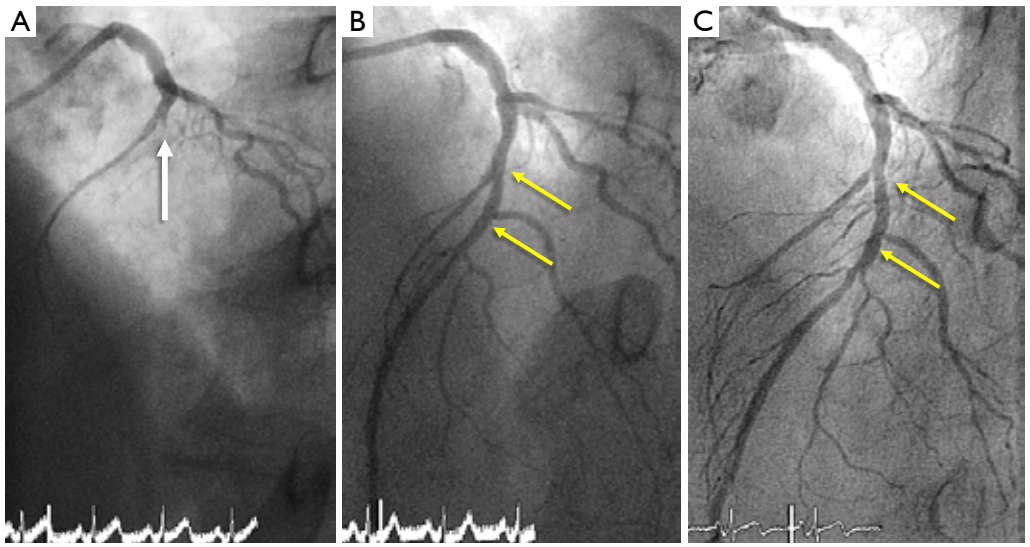

Figure 3 Angiographic images (left anterior oblique projection with cranial angulation) of a 68-year-old patient presenting with an anterior STEMI. (A) Before intervention an occlusion of the proximal segment of the left anterior descending coronary artery (arrow) was shown; (B) results immediately after BVS (3 mm × 12 mm) implantation (yellow arrows indicate the edges of the BVS); (C) findings at late (9 months) angiographic follow-up. STEMI, ST-segment elevation MI; BVS, bioresorbable vascular scaffolds.

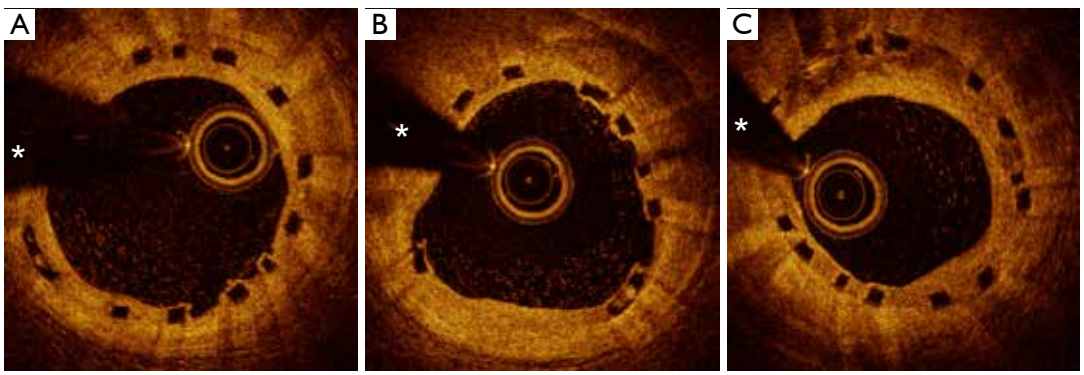

Figure 4 Optical coherence tomography images of the same patient as in *Figure 3*, at 9-month follow-up. The black-box characteristic images of the BVS struts are still readily recognized. (A,B) A nearly complete coverage of the BVS struts is detected suggesting a favourable healing process; (C) site depicting the maximal neointimal proliferation showing a large residual coronary lumen. *, wire artefact. BVS, bioresorbable vascular scaffolds.

structure on their coronary arteries.

Typical examples of BVS results in STEMI patients are presented in *Figures 1-4*.

Studies addressing the value of bioresorbable vascular scaffolds (BVS) in STEMI

Several preliminary observational studies demonstrated the safety and feasibility of BVS implantation in STEMI patients (16-20). PRAGUE 19 (19) was a prospective registry where consecutive patients with STEMI were treated with BVS as a default strategy. Of 142 patients treated with primary angioplasty 41 (29%) fulfilled criteria for BVS implantation that was successful in 98% of cases. The event-free survival for patients treated with BVS was 95% *vs*. 93% for a control group of STEMI patients treated with metallic stents. In a subsequent report from these investigators (20) computed tomographic angiography was performed after 1 year in 59 patients showing a binary restenosis rate of only 2%. Most of these early observational

studies, however, were limited by the lack of a control group, small sample size and short-term follow-up. More recently Cortese *et al*. (18) analyzed 563 patients with STEMI included in a large Italian registry; of these, 122 received BVS and 441 EES. At a median of 220 days, no significant differences were observed in terms of patient-oriented clinical end-points (BVS 4.9% *vs*. EES 7.0%, P=0.4); or individual endpoints including death (BVS 0.8%, EES 2.0%, P=0.4), MI (BVS 4.1%, EES 2.0%, P=0.2), target lesion revascularization (BVS 4.1%, EES 4.5%, P=0.8) or device thrombosis (BVS 2.5%, EES 1.4%, P=0.4). In addition, after careful propensity score matching, no differences in clinical endpoints were detected between BVS and EES at the longest available follow-up.

In an elegant study Brugaletta *et al*. (21) compared the results of BVS with those obtained with EES and BMS in the EXAMINATION trial. In this study the results of 290 consecutive STEMI patients treated with BVS were compared with those obtained in 290 STEMI patients treated with EES and 290 STEMI patients treated with BMS (21). A propensity score was used to adjust for potential confounders and obtain equally-sized groups of well-matched patients. Notably, pre and post-dilation was more frequently used in the BVS group. The primary end-point of the study was a device-oriented clinical outcome measure that included cardiac death, target vessel MI and target lesion revascularization. Interestingly, the primary end-point at 30 days and 1-year follow-up was low and similar (4.1%, 4.1% and 5.9%) for BVS, DES and BMS. Although, the rate of definitive/probable stent thrombosis was numerically higher for BVS than for DES or BMS, the differences were not statistically significant. However, the trend for a higher rate of early thrombosis after BVS compared with EES (2.1% *vs*. 0.3%, P=0.059) was a cause of concern (21).

On the other hand, results from head-to-head randomized comparisons of BVS *vs*. DES in patients with acute coronary syndrome are scarce. The EVERBIO II trial (22) randomized unselected "all-comers" patients, many of them presenting with an acute coronary syndrome (39% of patients but only 10% with STEMI), to BVS, EES or biolimus-DES. The primary endpoint of the study, the angiographic late lumen loss at 9-month follow-up, did not differ among the groups (0.28 mm in the BVS group, 0.25 mm in the DES groups). In addition, the combined clinical outcome measure was similar in the 3 arms. The ABSORB-STEMI-TROFI II was a multicenter randomized clinical trial that allocated (1:1) STEMI patients to BVS (95 patients) or EES (96 patients) (23). Randomization was performed after achievement of TIMI 2 flow following thrombus aspiration. In this trial thrombectomy was mandatory to reduce thrombus burden. Interestingly, postdilation was more frequently used in the BVS arm. Optical coherence tomography was used to compare arterial healing responses (non-inferiority design) with both devices as a surrogate for safety and efficacy. The primary endpoint was the comparison of the healing score (presence of uncovered struts, malapposed struts and intraluminal material) at 6 months assessed by optical coherence tomography (23). The healing score was lower (1.74 *vs*. 2.80, P for non-inferiority <0.001, P for superiority 0.053) in the BVS arm. This was mainly driven by a higher rate of uncovered and malapposed struts in the EES arm. However, the mean neointimal hyperplasia area was larger (1.52 *vs*. 1.35 mm^2, P=0.018) in the BVS group. In addition, on quantitative coronary angiography, the mean in-device late lumen loss at 6 months was higher (0.17 *vs*. 0.08 mm, P=0.024) in the BVS arm. Importantly, a device-oriented composite end-point (cardiac death, target vessel MI and clinically-driven target lesion revascularization) (1.1% *vs*. 0%) and stent thrombosis rates (1.1% *vs*. 0%) were similar in the BVS and EES arms, respectively. This study demonstrated that BVS implantation in STEMI patients is associated with a nearly complete arterial healing at follow-up, with morphological findings comparable with those seen with EES (23). This is of potential clinical relevance considering previous studies suggesting superior healing characteristics of EES compared with first-generation DES.

The currently ongoing ISAR-ABSORB-MI randomized trial (NCT 194207) is comparing the safety and efficacy of BVS with durable polymer EES (2:1 randomization scheme) in patients with acute MI. Patients with STEMI and those with non-ST segment elevation MI associated with a clear angiographic thrombus, are eligible. The primary outcome measure is the comparison of the percentage diameter stenosis at the protocol-mandated coronary angiography performed at 6-8 month follow-up using a non-inferiority study design. Main secondary clinical endpoints include a device-oriented composite clinical endpoint of cardiac death, target vessel-MI and target lesion revascularization and a patient-oriented composite clinical endpoint of death, any MI and any revascularization. Enrolling a total of 260 patients is planned.

Conclusions

BVS are very appealing for selected STEMI patients.

Results from available observational studies and randomized clinical trials are reassuring and very promising (16-23). Rates of early BVS thrombosis in adverse anatomic scenarios, including the presence of a highly thrombogenic milieu, however, appear to be not negligible. Therefore, careful lesion preparation, accurate scaffold sizing and, when required, postdilation, appear mandatory to ensure optimal BVS implantation in this complex scenario. Furthermore, thromboaspiration may be of particular value in patients with a large thrombus burden. In addition, the use of novel potent antiplatelet drugs is also highly appealing in these patients with enhanced platelet activity. The improvement in radial strength and reduction in strut thickness of new-generation BVS will hopefully represent a major step forward favouring optimal BVS deployment in this challenging anatomic setting. Current clinical data come from observational retrospective studies, registries with a control group of patients treated with DES, and randomized studies designed for surrogate primary end-points but not powered for major clinical events. As the potential advantages of BVS over metallic DES theoretically should accrue over time, a longer follow-up of the available studies will shed additional light on this issue. Meanwhile, the currently available information should be just considered as very promising but just hypothesis-generating. Further studies powered for clinical events are certainly needed to definitively establish the relative safety and efficacy of BVS versus new-generation metallic DES in STEMI patients.

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Footnote

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Bioresorbable vascular scaffolds—time to vanish?

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Provenance: This is an invited Perspective commissioned by the Section Editor Yue Liu (Associate professor, Department of Cardiology, The First Affiliated Hospital of Harbin Medical University, Harbin, China).

Abstract: The fully bioresorbable vascular scaffold (BVS) has been developed to reduce late adverse events after coronary stenting such as device thrombosis. The device consists of polylactic acid, which is gradually absorbed within the first few years after its implantation. The initial experience with the device in low-risk patients presenting with simple lesions was satisfying and generated optimism among interventional cardiologists by promising better patient outcomes. However, the unrestricted use of the device in patients presenting with a higher baseline risk and more complex lesions came at the cost of alarmingly high rates of early device thrombosis. The performance of the device largely depends on an optimal implantation technique, which differs from that employed with metallic drug-eluting stents (DES) due to the device's distinct physical propensity. Mid-term outcomes in large-scale randomized clinical trial were disappointing. Although its non-inferiority compared to metallic everolimus-eluting stents (EES) was formally met, there was a clear trend towards an increased occurrence of myocardial infarction and device thrombosis during the first year after device implantation. However, the BVS's putative advantages are expected to manifest themselves at long-term, that is 3 to 5 years after the device has been implanted. Evidence pertaining to these long-term outcomes is eagerly awaited.

Keywords: Bioresorbable vascular scaffold (BVS); percutaneous coronary intervention; coronary artery disease (CAD); ST-elevation myocardial infarction (STEMI)

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Why bioresorbable vascular scaffolds (BVS)?

Percutaneous coronary interventions have undergone a stepwise evolution with some tops and some flops since their inception by Andreas Grüntzig in 1977 (1). Bare metal stents (BMS), who suppressed the risk of occlusive dissection and lowered the risk of restenosis (2), dual antiplatelet therapy which decreased the risk of thrombosis, and drug-eluting stents (DES) which minimized the risk of restenosis were all significant advances. Other novelties, such as laser revascularisation and endobrachytherapy were nipped in the bud. Even the latest generation of metallic DES, despite continuous and significant improvements, may impair coronary vasomotion (3), trigger neoatherosclerosis and hamper surgical attempts to treat failed stented segments.

The studies on DES thrombosis in the years 2005 triggered a somewhat artificial emulation amongst stent-makers. From this, rose the concept and development of vanishing stents. Such temporary devices were thought to potentially restore lumen size and flow while disappearing over time and restoring vasomotor tone and normal coronary physiology. The first of these devices to receive CE-approval was the ABSORB (Abbot Vascular, Santa Clara, California, USA) BVS. Its technology relies on a polylactic acid polymer that serves as scaffold platform. It is coated with the antiproliferative drug everolimus, which is almost entirely eluted during the first 3 months after scaffold placement. Polylactic acid has been used in other

Table 1 Meta-analyses comparing BVS to metallic DES

Meta-analysis	Target lesion revascularization	Acute myocardial infarction	Thrombosis (definite and probable)	Cardiac death
Stone *et al*. [2016] (11)	1.14 (0.73–1.79)	1.45 (1.02–2.07)	2.09 (0.92–4.75)	1.26 (0.33–4.82)
	P=0.56	P=0.04	P=0.08	P=0.74
Cassese *et al*. [2016] (12)	0.97 (0.66–1.43)	1.36 (0.98–1.89)	1.99 (1.0–3.98)	0.95 (0.42–2.00)
	P=0.87	P=0.06	P=0.05	P=0.89
Lipinski *et al*. [2016] (13)	0.77 (0.48–1.25)	2.06 (1.31–3.22)	2.06 (1.07–3.98)	0.81 (0.42–1.58)
	P=0.36	P=0.002	P=0.03	P=0.54

Results are provided as odds or risk ratios with 95% confidence interval. Values >1 reflect increased risk or odds with the use of BVS. BVS, bioresorbable vascular scaffold; DES, drug-eluting stent.

medical specialities for quite a while as it induces minimal inflammation during bioresorption. The degradation of the polymer starts as early as 6 months after implantation, and full bioresorption may be reached after several years. Polylactic acid is transformed via the cycle of Krebs into carbon dioxide and hydrogen.

Putative advantages over conventional DES are early restoration of physiological processes, superior conformability, beneficial edge-vascular response, and suppression of late stent-related complications (i.e., in-stent restenosis and stent thrombosis).

From excitement to uncertainty

The initial reports from single-arm studies in highly selected patients with simple coronary lesions were very reassuring (4). However, an increasing body of evidence from "real-life" registries reported concerning rates of stent thrombosis as high as 3% at 1 year (5-7). Although several randomised-controlled trials have shown equivalent safety and efficiency outcomes at mid-term between BVS and other newer generation DES (8-10), all were of relatively small size and underpowered to assess differences in clinically relevant but rare events such stent thrombosis. To date, 3 meta-analyses have assessed the performance of the device compared to metallic DES (*Table 1*). There seems to be a definite trend towards higher rates of myocardial infarction and device thrombosis with the use of BVS.

There are several limitations to the unrestricted use of BVS that may explain these observations. First, accurate sizing is necessary when using the device in order to achieve optimal strut apposition (14). Choosing too small a scaffold diameter results in the need for overstretch dilation. Overstretching the BVS is limited to <1.0 mm above the nominal scaffold diameter. As the largest BVS is 3.5 mm and the maximal post-expansion recommended is 0.5 mm over the nominal diameter, major bifurcations and large vessels (≥4 mm) need best be avoided, including the left main coronary artery. There have been reports of polymer fracture after post-dilatation, triggered by overstretching of the device (15). Furthermore, local overexpansion might induce edge dissection. On the other hand, the use of an inappropriately large BVS results in oversizing and underexpansion, which has been linked to scaffold thrombosis (16). The use of the device in small vessels, particularly in vessels <2.25 mm, may augment the footprint of the device, i.e., the % of the vascular circumference occupied by the relatively thick BVS struts (150 μm) (17). The performance of the device is poor in small vessels and a high footprint has been identified as a predictor for scaffold thrombosis (7).

Secondly, the polymer platform is not as strong and has less radial strength than metallic stents (18), which is an issue in highly calcific lesions. As bioresorption progresses, radial strength further declines harbouring the risk for scaffold collapse.

The duration of dual antiplatelet therapy (DAPT) after BVS is an unresolved, important issue. Extended and efficient DAPT is indeed indicated. DAPT interruption results in high rates of scaffold thrombosis. In the acute phase after BVS placement, inflammation and the formation of micro-thrombi can be observed by histopathological examination (19). As time advances, struts are covered—a phenomenon, which can be visualised by optical coherence tomography (OCT) and is referred to as 'capping'. In metallic stents this 'capping' represents vascular healing and the visualized tissue is mainly composed of neointima. It might be that 'capping' of BVS-struts does not represent

Table 2 Reported adverse events in patients presenting with ACS/STEMI treated by BVS

First author and year of publication	Subset	No. of STEMI patients	Comparator	Timing of primary end point/mean follow-up	Device-related adverse events (%)	Patient-related adverse events (%)	Definite scaffold thrombosis (%)
Single arm or unadjusted studies							
Kajiya *et al*. [2013] (24)	STEMI	11	None	53.0±45.9 days	9.1	9.1	0.0
Wiebe *et al*. [2014] (25)	STEMI	25	None	132.7±68.7 days	4.2	4.2	0.0
Diletti *et al*. [2014] (26)	STEMI	49	XIENCE	30 days	0.0	2.6	0.0
Kočka *et al*. [2014] (27)	STEMI	40	DES and BMS	n/a	2.5	2.5	2.5
Dudek *et al*. [2014] (28)	ACS	16	None	1 year	4.0	n/a	1.0
Gori *et al*. [2015] (29)	ACS	51	None	1 year	n/a	13.5	2.3
RCT or PS-matched							
Brugaletta *et al*. [2015] (30)	STEMI	290	XIENCE/BMS	1 year	4.1	n/a	1.7
Sabaté *et al*. [2016] (31)	STEMI	95	XIENCE	6 months	1.1	1.1	1.1

n/a, unavailable; ACS, acute coronary syndrome; BMS, bare metal stent; DES, drug-eluting stent; PS, propensity score; RCT, randomized controlled trials; STEMI, ST-elevation myocardial infarction; BVS, bioresorbable vascular scaffold.

vascular healing but rather a correlate of thrombin apposition. The micro-thrombi visualized in the acute phase eventually grow and evolve into chronic organized thrombi visible on OCT imaging and undistinguishable from neointima. This mechanism possibly explains the deleterious effects of insufficient DAPT prescription, whether in efficacy or in duration.

The rate of thombosis has also been higher for BVS-treated ostial lesions compared to metallic stents where the abrasion of the catheter is thought to provoke more BVS strut distorsion (20). Another concern is the risk of side-branch occlusion, again, due to the bulky device with a higher scaffold to artery ratio (21). Interestingly, when the above issues are known and anticipated, a dedicated protocol for BVS implantation seems to be efficient in reducing the risk of thrombosis (7). Ultimately, and according to evidence gathered in the late 1960s by Charles Dotter, it is no surprise that contrary to the initial belief, BVS are not devoid of device thrombosis (22).

It is likely that, much like first-generation DES, the technical and bio-chemical limitations of first-generation BVS will be overcome. A new treatment standard for coronary artery disease (CAD) could be set if the industry manages to increase stretchability while creating stronger yet thinner backbones with less biodegradation-related inflammation. Several BVS devices are currently being tested clinically and many trials are ongoing, some of which will include patients with acute coronary syndrome (ACS) (4).

BVS in ST-elevated myocardial infarction

Percutaneous coronary intervention with a reperfusion strategy and stenting are all class I recommendations for the treatment of ST-elevation myocardial infarction (STEMI) (23). There is a of course a strong incentive to demonstrate clinical efficiency and safety of BVS in those who have the strongest indication for percutaneous coronary intervention.

And although BVS may have some limitations, their use in STEMI patients is particularly appealing. The lesions are indeed more often focal and less calcified. Moreover, patients tend to be younger than NSTEMI and other CAD-patients, and the advantages of BVS, such as a restoration of vasomotion or late lumen enlargement would be of greatest benefit on the long-term. However, STEMI-patients are also a high-risk patient subset, which present with higher rates of adverse events than patients with stable CAD.

The first reports of BVS-treated STEMI patients

The first reports of short to mid-term clinical outcome in BVS-treated STEMI patients were rather encouraging. However, the data stemmed from single-arm or unadjusted comparative studies (*Table 2*). Device related adverse events as defined by the academic research consortium ranged

from 0% to 9.1% in the 192 reported patients.

The BVS-EXAMINATION Study

Brugaletta *et al*. made an important contribution to our understanding of the application of BVS in STEMI patients by reporting the outcomes of 290 consecutive patients treated at 6 institutions across the globe (30). The study was published in the January issue of the JACC Cardiovascular Interventions in 2015. The BVS-treated patients were compared to 290 propensity score (PS) matched everolimus-eluting stents (EES) and 290 PS matched BMS treated patients enrolled in the EXAMINATION Trial. The investigators assessed the occurrence of device-oriented adverse events, as well as stent or scaffold thrombosis at 1 month and 1 year. There were no significant differences in individual end points but they observed a numerically higher rate of early definite scaffold/stent thrombosis in the BVS group.

The information provided on short and mid-term outcome in BVS treated STEMI patients is of utmost clinical relevance and raises the question whether the unrestricted use of the device in a subgroup with an increased baseline risk for stent thrombosis is reasonable. Indeed, owing to the novelty of the technique and the distinct physical properties of the device, treatment of STEMI patients may be accompanied by unforeseen complications. Even though not statistically significant, the numerically higher rate of early stent thrombosis is concerning and likely the result of an implantation technique that was not tailored to the decreased radial strength, the increased acute recoil, and the need for optimal lesion preparation to avoid mechanistic complications such as underexpansion or incomplete stent apposition. Relevant information on target lesion revascularization and target-vessel related MI rates suggested an acceptable hazard with BVS. However, the patient sample was relatively small and the data was observational in nature with residual differences in baseline characteristics between treatment arms.

The ABSORB-stemi TROFI II trial

Sabaté *et al*. made another important contribution by publishing the primary outcome of the multicentric, randomised, single-blinded TROFI II trial (31). They reported BVS to be non-inferior to EES in STEMI patients at six months for arterial healing based on a multimodal imaging score. Clinical outcomes were not different between the treatment groups. Clinical follow-up is still on-going and will explore the mid- and long-term outcomes. It is important to point out, however, that patients with cardiogenic shock and significant vessel tortuosity or calcifications were not included in this trial.

Conclusions

Is BVS better than the other DES in our cathlabs? No, and the evidence shows that it is, at best and for specific patients and lesions, non-inferior with a trend toward being inferior. The evidence for BVS implantation in STEMI patients is very limited. While it appears to be safe in the hands of experienced operators who are well aware of the technical limitations, the ABSORB BVS does show a trend towards a higher rate of myocardial infarction compared to other metallic DES. The major safety concerns from the initial European experience have led to more careful lesion selection and preparation thus reducing the risk of stent thrombosis. Is ABSORB BVS a step toward a paradigm shift? Maybe.

There is no convincing evidence that the hypothetical advantages of BVS are or will be of any benefit to patients. More definitive evidence will only be available in about 5 to 7 years. Until then, the "optimistic" will continue to use it and the "sceptic" will wait. In March 2016, the advisory panel of the Food and Drug Administration has given near-unanimous support for approval of the ABSORB BVS, while its use has drastically decreased in Europe. One can only hope that the fruit will continue to ripen, and for our patients to benefit from further technological enhancements.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Overlapping meta-analyses of bioresorbable vascular scaffolds versus everolimus-eluting stents: bringing clarity or confusion?

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The ABSORB (Abbot Vascular, Santa Clara, CA, USA) bioresorbable vascular scaffold (BVS) has been conceived to address some residual shortcomings of metallic drug-eluting stents (DES), including very late thrombosis and loss of vasomotion due to permanent caging of the coronary vessel. In Europe, BVSs were approved in 2011 mainly based on data from the ABSORB study, a two-stage single-arm investigation with multimodal imaging assessment including a total of 131 patients (1,2). To further investigate the device in a broader population and support European commercialization and reimbursement activities, the manufacturer initiated ABSORB II, a randomized controlled trial of 501 patients, where BVSs were tested on two surrogate co-primary endpoints (i.e., vasomotion and late lumen loss) against the cobalt-chromium XIENCE (Abbott Vascular, Santa Clara, CA, USA) everolimus-eluting stent (EES) (3). Interim 1-year results of ABSORB II have been published in 2015, showing no significant differences between BVSs and EESs, but these findings are at best hypothesis generating, due to the low statistical power of the study for clinical endpoints (4).

In the United States, China and Japan, other randomized comparisons versus EESs have been conducted to support approval by local regulatory authorities. The ABSORB III trial (N=2,008) was designed as a non-inferiority study, with a margin of 4.5% for the putative risk difference between BVSs and EESs in 1-year target lesion failure (TLF, a composite of cardiac death, target vessel myocardial infarction and ischemia-driven target-lesion revascularization) (5). This margin of non-inferiority was selected based on Food and Drug Administration (FDA) recommendations, in that it represents the 50% of the lower boundary of the 90% confidence interval of the treatment effect for EESs as compared with bare metal stents. ABSORB 3 showed a risk difference in 1-year TLF of 1.7% (7.8% in the BVS group and 6.1% in the EES group), with the 95% upper bound of the confidence interval corresponding to 3.9%, a figure below the pre-specified non-inferiority margin (6). ABSORB China was also designed under a non-inferiority assumption, but the trial was powered only for a 0.15 mm margin in the difference of 1-year in-segment late lumen loss. This resulted into a smaller sample size than ABSORB 3 (N=480), but non-usable conclusions at the clinical level. The difference in 1-year in-segment late lumen loss was 0.06 mm (0.19±0.38 mm in the BVS group and 0.13±0.38 mm in the EES group), and the upper bound of the confidence interval was just 1 mm below the non-inferiority threshold (7). ABSORB Japan used a wide non-inferiority margin for the difference in 1-year TLF (8.6%), based on an agreement with the Japanese Pharmaceutical and Medical Device Agency, which resulted in a small sample size (N=400). The trial showed a 0.4% risk difference in 1-year TLF between BVSs and EESs (4.2% in the BVS group and 3.8% in the EES group), and the upper bound of the confidence interval was 4.0% (8). The sample size of Absorb Japan was sufficient to power a test of non-inferiority for late lumen loss at 13 months, using a 0.20 mm non-inferiority margin, which ultimately

showed a difference of 0.01 mm (0.13±0.30 mm in the BVS group and 0.12±0.32 mm in the EES group), with a 0.06 mm upper bound of the 95% confidence interval.

The 1-year results of the 4 ABSORB randomized trials invoke the idea of BVSs being non-inferior to EESs. Non-inferiority designs are used and perhaps abused in contemporary trials of new coronary devices, which unfortunately does not contribute to progress significantly the field of interventional cardiology (9). In the case of BVSs, one may advocate that establishing non-inferiority at 1 year is enough for a device whose benefits over metallic DESs are expected to accrue after bioresorption. The ABSORB IV trial (NCT02173379), which is currently testing the hypothesis that BVSs are noninferior (with reflex to superiority) to EESs in the landmark analysis of TLF between 1 and 5 years, will contribute to define the role of BVSs in modern practice. In the meantime, taken separately, all the ABSORB trials have limitations in the strength of their clinical conclusions. Indeed, ABSORB II and ABSORB China were not statistically powered for clinical outcomes, ABSORB Japan used a wide non-inferiority margin and had a lower than anticipated event rate, and ABSORB III was not designed to address individual endpoints or to exclude small differences in TLF.

When independent trials are not sufficient to address the effect of an intervention, meta-analyses increase the statistical power of treatment comparisons beyond that of individual studies, with the ultimate goal of informing clinical practice and guiding healthcare decisions. But what happens if a plethora of meta-analyses of BVSs *vs*. EESs become simultaneously available on the same topic and display mixed results? *Table 1* summarizes the characteristics and results of 5 meta-analyses of BVSs versus EESs published in 2016. Stone *et al.* pooled 3,389 patients from the 4 ABSORB trials on a patient-level basis (10). Cassese *et al.* (12) and Bangalore *et al.* (13). combined study-level data of 3,738 patients from the ABSORB trials and two additional small investigator-driven randomized studies of BVSs versus EESs named EVERBIO 2 and TROFI 2 (15,16). Lipinski *et al.* also combined study-level data but included only two randomized studies (ABSORB II and TROFI 2) and a number of non-randomized comparisons (11). Finally, Kang *et al.* performed a network meta-analysis of 147 stent and scaffold trials, where the comparison of BVSs and EESs represents just one node of the framework, and the results reflect the combination of direct and indirect evidence estimates (14). When appraising if consistency exists in the results of overlapping meta-analyses of BVSs, a first major conundrum is that these results have not been uniformly reported for all the potential endpoints of interest. Also, the available follow up was shorter in the meta-analysis of Lipinski *et al.* (11), and in some cases there was a variation in endpoint definitions (i.e., myocardial infarction as opposed to target-vessel myocardial infarction; target lesion revascularization as opposed to ischemia-driven target lesion revascularization). The device-oriented clinical endpoint of TLF was appraised by only two meta-analyses (10,12) and shown to be similar between BVSs and EESs. Similarly, none of the meta-analyses displayed a difference in all-cause and cardiac death. Myocardial infarction was significantly increased only in the meta-analysis from Lipinski *et al.* (11), but trended towards statistical significance in the other four studies. Target-lesion and target-vessel revascularization did not differ between BVSs and EESs. Finally, a consistent finding across all meta-analyses was the approximately 2-fold increase in definite or probable device thrombosis with BVSs, which was significant in three out of five studies (11,12,14). Overlapping meta-analyses can result in a certain degree of ambiguity when they come to discordant conclusions (17). Indeed, the conclusions of the abstract of these meta-analyses also sound different, ranging between the positive outlook of Stone *et al.* ("*BVS did not lead to different rates of composite patient-oriented and device-oriented adverse events at 1-year follow-up compared with cobalt-chromium EESs*") (10), and the negative viewpoint of Lipinski *et al.* ("*BVS had increased definite/probable device thrombosis and myocardial infarction during follow-up compared with DES*") (11).

How can we reconcile all the disparate results and conclusions of the five meta-analyses of BVSs *vs*. EESs in view of their non-uniform eligibility criteria, and overall differences in target population analyzed, follow up and endpoint definitions? One way is to realize individual strengths and weaknesses of these studies. Patient-level meta-analyses allow better alignment of definitions and follow-up, and enable ancillary tests that would be unfeasible at the study-level. These latter include generating time-to-event curves, identifying independent prognostic factors, and testing for interaction effects. As such, the meta-analysis from Stone *et al.* provides the reader with unique insights—for example, over the distribution of TLF events at follow-up (i.e., with a steep rise in the first month, followed by continuous increase up to 12 months) and the detrimental impact of baseline conditions (i.e., diabetes, small vessels, and/or complex angiographic features) (10). Study-level meta-analyses such as those by Cassese *et al.* and Bangalore

Table 1 Overlapping meta-analyses of BVS *vs.* EES

Study characteristic	Stone *et al.* (10)	Lipinski *et al.* (11)	Cassese *et al.* (12)	Bangalore *et al.* (13)	Kang *et al.* (14)
Publication date	2016	2016	2016	2016	2016
Journal	*Lancet*	*JACC CI*	*Lancet*	*Int J Cardiol*	*JACC CI*
Type	Patient-level	Study level	Study level	Study level	Bayesian
Search date	October 2015	July 2015	October 2015	November 2015	December 2015
Screened studies	NA	449	171	NA	2,516
Pooled patients	3,389	4,098	3,738	3,738	126,526
Model	Fixed-effects	Random-effects	Fixed-effects	Fixed-effects	Random-effects
Summary measure	RR (95% CI)	OR (95% CI)	OR (95% CI)	RR (95% CI)	OR (95% CrI)
Studies included	4 RCTs	2 RCTs, 7 OSs	6 RCTs	6 RCTs	147 RCTs
Follow up	1 year	6 months (mean)	1 year (median)	13 months (mean)	1 year
Target lesion failure	1.22 (0.91–1.64)	NA	1.20 (0.90–1.60)	NA	NA
All-cause death	1.12 (0.47–2.69)	0.40 (0.15–1.06)	0.95 (0.45–2.00)	1.11 (0.53–2.33)	1.13 (0.52–2.73)
Cardiac death	1.26 (0.33–4.82)	0.81 (0.42–1.58)	NA	1.39 (0.43–4.43)	1.39 (0.43–5.46)
Myocardial infarction	1.34 (0.97–1.85)	2.06 (1.31–2.22)	1.36 (0.98–1.89)	1.35 (0.98–1.86)	1.44 (0.99–2.13)
Target vessel myocardial infarction	1.45 (1.02–2.07)	NA	NA	NA	NA
All revascularization	1.02 (0.80–1.30)	NA	NA	NA	NA
Target-lesion revascularization	NA	0.77 (0.48–1.25)	0.97 (0.66–1.43)	1.06 (0.73–1.54)	1.08 (0.63–1.84)
Ischemia-driven	1.14 (0.73-1.79)	NA	1.13 (0.74-1.71)	NA	NA
Target-vessel revascularization	NA	NA	NA	1.00 (0.74–1.35)	1.03 (0.71–1.49)
Ischemia-driven	1.14 (0.80–1.62)	NA	NA	NA	NA
Definite or probable device thrombosis	2.09 (0.92–4.75)	2.06 (1.07–3.98)	1.99 (1.00–3.98)	2.11 (0.99–4.47)	2.28 (1.07–6.29)
Early	1.76 (0.72–4.34)	2.02 (0.69–5.93)	NA	NA	1.98 (0.55–8.43)
Acute	NA	NA	0.36 (0.07–1.71)	NA	NA
Subacute	NA	NA	3.11 (1.24–7.82)	NA	NA
Late	4.10 (0.52–32.56)	NA	NA	NA	4.09 (0.51–82.46)
Definite device thrombosis	2.06 (0.85–5.03)	1.91 (0.82–4.46)	1.98 (0.94–4.16)	2.15 (0.94–4.89)	2.49 (0.90–8.20)
Probable device thrombosis	2.28 (0.28–18.51)	NA	NA	NA	NA

Effect sizes are displayed for the comparison of BVSs *vs.* EESs. BVS, bioresorbable vascular scaffold; EES, everolimus-eluting stent; CI, confidence interval; CrI, credible interval; NA, not available; OR, odds ratio; OS, observational studies; RCTs, randomized clinical trials.

et al. are more flexible in that they can incorporate data pertaining to trials whose full datasets have not been made available (i.e., EVERBIO 2 and TROFI 2). Notably, only Cassese *et al.* reported on subacute thrombosis, which was significantly increased in the BVS arm (12). Bangalore *et al.* used 5 different pooling models and complemented their study with a trial sequential analysis indicating the lack of a strong evidence for a hypothetical 30% increase in device thrombosis with BVSs when compared with EESs, thus concluding that the current accumulated information size is underpowered to make any firm conclusions (13). Lipinski *et al.* included more patients than did the other meta-analyses, extending their inclusion criteria to single-arm and case-control observational studies reflecting less selected populations than in the trial setting (11). This also allowed the authors to provide summary estimates for a wide range of clinical outcomes, and to run meta-regressions on the impact of variables such as prevalence of acute coronary syndromes in the study population and date of study initiation. Finally, the network meta-analysis approach chosen by Kang *et al.* permitted to incorporate the direct evidence from the available trials of BVSs *vs.* EES and the indirect evidence from bare metal stents and DESs trials using common comparators. This enabled a consolidated ranking of contemporary coronary devices for the outcome of 1-year definite or probable thrombosis, with BVSs positioned at the lower end of the safety spectrum, at the same level of paclitaxel-eluting stents and bare metal stents (14).

In conclusion, which of the meta-analyses published so far is the most applicable to the important clinical question of the efficacy and safety of BVSs in current practice, and which one is the most methodologically sound? At this early stage of data collection (i.e., with only ≤1-year data available in most BVSs studies), and because judgment inevitably involves assigning subjective weights to pros and cons of each meta-analytical approach, the answer may be arbitrary. The reader may personally refer to published methods and checklists to map the quality of the 5 meta-analyses described in this article, and come to a personal conclusion (17).

An FDA panel has recently reached a consensus on the fact that BVS is an effective treatment and most panelists felt that the benefits of scaffolds outweigh the risks (18). Residual skeptics and purists will contend that even meta-analyses of BVSs *vs.* EESs have not reached the sufficient information size to address important residual safety and efficacy questions, particularly at long-term. Indeed, these studies cannot rule out (but also cannot conclusively demonstrate) that BVSs increase thrombosis and myocardial infarction compared with best-in-class DESs at one year, but the similar risk of TLF is reassuring and supports the use of BVSs in current practice for selected patients and lesions.

To reflect the evolving knowledge in the field, BVSs meta-analyses will continue to be regularly updated as new studies become available. When preparing and submitting a new meta-analysis, the authors should take responsibility for trying to advance meaningfully the field and fairly evaluate the added value of having a new publication on the same topic. Similarly, peer reviewers and editorial boards should carefully evaluate the incremental qualities of new meta-analyses under review, to prevent the proliferation of overlapping meta-analyses bringing more confusion than clarity.

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Footnote

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Bioresorbable vascular scaffolds—what does the future bring?

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Abstract: Bioresorbable vascular scaffolds (BVS) have emerged as an interesting alternative since the presence of the prosthesis in the coronary artery is transient. This technology enables to restore the normal vasomotor tone and allows positive remodeling, simultaneously reducing the trigger for persistent inflammation and facilitating further interventions by percutaneous or surgical means. Absorb BVS® is the first generation everolimus-eluting poly-L-lactide (PLLA) bioresorbable scaffold. In recent meta-analyses Absorb BVS® was definitely proved to be safe and effective device in the treatment of symptomatic coronary artery disease. This was recently confirmed by FDA advisory panel of experts who recommended approval of the device based on an analysis of its risks and rewards. Nevertheless, still there are some concerns regarding stent thrombosis, and the real vessel functionality restoration at long-term observation. Worth mentioning is the fact that apart from stable coronary disease Absorb BVS® is used successfully in a series of off-label clinical settings such as acute coronary syndromes including STEMI, in-stent restenosis, coronary bifurcations, left main stenting or chronic total occlusions. Moreover, new bioresorbable scaffolds are under development with DEsolve® and DREAM 2G®, which are the most advanced.

Keywords: Absorb; DEsolve; DREAM 2G; hybrid approach

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Introduction

Drug-eluting stents (DES) have significantly improved long-term outcomes of percutaneous coronary interventions (PCI) by decreasing the excessive growth of neointima. However, the permanent presence of the metallic platform and the durable polymer might impair the natural healing process of the coronary vessel wall, leading to the prolonged inflammatory response and untoward clinical outcomes (1,2).

Recently, PCI with bioresorbable vascular scaffolds (BVS) have emerged as an interesting alternative since the presence of the prosthesis in the coronary artery is transient. This technology enables to restore the normal vasomotor tone and allows positive remodeling, simultaneously reducing the trigger for persistent inflammation and facilitating further interventions by percutaneous or surgical means. Also, in theory it should offer reduced or even abolished late/very late stent thrombosis risk (3).

The balloon-expandable Absorb BVS® (Abbott Vascular) consists of a poly-L-lactide (PLLA) backbone (strut thickness 150 μm), the anti-proliferative drug everolimus at the concentration of 100 μg/cm^2 (Novartis Pharmaceuticals Corporation) and poly-D, L-lactide polymer in a 1:1 ratio (PDLLA). Both PLLA and PDLLA are fully bioresorbable. PDLLA is thought to be totally resorbed in nine months and PLLA in approximately 24–36 months. A lactic acid is the final product of both

PLLA and PDLLA degradation (4).

Absorb BVS as good as Xience?

Recently, in the *Lancet* journal, Stone *et al.* published a paper comparing Abosrb BVS® and Xience® (cobalt-chromium everolimus-eluting stent) (5). It was a meta-analysis of four randomized trials (ABSORB II, ABSORB Japan, ABSORB China, and ABSORB III) in which patients with stable coronary artery disease or a stabilized acute coronary syndrome were enrolled. This meta-analysis of 3,389 randomly assigned patients provided greater power to analyze effectiveness and safety profile of Absorb BVS® versus Xience® than each individual study alone. The analysis yielded similar results for Absorb BVS® and for Xience® regarding the patient-oriented composite endpoint (all-cause mortality, all myocardial infarction, or all revascularization) as well as the device-oriented composite endpoint (cardiac mortality, target vessel-related myocardial infarction, or ischemia-driven target lesion revascularization) at 1 year. Although Absorb BVS® is the first-generation BVS technology and despite the fact that in these trials Absorb BVS® was compared with one of the lowest rate of stent thrombosis devices, the accumulation of available data supported the safety and effectiveness of Absorb BVS® at 12 months in the treatment of patients with stable coronary artery disease or stabilized acute coronary syndromes.

However, one should also mention some limitations of this paper. In three from four analyzed studies (Absorb Japan, Absorb China, Abosrb III) the device overlap was forbidden unless bailout stenting was required. Moreover, the treated lesion length was rather short (mean value: 13 mm). Also in the group of Absorb BVS® significantly more frequently more potent new generation P2Y12 inhibitors (ticagrelor, prasugrel) were used (24% *vs.* 21%, P=0.047). And finally, the routine angiography was performed very diversely (not at all in Absorb III or after 3 years in Absorb II) what also might influence on the target lesion revascularization/target vessel revascularization rates.

On the top of it, the procedure success rate was worse in the Absorb BVS® comparing with Xience® (95.6% *vs.* 99.4%, P<0.0001). And despite more aggressive optimization in the Absorb BVS® group or maybe because of it (post-dilatation 66.2% *vs.* 55.3%, P<0.0001), target lesion failure tended to be higher with Absorb BVS® comparing with Xience® within 30 days (target vessel related myocardial infarction 5.1% *vs.* 3.3%, P=0.04). Also, worth pointing out is the fact that authors stress many times in the paper very late thrombosis issue, but they presented only one year results. Moreover, in the presented data there was a trend for higher thrombosis rates in the Absorb BVS® group (definite/probable stent thrombosis 1.3% *vs.* 0.6%, P=0.08). Also, other recently published meta-analyses confirm similar target revascularization rates between Absorb BVS® and Xience®, but simultaneously they stress the increased risk of stent thrombosis as well (6-8).

And finally, the aim of developing BVS was to ensure vascular restoration therapy at long-term observation. However, although Absorb BVS® is available on the market for several years up to now there are published clinical trials showing only the vessel status after complete Absorb BVS® decomposition, and no vessel reactivity assessment (e.g., vessel lumen response to acetylcholine infusion) (4). However, there are two *in vivo* studies showing promising results in mid- and long-term follow-up (9,10). But today it already looks that stent struts should be thinner and probably the most advanced coronary lesions (calcified, severely fibrotic) do not prognosticate for regain of vessel function.

Hybrid approach—does it make sense?

Absorb BVS® deployment might facilitate to avoid performing the so-called "full metal jacket". As such, the hybrid use of BVS and classical DES might be an interesting approach. This strategy can be applied to reduce the costs of the PCI procedure as well as the length of a metallic scaffold. Moreover, BVS use only in long lesions with significantly calcified segments may not be reasonable if lesion preparation is inadequate or significant residual stenosis remains after balloon pre-dilatation. One should be aware that there are crucial differences in the sequence of stent (DES)—scaffold (BVS) deployment (11). In the hybrid DES-BVS technique, BVS lays on top of the metallic scaffold at the overlapped segment. If the BVS was positioned first proximally and then overlapped distally with a DES, the thinner metallic struts lay on top of the thicker BVS scaffold at the overlapped segment. Once the BVS scaffold under the metallic strut resorbs, it leaves an overhanging metallic strut segment that is not apposed to the vessel wall. The longer the overlapped segment, the longer the potentially malapposed stent segment is. Also, the expansive remodelling property of the BVS may contribute to the malapposition at the DES-BVS overlap junction. Therefore overlapping DES-BVS during PCI

must be done adequately to minimize the potential risk of in-stent thrombosis (12). This approach was recently proved safe and effective (13).

Absorb BVS in various clinical settings

Apart from stable coronary disease Absorb BVS® is used successfully in a series of off-label clinical settings such as acute coronary syndromes including STEMI (14-16), in-stent restenosis (17), coronary bifurcations (18), left main stenting (19) or chronic total occlusions (20). However, larger studies with long-term follow-up are needed to adequately address the safety and efficacy of Absorb BVS® use in such settings.

Future directions

Absorb BVS® is not the only biodegradable scaffold under development. As always with new technologies there are many issues in the prototype device introduced into the market that can be improved. The Absorb BVS® strut thickness is deemed to be potentially accountable for the increased adverse event rate. The new scaffolds being under development, as the DEsolve®, the MeRes100® or the Biolute® have strut thickness of 100, 100 and 108 μm, respectively (21). This improvement if successful allow for obtaining the proper radial strength with simultaneous decrease in the crossing profile. Additionally, thinner struts might minimize coronary blood flow perturbations and strut protrusion into the vessel lumen when overlapping as well as this can lead to the decreased thrombogenicity of such devices. Analogous technical improvement can be observed in the Mirage BVS® (a microfiber scaffold with streamlined strut geometry—round struts) that is supposed to decrease blood flow separation and ensure high shear stress with subsequent reduced platelet activation (21).

The another key issue is to establish the ideal right time for resorption bearing in mind that radial strength reduction cannot be too rapid. Shortening the resorption process might reduce the risk of stent thrombosis but also might account for the increased risk of vessel/plaque recoil. In this respect, promising results were reported with the DEsolve scaffold. Its biodegradation and bioresorption take place in one and two years, respectively (22).

Also, the possibility to post-dilatate the scaffold (preferably overexpand) without fracture poses another important issue. In this regard, the Fantom® (a desaminotyrosine-derived polycarbonate scaffold), the DEsolve® and the Amaranth Fortitude® (both PLLA-based polymer scaffolds) showed greater resistance to overexpansion. Moreover, magnesium-based metallic bioresorbable scaffolds were developed in order to ensure mechanical characteristics of a classic DES. After the initial discouraging results, the DREAMS 1G® (paclitaxel-eluting) and the DREAMS 2G® (sirolimus-eluting) scaffolds yielded promising results, as in BIOSOLVE II study (23,24).

Conclusions

Absorb BVS® was definitely proved to be safe and effective device in the treatment of symptomatic coronary artery disease. This was recently confirmed by FDA advisory panel of experts who recommended approval of the device based on the analysis of its risks and rewards. Also, Abbott Vascular Company said that 5-year superiority data will be presented in 2020, from its 5-year Absorb IV trial. Nevertheless, still there are some concerns regarding stent thrombosis, and the real vessel functionality restoration at long-term observation.

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Footnote

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Bioresorbable scaffold—the holy grail of percutaneous coronary intervention: fact or myth?

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When Grüntzig preformed the first balloon angioplasty in 1977 (1), it revolutionized the treatment of obstructive coronary artery disease (CAD) and provided an alternative to coronary bypass surgery. While a reasonable procedural and clinical outcome was achievable with balloon angioplasty alone, sustained arterial patency was ultimately undermined by elastic recoil, acute secondary closure and constrictive remodeling (2). The second technological leap in percutaneous coronary intervention (PCI) occurred with the advent of bare metal stents (BMS), which promised to overcome these issues by providing a mechanical scaffold within the coronary arteries (3). Longitudinal studies however have since demonstrated suboptimal long term outcomes with the use of BMS due primarily to the high incidence of in-stent restenosis (ISR) (4). The development of drug eluting stent (DES) represented the third paradigm shift in the field of interventional cardiology, whereby the coating of BMS with anti-proliferative agents resulted in a significant reduction in the incidence of ISR and improvement in patient outcome (5). The benefit was further enhanced by new stent designs and evolution in polymer technology (6), with the second generation DES now widely accepted as the percutaneous treatment of choice for obstructive CAD. The persistence of stent struts within the coronary artery remains a significant pitfall however, with ongoing issues relating to the risk of stent thrombosis (ST) (7), neoatherosclerosis (8), loss of vasomotion (9) and preclusion from future bypass surgery.

The development of bioresorbable scaffold (BRS) marks the beginning of a fourth revolution in PCI, providing an alternative stent platform that has the ability to deliver drugs locally, provide initial mechanical support, and degrades over time once its desired effect is achieved. Many such devices are currently under investigation, while two have received Conformité Européenne (CE)-mark approval for use in clinical practice. Of the two, the ABSORB bioresorbable vascular scaffold (BVS; Abbot Vascular, Santa Clara, CA, USA) was the first BRS to undergo comprehensive clinical evaluation and is now available for clinical use worldwide. ABSORB BVS is an everolimus-eluting BRS composed of poly-L-lactic acid (PLLA) and poly-DL-lactic acid (PDLLA). The polymeric BRS maintains its radial strength for 6 months after implantation and auto-hydrolyzes into carbon dioxide and water over a space of 2–4 years (10).

ABSORB BVS has been benchmarked against the cobalt-chromium based everolimus eluting metallic stent (CoCr-EES; Abbott Vascular, Santa Clara, CA, USA) in several clinical trials, with the latter being considered as the current gold standard in DES technology in terms of its efficacy and safety. Each individual trial however was relatively under-powered to detect small differences in low frequency events such as ST and death, while subgroup analyses were similarly precluded. With this in mind, Stone *et al.* performed a patient-level, pooled meta-analysis of four completed randomized trials of ABSORB BVS, and leveraged the improved statistical power to characterize the safety and efficacy of the BVS as compared with the

CoCr-EES (11). The methodology was robust, and while the study was funded by the BVS manufacturer, the author had jurisdiction over the final report. Overall, 3,389 stable and stabilized patients with acute coronary syndrome were included in the analysis. In effect, the study demonstrated equipoise between the two devices in terms of the patient- and device-oriented composite endpoints at 12 months, with no statistical differences in the relative rates of all-cause and cardiac mortality, all myocardial infarction (MI), ischemia-driven target lesion revascularization, and all revascularization. The authors concluded by stating that there was a non-significantly different rate of overall outcome at 1-year follow-up between the two devices.

While this represents a valuable contribution to the evidence base of ABSORB BVS, certain caveats need to be carefully considered. Specifically, both device (95.6% *vs.* 99.4%, P<0.0001) and procedural (94.9% *vs.* 97.0%, P=0.003) successes rates were significantly lower in the BVS arm. Secondly, numerically more early target lesion failure was observed with BVS (4.1% *vs.* 2.6%, P=0.051), likely reflecting early mechanical issues following device implantation. Lastly, there is a numerical trend towards higher incidence of definite/probable ST (1.3% *vs.* 0.6%) and MI (5.7% *vs.* 4.0%) at 12 months in the BVS arm, which echo observations made previously by other large clinical registries (12).

It is important to note that current data pertains exclusively to first generation ABSORB BVS, which has a relatively thick strut (157 microns)—a design feature considered necessary to maintain its radial strength. The crimping process further increases its crossing profile (1.4 mm), which is considerably larger than a contemporary metallic stent (1.0 mm) (13). This limits the deliverability, trackability and pushability of these devices and may explain the differences observed in procedure duration, procedural as well as device success rate, and a numerical increase in the incidence of ST and MI at 12 months. The outcome is further compounded by the variation in operators' experience, with optimal scaffold implantation potentially undermined by inconsistencies in device sizing, lesion preparation, routine high pressure post-dilatation and guidance with intra-coronary imaging. Only 66.2% of patients in the ABSORB arm had post-dilation, while 23.9% underwent intracoronary imaging. Indeed, the importance of proper implantation technique including pre-implantation plaque modification, routine high pressure scaffold post-dilatation with non-compliant balloons, and liberal use of intracoronary imaging such as optic coherent tomography (OCT) to evaluate scaffold apposition and coverage have since been appreciated and advocated.

Furthermore, the manufacturer's restriction on scaffold size has not been universally observed, with a significant proportion of BVS being implanted in vessels with a reference diameter of <2.5 mm. In ABSORB III, if vessels smaller than 2.25 mm were excluded from the analysis, the incidence of ST were in fact equivalent between the two arms (14). Adherence to vessel sizing guidelines may therefore further off-set target lesion failure by reducing the incidence of recurrent MI and ST both at 30 days and 1 year. Notably, while the target vessel related MI was higher in the ABSORB arm, it was due in part to a higher incidence of peri-procedural myocardial infarction (PMI). This may be related to higher degree of residual diameter stenosis and scaffold mal-apposition, though other factors may be at play such as small side-branch occlusion. Importantly however, the incidence of clinically significant PMI as defined by the Society of Cardiac Angiography and Intervention (15) did not vary significantly between the two arms. The clinical relevance of this observation therefore remains unclear.

Another pertinent point to consider relates to the short follow-up in this study. While the outcomes are similar between the two study arms at 12 months, most of the anticipated benefits of BVS are not expected to become apparent until 3–5 years after implantation when the treated arteries are completely "uncaged", leading to restoration of vessel geometry, physiological vasomotion, late luminal gain and late expansive remodeling (16). This is particularly important in younger patients undergoing PCI, with annualized rate of target lesion failure with second generation DES remaining at around 1.8% with no observable plateau (7). Further, studies thus far have focused primarily on relatively uncomplicated lesions and clinical contexts, with deliberate exclusion of patients with heavily calcified vessels, left main diseases, chronic total occlusions, and acute coronary syndromes. In its current form, BVS have several practical limitations including its deliverability that may restrict its use in these scenarios, and penalties such as longer procedural time, need for more aggressive lesion preparation, higher incidence of PMI, and significantly lower procedural success have been observed (17). However, a number of studies focusing on real life application of the BVS technology have now demonstrated its feasibility in a broad range of clinical contexts including calcified and bifurcational lesions, particularly with meticulous implantation techniques (17,18). The long term implications of off-label application of BVS however need to be further

delineated by prospective trials (COMPARE ABSORB, NCT02486068) before its generalized adoption could be encouraged in routine clinical practice.

Several questions remain unanswered by this analysis, such as the interaction between patients' outcome and the choice of P2Y12 antiplatelet therapy as well as their baseline attribute including diabetes. These will require further exploration with long term and adequately powered randomized trials (Absorb IV, NCT02173379). The impact of optimal implantation techniques and improved strut design also needs to be ascertained, incorporating features such as thinner struts, improved expansile capability, and earlier strut degradation, which may improve the outcomes further compared with current iteration of BVS. Finally, a cost-effective analysis needs to be performed to assess the benefit of BVS in a wider population context.

The ability to liberate the coronary vessels from permanent metallic caging is an inherently appealing concept, and the present study has helped push it one step closer to reality by demonstrating equipoise in both the efficacy and safety endpoints between an established gold standard and the ABSORB BVS, notwithstanding the limitations of a first generational device. With ongoing randomized trials still many years away from completion, the results of the current analysis should be treated with respect and embraced with a degree of cautious optimism. It is hoped that further studies will eventually confirm the sustained benefit as well as the versatility of ABSORB BVS, and indeed the technology BRS as a whole, and complete the fourth wave of revolution in the field of interventional cardiology.

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Predictive scores in chronic total occlusions percutaneous recanalization: only fashionable or really useful?

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Introduction

Chronic total occlusions (CTOs) remain one of the last challenges in percutaneous coronary intervention (PCI). During the last decade, following the Japanese pioneers, the interest of interventionalists' community in CTO PCI has dramatically increased leading to an important development in equipment and techniques (1,2), and a growing expertise among dedicated operators, both resulting in increased success rates (3).

CTO PCI attempts are considered to be more costly and cumbersome procedures in comparison with continuous lesions angioplasty; and might be associated with higher incidence of peri-procedural complications (4). Different reports have underlined the importance of patients' selection in CTO PCI (5,6). Indeed, the decision-making process of whom to undergo CTO percutaneous attempt, should pass through a rational analysis, taking into account clinical and anatomical factors and operator's experience (6). In addition, it is well recognized that patients affected by CTOs and successfully revascularized showed better clinical long-term outcome and improved quality of life as compared with those who underwent failed CTO PCI attempt (7,8).

For all these reasons, establishing scores able to strongly predict the success of CTO recanalization and to select appropriate candidates for a percutaneous attempt among CTO patients, and could represent a key issue to achieve optimal immediate and long-term outcome.

Predictive scores in CTO PCI

The Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is an angiographic tool that can quantify the degree of atherosclerosis in the entire coronary arterial tree, including the culprit lesions and is useful to select appropriate candidates for coronary artery bypass graft (CABG) surgery or PCI with drug-eluting stents in patients with left main and/or three-vessel disease (9). Nagashima *et al.* reported lower procedural success of CTO PCI in patients with a high SYNTAX (>22) score than those with a low SYNTAX score (74.7% *vs.* 91.8%, respectively; P<0.0001) (10). Moreover, a SYNTAX score >22 was also an independent predictor of 30-day major adverse cardiac events (odds ratio =4.80, 95% CI: 1.03–22.42) (10). Nonetheless, the use of SYNTAX score is more appropriate for diseased patent coronary arteries than CTOs, particularly when PCI is indicated. Indeed, the weight given to the presence of a CTO in the calculation of the SYNTAX score is such that very few patients with multi-vessel disease and a CTO will qualify for PCI, because a complex left anterior descending (LAD) CTO will almost be sufficient by itself to reach the surgical threshold of 23 (or 33 if the left main is involved). Therefore, specific scores to the setting of CTO lesions have been developed (*Table 1*).

The Japanese Multicenter CTO Registry (J-CTO) score was originally developed by Morino *et al.* (11) to predict the

Table 1 Specific CTO predictive scores

Specific CTO score	CTO lesions (n)	Success (%)	Variables				Primary endpoint
			N	Clinical	Angiographic	CCTA	
J-CTO score, Morino *et al.* (11)	494	88.6	5	Prior attempt (+1)	Heavy calcification (+1) Bending ≥45° (+1) Blunt stump (+1) Occlusion length >20 mm (+1)	–	GW crossing within 30 min
CT-RECTOR score, Opolski *et al.* (12)	240	65.0	6	Prior attempt (+1) Occlusion duration ≥12 months or unknown (+1)	–	Multiple occlusion (+1) Blunt stump (+1) Calcification ≥50% CSA (+1) Bending ≥45° (+1)	GW crossing within 30 min
CL score, Alessandrino *et al.* (13)	1,657	72.5	6	Previous CABG (+1.5) Previous MI (+1)	Severe calcification (+2) CTO length >20 mm (+1.5) Non-LAD CTO (+1) Blunt stump (+1)	–	Successful antegrade first attempt
PROGRESS-CTO score, Christopoulos *et al.*(14)	781	92.9	4	–	Proximal cap ambiguity (+1) Moderate/severe tortuosity (+1) LCx CTO (+1) Absence of "interventional" collaterals (+1)	–	Successful hybrid approach
ORA score, Galassi *et al.* (15)	1,073	91.9	3	Age ≥75 years (+1)	Ostial location (+1) Collateral filling < Rentrop2 (+2)	–	Technical failure by both antegrade and/or retrograde techniques
Liu *et al.* (16)	728	N/A	3	Age ≥75 years (+1) LVEF <40% (+1) Baseline Scr >1.5 mg/dL (+2)	–	–	Contrast induced nephropathy

CTO, chronic total occlusions; CCTA, coronary computed tomography angiography; GW, guidewire; CSA, cross sectional area; MI, myocardial infarction; CABG, coronary artery bypass graft; LAD, left anterior descending; LCx, left circumflex; N/A, not available; LVEF, left ventricular ejection fraction; SCr, serum creatinine.

likelihood of successful guidewire (GW) crossing within 30 min. Independent angiographic predictors of failure (each given 1 point) that made up the J-CTO score included prior failed attempt, angiographic evidence of heavy calcification, bending ≥45° within the occluded segment, blunt proximal stump, and occlusion length >20 mm (11). Accordingly, CTO lesions were then graded as easy, intermediate, difficult, and very difficult (J-CTO scores of 0, 1, 2, and ≥3 respectively). Since then, the J-CTO score has been found to predict the overall likelihood of CTO PCI success (10,17); however, other reports demonstrated low calibration and discrimination of J-CTO score in predicting technical success of CTO percutaneous attempts (15,18). Similarly to Christopoulos *et al.* (17), we have shown that the higher the J-CTO score, the greater the use of antegrade dissection reentry techniques and retrograde approaches. This latter finding suggests that for difficult and very difficult lesions as assessed by J-CTO, early change of crossing strategy is recommended to avoid unnecessary delays predisposing to failure and complications. Recently, Galassi *et al.* (19) demonstrated that J-CTO score ≥3 was not only associated with procedural failure but also an independent predictor of worse cardiovascular long-term outcome (hazard ratio: 2.08; 95% CI: 1.32–3.27; P=0.002) in CTO patients attempted retrogradely.

In terms of pre-procedural evaluation, multiple studies have demonstrated a high diagnostic accuracy of coronary computed tomography angiography (CCTA) for the assessment of CTOs (12,20,21). Li *et al.* showed that a J-CTO$_{CT}$ score determined by coronary CCTA closely correlates to the angiographic J-CTO score (20). Opolski and coworkers developed the Computed Tomography Registry of Chronic Total Occlusion Revascularization (CT-RECTOR) score including the following clinical (previous attempt, occlusion duration ≥12 months or unknown) and CCTA (multiple occlusions, blunt stump, calcification ≥50% of CTO cross-sectional area, and bending ≥45°) variables (12). By assigning 1 point for each variable and summing all points accrued, the established CT-RECTOR score was able to strongly predict the probability of GW crossing within 30 min (12). Other CCTA parameters have been demonstrated to predict procedural success. Chen *et al.* showed that the attenuation of the proximal segment of CTO lesions, along occlusion length and total coronary calcium score as assessed by CCTA have predictive value for PCI outcomes (21).

In patients who underwent first antegrade attempt, Alessandrino *et al.* (13) established the CL-score, including both clinical and angiographic score variables [previous CABG (+1.5), previous myocardial infarction (MI) (+1), severe lesion calcification (+2), CTO length >20 mm (+1.5), non-LAD CTO (+1), and blunt stump (+1)]. Score values of 0 to 1, >1 and <3, ≥3 and <5, and ≥5 identified subgroups at high, intermediate, low, and very low probability, respectively, of CTO-PCI success rates. Hence, CL score could be suitable to be applied at centers where the retrograde or hybrid approach has not yet been implemented.

In the Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS CTO), the investigators reported the efficiency and the safety of hybrid approach in CTO recanalization (22). A prediction model (PROGRESS CTO score) for estimating technical success using such an approach was developed and consisted of four angiographic variables [proximal cap ambiguity (1 point), moderate/severe tortuosity (1 point), circumflex artery CTO (1 point), and absence of "interventional" collaterals (1 point)] (14).

Very recently, we have established the ORA score [O: ostial location (1point); R: collateral filling < Rentrop 2 (2 points); A: age ≥75 years (1 point)] (15). This simple and easy to remember prediction model, demonstrated satisfactory calibration and discrimination for predicting technical failure using both antegrade and retrograde CTO techniques, and categorized CTO procedures into four groups with increased difficulty and reduced likelihood of success.

Finally, Liu *et al.* (16) developed a risk scoring system [age ≥75 years (1 point), left ventricular ejection fraction (LVEF) <40% (1 point) and baseline serum creatinine (SCr) >1.5 mg/dL (2 points)] with similar accuracy to Mehran score for predicting contrast induced nephropathy after CTO PCI.

Conclusions

In conclusion, to answer to the title question, predictive scores are not only fashionable but also very useful tools to estimate the likelihood of GW crossing, the probability of procedural success and even clinical outcome after CTO PCI. Therefore, their use should be further expanded. The most difficult challenge for the operator is to clarify the multiple information given from different scores and to draw the right conclusions. Indeed, they could be even

applied to select the appropriate candidates for PCI among CTO patients to ensure a better cardiovascular outcome.

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Footnote

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Scoring systems for chronic total occlusion percutaneous coronary intervention: if you fail to prepare you are preparing to fail

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While the benefit of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has not yet been demonstrated in randomized controlled trials, several observational studies have shown that, as compared with failed procedures, successful CTO PCI is associated with significant clinical benefit (1). It is, therefore, imperative to maximize the likelihood of CTO PCI success. Accordingly, the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions PCI guidelines, have assigned a class IIa recommendation for CTO PCI to be performed in patients with suitable anatomy by operators with sufficient expertise (2). A key contributor to achieving success in CTO PCI is meticulous preparation; to aid with planning, operators and centers from around the world have created CTO PCI prediction scores (*Table 1*) (3-11).

Scoring systems can be useful in several ways. First, they provide a quantitative measure of the likelihood of success and complications that can be shared with the patient and help with clinical decision-making. Second, by providing the means for more objective assessment of anatomic and clinical complexity, CTO scores enable better case selection: while seasoned operators can tackle even the toughest of cases with high success rates (12), operators early in the CTO PCI learning curve can select "simpler" cases, referring the more unfavorable cases to specialized centers, or performing them with the guidance of a proctor. Within the heart team, the decision to revascularize and the optimal strategy can be tailored to each patient, taking into account the objective probability of achieving technical/angiographic success with PCI. Third, CTO scores provide a valuable template for guiding review of the coronary angiogram. At least 15 minutes of careful review and evaluation are essential to understand the lesion and develop a "plan of attack" (primary retrograde *vs.* antegrade approach, intimal or sub-intimal and wire or crossing device based strategies) (13,14). Fourth, standardized classification of CTO lesion complexity allows comparison of outcomes with different approaches, between operators, centers, countries and even continents, for both quality improvement and clinical research.

The first CTO scoring system was the J-CTO (multicenter CTO registry in Japan) score, created by Morino *et al.* to predict successful guidewire crossing within 30 minutes (3). The J-CTO score is currently the most widely used score, and its inception sparked a series of scoring systems created to predict not only successful wiring and procedural efficiency, but also technical success, contrast induced nephropathy and even complications. Newer scores use various clinical, imaging and laboratory parameters. But is the creation of more than one score necessary and useful? The answer is definitely yes, and here is why:

First, development of new scoring systems helps validate previously published scores. For example, in the J-CTO score proximal cap morphology, coronary calcification and tortuosity are variables affecting the outcome of CTO PCI; as shown in the Table, these variables are included in most other scores, reinforcing their importance. The ability of the J-CTO score to predict quick guidewire crossing (15), the need for advanced crossing techniques (8,12), as well as mid- and long-term outcomes (16,17) has been confirmed in multiple studies; however, its ability to predict technical success was not consistent in all studies (6,8,15).

Table 1 Currently available scoring systems for CTO PCI

Score variables	J-CTO score (3)	CL score (4)	PROGRESS-CTO score (5)	ORA score (6)	Chai *et al.* (7)	Wilson *et al.* (8)	Liu *et al.* (9)	CT-RECTOR score* (10)	Ito *et al.** (11)
Number of cases (n)	494	1,657	781	1,073	228	1,156	728	240	263
Endpoint	GW crossing <30 min	Technical success	Technical success	Technical success	Technical success-retrograde	Technical success	CIN	GW crossing ≤30 min	MACE during follow-up[‡]
Age (years)	–	–	–	+ (≥75)	–	+ (>65)	+ (≥75)	–	–
Prior CABG	–	+	–	–	–	+	–	–	–
Prior failure	+	–	–	–	–	–	–	+	–
Proximal cap	+ (blunt)	+ (blunt)	+ (ambiguous)	+ (ostial)	–	+	–	+ (blunt)	–
Tortuosity	+ (>45° in lesion)	–	+ (moderate[†], proximal)	–	–	+	–	+	–
Calcification	+	+ (severe)	–	–	–	+	–	+ (severe)	+ (severe)
Lesion length	+ (≥20 mm)	+ (≥20 mm)	–	–	–	+	–	–	+ (>25.4 mm)
Target vessel	–	+ (non-LAD)	+ (LCX)	–	–	–	–	–	–
Collateral quality	–	–	+ (lack of interventional)	+ (Rentrop <2)	+ (Werner, tortuous)	–	–	–	–
Other	–	Prior myocardial infarction	–	–	Distal segment diameter	BMI >30; non-proximal location	LVEF <40%; SCr >1.5 mg/dL	Multiple occlusions; duration ≥12 months	Minimal vessel area <11.9 mm^2

*, computed tomography angiography based; [†], moderate tortuosity defined as 2 bends >70° or 1 bend >90° proximal to the lesion; [‡], defined as cardiac death, myocardial infarction, stent thrombosis or target lesion revascularization at median 4.0 years follow-up; +, variable included in score. CTO, chronic total occlusion; PCI, percutaneous coronary intervention; J-CTO, multicenter CTO registry in Japan; CL, clinical and lesion-related; PROGRESS CTO, Prospective Global Registry For The Study of Chronic Total Occlusion Intervention; CT-RECTOR, Computed Tomography Registry of Chronic Total Occlusion Revascularization; ORA, ostial location, Rentrop grade <2, age ≥75 years; BMI, body mass index; CABG, coronary artery bypass grafting; CIN, contrast induced nephropathy; GW, guidewire; LAD, left anterior descending artery; LCX, circumflex artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; SCr, serum creatinine.

Despite similarities, newer scores often include different variables previously unexplored or found to not be predictive of outcome, highlighting the variety in approaches to CTO PCI. For example, the ORA (ostial location, Rentrop grade <2, age ≥75 years) score by Galassi *et al.* reflects the creator's extensive experience with retrograde techniques and may thus be more suitable for hybrid or retrograde operators (6). The clinical and lesion-related (CL) score by Alessandrino *et al.* was created based on primarily antegrade procedures and may thus perform better for antegrade-only operators (4). The PROGRESS CTO (Prospective Global Registry for the Study of Chronic Total Occlusion Intervention) score variables align with the hybrid algorithm for CTO PCI (5). In centers with high computed tomography angiography utilization, CT-based scores such as the CT-RECTOR (Computed Tomography Registry of Chronic Total Occlusion Revascularization) score may be of great value (10).

One disadvantage of scoring systems lies within the misconception that a high score (usually corresponding to complex coronary anatomy) is synonymous with failure. This is unfounded, since expert centers from around the world have reported very high success rates even with very complex CTOs (12).

In conclusion, CTO PCI scoring systems can be a tremendous resource for both the novice and experienced CTO operator, to aid with case and approach selection as well as to predict procedural efficiency and the probability for success and even complications. The creation of new scores to suit different CTO practices, and the validation of already existing scoring systems should be encouraged.

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Chronic total improvement in ventricular function and survival

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Provenance: This is a Guest Editorial commissioned by the Section Editor Yue Liu (Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China).

Abstract: Coronary chronic total occlusions (CTOs) represent a frequent lesions' subset observed in everyday catheterization laboratory practice. Previously considered to be an indication for surgical myocardial revascularization, the interest of interventional community in CTOs has exponentially grown during the last decade, particularly thanks to an important development in dedicated equipment and techniques, and has led to the achievement of high rates of success and low rates of complications by expert operators. In absence of available data from randomized trials, several observational studies have shown the benefits of CTO percutaneous coronary intervention (PCI) in insuring better cardiovascular outcome, particularly by improving ventricular function and reducing cardiac mortality.

Keywords: Chronic total occlusion (CTO); percutaneous coronary intervention (PCI); left ventricular function; clinical outcome

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Introduction

Coronary chronic total occlusions (CTOs) are defined as an occluded coronary segment with thrombolysis in myocardial infarction (TIMI) flow 0 for ≥3 months duration (1). According to EuroCTO club consensus, the occlusion duration could be divided into 3 levels of certainty: (I) "certain" (angiographically confirmed), in cases where a previous angiogram performed greater than 3 months ago, confirmed the presence of TIMI 0 flow; (II) "likely" (clinically confirmed), objective evidence of an acute myocardial infarction in the territory of the occluded artery without other possible culprit arteries of more than 3 months before the current angiogram; (III) "undetermined", TIMI 0 flow and angiographic anatomy suggestive of long-standing occlusion with stable anginal symptoms unchanged in the last 3 months or evidence of silent ischemia (1). Coronary CTOs represent a frequent lesions' subset observed in ~15% of patients undergoing coronary angiography, with a higher prevalence in those with previous coronary artery bypass grafting (CABG) (2,3). Previously considered to be an indication for surgical myocardial revascularization, the interest of interventional community in CTOs has exponentially grown during the last decade, particularly thanks to an important development in dedicated equipment and techniques (4), and has led to the achievement of high rates of success and low rates of complications by expert operators.

In absence of available data from randomized trials, several observational studies (5-10) have shown the benefits of CTO percutaneous coronary intervention (PCI) in insuring better cardiovascular outcome, particularly by improving ventricular function and reducing cardiac mortality.

Impact of successful CTO PCI on left ventricular function

Although ipsi- and contralateral collaterals are generally well developed in presence of a CTO, coronary flow

reserve is significantly reduced in 95% of the cases, thus not preventing ischemia, but ensuring myocardial viability which allows further recovery after revascularization (11). Indeed, when coronary flow is restored, the hibernating or stunned but viable myocardium at least partially restores the contractile function, resulting in regional and global left ventricular function improvement (5).

Several methods have been used to assess left ventricular function before and after CTO PCI such as: left ventricular angiography, echocardiography, nuclear imaging, and magnetic resonance imaging (MRI). Chung *et al*. (6) showed, 6 months after successful CTO recanalization, a significant improvement in left ventricular ejection fraction (LVEF) in patients without previous myocardial infarction (from 59.5%±13.7% to 67.3%±14.6%, P<0.001), while in patients with prior myocardial infarction the LVEF increased, albeit not significantly. Erdogan *et al*. (7) reported a significant increase in global longitudinal strain after successful CTO PCI; furthermore, this increase in the global longitudinal strain was correlated with an increase in LVEF. Although LVEF did not change significantly, Baks and colleagues (8) observed a favorable effect on ventricular remodeling with a significant decrease in both mean end-systolic and end-diastolic volume indexes as assessed by MRI.

Recently, Hoebers and coworkers (12) performed a weighted meta-analysis of 34 studies (including 2,243 patients) addressing the change of LVEF after successful CTO PCI. After a follow-up period ranging from 1 to 36 months, LVEF increased significantly with a pooled estimate of 4.44% [95% confidence interval (CI): 3.52-5.35, P<0.01]. Although it is common to consider a difference of at least 5% in LVEF as clinically significant, the impact of CTO revascularization on LVEF was relatively underestimated in the latter meta-analysis because of the heterogeneity (I^2=44%) between studies due to the difference in cohort sizes, CTO definition, CTO location, success definition, imaging modality and follow-up duration. Conversely, in patients with failed CTO procedures, a non-significant increase in LVEF was observed [2.21% (95% CI, 3.52-5.35; P=0.24)]. Whereas, in case of re-occlusion of the CTO-target vessel, LVEF was similar and even relatively worse than that at baseline [–0.15% (95% CI, –3.14 to 2.83; P=0.92)]. This latter fact might be explained by the loss of the protective effect of collaterals after initial restoration of antegrade flow.

In addition to LVEF, Hoebers *et al*. (12) analysed the impact of CTO PCI on ventricular remodeling. At follow up, the left ventricular end-diastolic volume, assessed in 8 studies (including 412 patients) was reduced by 6.14 mL/m^2 (95% CI, –9.31 to –2.97, P<0.01) as compared to baseline, reflecting less adverse remodeling after successful CTO PCI.

It is well established that the improvement of LVEF and cardiac remodeling contributes to better cardiovascular outcome. Moreover, successful CTO PCI was reported to be associated with enhanced myocardial flow (5) and decreased arrhythmic vulnerability (9). For these reasons, CTO revascularization plays an important role in reducing mortality in patients with coronary artery disease.

Impact of successful CTO PCI on cardiac mortality

In a single centre experience, Jones *et al*. (10) reported the long-term survival of patients with stable angina who underwent CTO PCI attempts, showing a reduction of mortality in patients with successful CTO revascularization, in comparison with patients with PCI failure (4.5% *vs*. 17.2%, respectively; P<0.0001). Similarly, in a prospective multicenter registry, Mehran *et al*. (13), showed that successful PCI was an independent predictor of lower cardiac mortality and reduced need for CABG at long-term follow up. In a recent analysis of UK Central Cardiac Audit Database, George *et al*. (14) reported that successful PCI of at least one CTO was associated with improved survival [hazard ratio (HR): 0.72; 95% CI, 0.62-0.83; P<0.001]. Likewise, a reduction of cardiac mortality was also observed with successful retrograde and antegrade dissection/re-entry techniques (15,16).

A meta-analysis of 13 observational studies by Joyal *et al*. (17), addressed the outcomes of patients who underwent successful versus unsuccessful CTO interventions. The investigators demonstrated a survival benefit for those who underwent CTO recanalization [14.3% *vs*. 17.5%; odds ratio (OR): 0.56] as well as reductions in the need for subsequent CABG and in residual or recurrent angina. A more recent meta-analyzing of 27 studies (15,432 CTO patients) confirmed that successful CTO PCI was associated with reduced mortality in comparison to failed CTO PCI (OR: 0.52; 95% CI, 0.43-0.62; P<0.01) (9).

On the other hand, comparing the different management strategies of patients affected by CTOs, outcome data reported in the Italian Registry of Chronic Total Occlusion (IRCTO) were in favor of PCI. Indeed, at 1 year follow-up, patients undergoing PCI showed lower rate of cardiac death (1.4% *vs*. 4.7% and *vs*. 6.3%; P<0.001 and P<0.001) in comparison with those treated with only medical therapy

and CABG, respectively (18). Interestingly, this benefit remains after propensity score matching analysis.

However, despite the high achievable success rates and the development of equipment and techniques, a wise patients' selection remains the key issue able to insure the best clinical outcome of CTO PCI and to avoid complications. In fact, the decision-making process of whom to undergo CTO PCI, should pass through a rational analysis, taking into account patient's symptoms, ischemia burden, and viability demonstration (19). In addition, operator's experience was reported to be closely correlated to the success of CTO PCI (15). Thus, current guidelines state that CTO PCI is reasonable in "patients with appropriate clinical indications and suitable anatomy when performed by operators with appropriate expertise" (Class IIA) (20).

Ongoing randomized trials

At least three major randomized trials are under way. The EXPLORE trial is a randomized clinical trial aiming to investigate the impact of recanalizing a CTO in a non-infarct related artery after primary PCI for STEMI. Three hundred patients were randomized to either elective PCI of the CTO within seven days or standard medical treatment. The primary endpoints are LVEF and left ventricular dimensions, as assessed by MRI; the results are expected during 2015. A Korean group is currently randomizing patients with CTOs and stable angina to PCI *vs*. medical therapy [DECISION-CTO (NCT01078051)] to evaluate the impact of the intervention on cardiac mortality and myocardial infarction during a 5-year follow-up period. Finally, the EURO-CTO trial (NCT01760083), is focusing on the impact of PCI on the quality of life parameters as compared to optimal medical therapy alone within 12 months of treatment. Moreover, the safety of PCI is being assessed by comparing clinical endpoints at 3 years. The results of this latter trial are not expected before 2016.

Conclusions

In conclusion, in experienced hands PCI represents an efficient and safe alternative in treating patients affected by CTOs able to restore at least in part left ventricular function and to reduce cardiac mortality. The expected results of the ongoing randomized trials might confirm those of observational studies and hence increase the appropriateness of CTO PCI in future guidelines.

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Footnote

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The impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcomes

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Provenance: This is a Guest Editorial commissioned by the Section Editor Yue Liu (Department of Cardiology, The First Affiliated Hospital of Harbin Medical University, China).

Abstract: A meta-analysis by Hoebers *et al*. reported that successful chronic total occlusion (CTO) recanalization resulted in an increase in left ventricular (LV) ejection fraction by 4.44% (P<0.01) and a reduction in LV end-diastolic volume by 6.14 mL/m^2 during follow-up as compared with baseline, suggesting beneficial LV remodeling. These findings are important as the myocardium supplied by a CTO frequently has sustained irreversible injury and further support the clinical benefits of CTO interventions.

Keywords: Percutaneous coronary intervention (PCI); chronic total occlusion (CTO); left ventricle; outcomes

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Percutaneous coronary interventions (PCIs) of chronic total occlusions (CTOs) can provide significant clinical benefits (1). Although no randomized controlled trial has been performed to date, several observational studies and meta-analyses have shown significant reduction in mortality, angina severity, need for coronary bypass surgery (CABG), major adverse cardiac events (MACE) and stroke after successful *vs*. failed CTO PCI (2-7).

Another important potential benefit of CTO PCI is left ventricular (LV) function improvement. Several studies have shown LV function improvement following successful CTO PCI, but the power of each individual study to detect a difference was low due to small sample size. To overcome this limitation Hoebers *et al*. performed an elegant systematic review and meta-analysis on the impact of CTO PCI on LV function [left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume (LV-EDV)] and on long-term mortality (8). They found that successful CTO recanalization resulted in an increase in LVEF by 4.44% (P<0.01) and a reduction in LV-EDV by 6.14 mL/m^2 during follow-up as compared with baseline, suggesting beneficial LV remodeling. However, the LVEF improvement disappeared upon re-occlusion of a previously successfully treated CTO vessel. Similar to prior meta-analyses long-term mortality was lower after successful *vs*. failed CTO PCI (OR: 0.52, P<0.01) (2-7).

The finding of improved LVEF after successful CTO PCI is of particular importance since myocardium perfused by a CTO vessel is likely to have sustained irreversible injury. Choi *et al*. performed magnetic resonance imaging in 170 consecutive patients with coronary CTOs showing evidence of prior myocardial infarction by late gadolinium enhancement in 86% of patients, a much higher proportion that previously recognized, even though only 25% of patients had Q waves on their electrocardiogram (9). The percent hyper-enhancement in another study by Cheng *et al*. was 47% for CTO lesions *vs*. 29% for non-CTO lesions, suggesting larger area of irreversible injury in myocardium perfused by a CTO (10). The significant improvement in LVEF and decrease in LV-EDV shown in the Hoebers meta-analysis suggests that CTO PCI can improve LV function among patients undergoing clinically-indicated CTO PCI, in spite of pre-existing myocardial injury. The actual magnitude of improvement may be larger among patients with decreased baseline LVEF, although the granularity of published reports was not detailed enough to

answer this question in the present meta-analysis.

Will LVEF improve in all patients undergoing CTO PCI? The answer is likely no, as the extent of potential recovery likely depends on baseline myocardial viability. In the study by Choi *et al.*, increased angiographic collateral flow was associated with lower degree of late gadolinium enhancement transmurality, providing an indirect means of predicting the likelihood of LV function improvement after CTO recanalization: poorly collateralized myocardial segments would be less likely to recover function as compared with well collateralized segments. Similar findings were reported by Ripley *et al.*: viable myocardium was present in 83% of patients with good collaterals *vs.* 38% of those with poor collaterals (11).

Should all patients undergoing CTO PCI undergo myocardial viability testing? The answer to this question is also likely no. The clinical indication for CTO PCI in most cases is improvement of symptoms, rather than a desire to improve LVEF (12,13). CTO PCI is indicated in patients with classic angina uncontrolled by medical therapy (14), but ischemia and viability testing may be of particular importance in patients with no symptoms or atypical symptoms, such as dyspnea.

How can one optimize the likelihood of LV function improvement? By completely revascularizing the patient (15) and by preserving the patency of all major side branches, as occlusion of side branches during CTO PCI has been associated with higher risk for periprocedural myocardial infarction (16,17), as well as coronary perforation and tamponade (18). It may be preferable to use antegrade crossing techniques for CTO recanalization, as retrograde crossing techniques have been associated with higher risk for periprocedural myocardial infarction and procedural complications (17,19). However, retrograde techniques may often be needed for recanalizing complex CTOs and preserving bifurcations (20,21). Although the success of CTO PCI has been steadily increasing over time (22,23), it remains heavily dependent on operator experience (24,25), hence complex cases may be best performed at high-volume expert CTO centers (21,26).

As outlined by the authors, their meta-analysis has important limitations. First, several imaging modalities were used to assess LVEF, each with different accuracy and reproducibility. Second, and most important, all studies included in the meta-analysis were observational, limiting the ability to derive definitive conclusions, as conclusive proof of a beneficial effect of a treatment can only be provided by adequately powered, prospective, randomized-controlled clinical trials (1). The first randomized controlled CTO PCI trial with LVEF as the primary endpoint is the Evaluating Xience V and LV function in PCI on occlusions after ST-Elevation myocardial infarction (EXPLORE) trial (http://www.exploretrial.com/). EXPLORE randomized 300 patients presenting with ST-segment elevation acute myocardial infarction and a CTO in a non-infarct vessel to either CTO PCI within 7 days of presentation or standard medical therapy. The study's primary endpoint is LV ejection fraction and end-diastolic volume at 4 months, measured using cardiac magnetic resonance imaging. Enrollment in the study was recently completed and results are anticipated to be presented at the 2015 Transcatheter Cardiovascular Therapeutics meeting. The EXPLORE trial results are eagerly anticipated as they will provide novel insights on the impact of CTO PCI on LV function and structure.

In conclusion, the carefully designed and executed meta-analysis by Hoebers *et al.* adds to our understanding of the benefits and underlying mechanisms of successful CTO PCI (8), providing further (albeit indirect) support of its clinical utility and need for continued development.

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Chronic total occlusion: no more meta-analysis, please—a randomized clinical trial is urgently needed

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Percutaneous treatment of chronic total occlusions (CTO), defined as >3 months old, total obstruction of a coronary artery, is a phenomenon that has gained popularity in the portfolio of Cardiac Cath Lab Units, facilitated by the development of new technologies that allow addressing cases not feasible a few years ago. Despite its growing popularity, these are procedures that require a highly experienced operator, long sessions with increasing radiation dose to the patient and operator, and the risk of potentially serious complications. It is therefore very important to know the risk-benefit balance that this technique can provide in a given patient. The recent meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome by Hoebers (1), offers new and interesting facts that force once more to ponder. In an extensive review of all studies published in the literature, Hoebers concluded that a successful percutaneous treatment of a CTO is associated with an improvement in the ejection fraction (EF) with an absolute increase of 4.44%, a reduction in the adverse remodeling and an improvement in survival (OR: 0.52). Without wanting to question the validity of this meta-analysis, the data provided by Hoebers also allows another interpretation. When the authors selected only studies in which there is a clear definition of the treated population, confirming that all patients have a CTO at least 3 months old and an evaluation period post procedure for more than 4 months, the average difference between pre and post procedure EF is 4.71 (95% CI: 3.26-6.16) in the successfully treated group of patients and 2.21 (95% CI: –1.46 to 5.89) in the technique failure group of patients. So, in both groups the EF increases very slightly (only in the first case being statistically significant) and the difference between the increases in EF in both groups is actually 2.5 points. Whether this way of analyzing a meta-analysis can be very questionable from a statistical point of view, what we have no doubt about is that this small difference, quite probably less than the coefficient of variation of many techniques that analyze the EF, is clinically very poor. Therefore, despite the conclusions of Hoebers's meta-analysis, we are not sure that percutaneous treatment of a CTO, associated with an improvement in the EF, can provide any clinical significance.

The second outcome of Hoebers's meta-analysis indicates that successfully revascularized patients have a better prognosis than patients without it. There is no doubt in this statement, but we question that this better outcome is due to the success of the procedure and not due to other confounding variables. In a review of 13 studies included in a previous meta-analysis by Joyal (2), many variables that are associated with the prognosis were not described in baseline studies, so there is a possibility that both groups compared (successfully and unsuccessfully revascularized patients) were different (3). In the absence of a control group (not revascularized patients), it's very difficult to know what the specific role of revascularization in these patients is.

In our point of view, in order to understand the role of revascularization in patients with CTO, at least these four important concepts, should be previously clarified.

First, it is unclear what is the impact of a CTO, in the prognosis of patients with chronic ischemic heart disease or after an ACS. For example, patients with CTO included in the Horizons study, had worse prognosis than

patients without CTO (4). In this study, patients with CTO were older and had more hypertension, diabetes, kidney failure, worse EF and Killip class, and had more history of myocardial infarction, angioplasty and bypass surgery. The authors conclude literally: "The present study is a post hoc analysis from a large randomized clinical trial of patients with STEMI undergoing primary PCI and is limited by its observational nature. There were numerous differences in baseline clinical, angiographic, and procedural characteristics between the groups, and although multivariable Cox's proportional hazards analysis was performed, residual unmeasured confounders cannot be excluded. As such, the results of the present analysis should be considered hypothesis-generating". The Horizons study is included in the recent meta-analysis in which O'Connor concludes that patients with acute myocardial infarction and a no culprit artery CTO have a worse prognosis than patients without CTO (5). Unfortunately, in this meta-analysis there is no reference to differentiate baseline characteristics of the patients in both groups, which could explain the difference in prognosis, regardless of the presence of a CTO. It is interesting to note the observational study of Ariza-Solé, in which the presence of a CTO in patients with STEMI treated with primary angioplasty loses the prognostic value when the COX regression model with all variables are included [HR of 2.79 (95% CI: 1.71-4.56), P=0.001 in univariate analysis and HR of 1.76 (95% CI: 0.85-3.75), P=0.166 in multivariate analysis] (6).

Secondly, in our opinion the role of myocardial ischemia in the absence of angina, as an indication for revascularization, is not fully clarified, which frequently occurs in patients with CTO treated percutaneously. The current indications for revascularization in the clinical practice guidelines have, in our opinion, a very weak scientific base (7). In the Courage study, angioplasty was associated with a greater reduction in the ischemic area, quantified exercise tests, compared to medical treatment (8), but angioplasty in patients with moderate to severe ischemia did not affect the prognosis of patients compared to medical treatment (9). In addition, a meta-analysis of studies that have evaluated the effect of ischemia treated with angioplasty, has concluded that there is no effect on mortality, reinfarction or angina at follow-up. It is important to be aware of the ISCHEMIA TRIAL trying to prove whether treatment of moderate to severe ischemia detected by imaging techniques benefit from revascularization, something currently unknown in our opinion (10).

Thirdly, it is very risky to conclude that the improvement in ventricular function after a revascularization technique, improves prognosis in patients with ventricular dysfunction. In this sense, the STICH study failed to prove benefit from a complete revascularization with coronary bypass surgery, in patients with ventricular dysfunction and multivessel disease (11). Surprisingly, in this study, this lack of benefit was not dependent on the existence of viable myocardial territory (12). It is important to emphasize this, because often myocardial viability is required, something that at the moment is very difficult to assess.

Finally, as noted earlier, there is a strong suspicion that patients with CTO successfully treated are substantially different from patients in which the technique fails. This suspicion is supported by the fact that, when all prognostic variables are included in the multivariate analysis, the success in treating a CTO has no longer impact in the prognosis. This hypothesis is what has been reported by two major Japanese groups with experience in the treatment of CTO. In the series of CREDO-Kyoto registry cohort-2, including 1,524 patients, Yamamoto described in the multivariate analysis that the success in treating a CTO has no impact in reducing mortality or reinfarction (13). In the series of the National Cardiovascular Center in Osaka (Japan), which includes a total of 820 patients, the analysis adjusted for confounding variables concludes that there is no benefit in the treatment of chronic occlusions compared to medical treatment (14).

So, waiting for ongoing randomized studies, seems prudent at the present time, that only symptomatic patients (angina despite optimal medical treatment) are treated in order to improve them (15). In the absence of any symptoms, other indications to improve prognosis (ischemia, viability, etc.) should be carefully evaluated.

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Footnote

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Meta-analyses and randomized trials investigating percutaneous coronary intervention of chronic total occlusions: what is left to explore?

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Christakopoulos GE, Tarar MN, Brilakis ES, *et al*. The impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcomes. J Thorac Dis 2015;7:1107-10.

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The field of percutaneous coronary intervention of coronary chronic total occlusions (CTO PCI) is highly dynamic. This is mainly illustrated by the large number of technical advances that have propelled success rates of CTO PCI from 60%–70% to as high as >90% in recent (selected) case series (1). However, the rationale for performing CTO PCI is currently largely based on observational data and untested hypotheses. Observational studies have suggested a reduction in the need for coronary artery bypass graft surgery (CABG), a reduced incidence of ventricular arrhythmias, and even reduced mortality after successful CTO PCI (2-6). Further hypothesis-generating research was recently published by our group in the form of a meta-analysis of observational studies investigating the evolution of left ventricular ejection fraction (LVEF) and left ventricular end diastolic volume (LVEDV) after CTO PCI (7). This study indicated a significant increase in LVEF of 4.44% [95% confidence interval (CI): 3.52–5.35%, P<0.01] after successful CTO PCI at a follow-up duration ranging from 1 to 36 months in 34 studies which included a total of 2,243 patients. Moreover, LVEDV was reduced by 6.14 mL/m^2 in a meta-analysis of eight studies comprising 412 patients that evaluated LVEDV after successful CTO PCI.

The results of our study were discussed in two editorial comment articles by Dr. Christakopoulos *et al*. and Dr. Boukhris *et al*. (8,9) The editorial by Dr. Christakopoulos and colleagues raised an important argument about the presumed importance of viability testing to guide the decision to perform CTO PCI aimed at improving LVEF. Prior research has shown that the extent of scar tissue transmurality can reliably and reproducibly be assessed using cardiovascular magnetic resonance imaging (CMR) using late enhancement with a gadolinium-based contrast agent (10). Currently, a threshold of 75% transmurality is accepted to discriminate between viable and non-viable myocardium. This value was derived from a cohort of 21 patients undergoing CTO PCI who underwent contrast-enhanced CMR before the index procedure and at 5-month and 3-year follow-up (11). Regional myocardial function, measured as segmental wall thickening (SWT), improved in segments with a transmural extent of infarction (TEI) of <75%, and was unchanged in patients with TEI ≥75%. A study of 50 consecutive patients with a CTO who underwent contrast enhanced CMR showed that 32 patients (64%) had inducible ischemia and myocardial viability within the CTO territory (12). These 32 patients underwent a second CMR at 3 months after CTO PCI. An improvement in LVEF (63%±13% to 67%±12%, P<0.0001) and improvement in LVEDV (65±38 to 56±38 mL, P<0.001) was reported. This recent study elegantly illustrates the importance of adequate patient selection for CTO PCI using state-of-the-art imaging techniques.

The editorial by Boukhris *et al*. pointed out that our meta-analysis also showed a small, non-significant increase in LVEF in patients with failed CTO PCI procedures

(improvement of 2.21%, 95% CI: –1.46 to 5.89, P=0.24) and interestingly, a slight deterioration in LVEF in patients with successful CTO PCI with re-occlusion (–0.15%, 95% CI: –3.14% to 2.83%, P=0.92). The authors of the editorial pointed out that this may be a result of the loss of collateral circulation which leads to myocardial infarction in case of re-occlusion after CTO PCI (8). However, these studies were performed before the widespread uptake of drug-eluting stents. The incidence of restenosis and reocclusion, even in CTO lesions has significantly declined with current-generation drug-eluting stents (13). Therefore, this does not seem to be an important concern in the current era.

An important concern raised in both editorial articles remains the (relative) lack of availability of data from randomized controlled trials in the field of CTO PCI. Two randomized trials are currently enrolling patients. EURO-CTO trial (NCT01760083) which evaluates quality of life in patients undergoing CTO PCI compared with optimal medical therapy at 12-month follow-up and clinical endpoints at 3-year follow-up. The DECISION-CTO trial (NCT01078051) evaluating cardiac mortality and myocardial infarction up to 5-year follow-up in patients randomized to optimal medical therapy or CTO PCI.

The results of the first randomized controlled trial in the field of CTO-PCI were recently presented at the 2015 annual TCT meeting in San Francisco (14). In EXPLORE, 304 patients undergoing primary PCI for acute ST-elevation myocardial infarction (STEMI) and with a concurrent CTO in a non-infarct related artery were randomized to additional CTO PCI within 1 week after the index procedure or no additional CTO PCI. All patients underwent contrast enhanced CMR after 4 months to determine the primary endpoints of LVEF and LVEDV. At 4-month follow-up no difference was observed in terms of LVEF (CTO PCI 44.1%±12.2% *vs*. no CTO PCI 44.8%±11.9%, P=0.60) or LVEDV (CTO PCI 215.6±62.5 mL *vs*. no CTO PCU 212.8±60.3 mL, P=0.70). Rates of major adverse cardiovascular events, a composite of cardiac death, myocardial infarction, and CABG were low in both groups (5.4% *vs*. 2.6%, P=0.25). A significant interaction was observed between CTO location and randomized treatment allocation in terms of LVEF at 4 months; in patients with a CTO located in the left anterior descending (LAD) coronary artery a significant improvement in LVEF was observed in patients undergoing CTO PCI *vs*. patients not undergoing CTO PCI (47.2%±12.3% *vs*. 40.4%±11.9%, P=0.02).

The EXPLORE trial is an important first step towards a robust body of evidence concerning clinical outcomes after CTO-PCI. Nonetheless, as of now many questions remain unanswered. The results from EXPLORE warrant further investigation into additional CTO-PCI in STEMI patients with a concurrent CTO located in the LAD. Moreover, the data from EXPLORE suggest that early PCI of a CTO located in the RCA or the RCX is not beneficial in STEMI patients with a concurrent CTO. Because EXPLORE only included patients post-STEMI, future studies investigating clinical outcomes after CTO PCI in other settings are direly needed. The results from the EURO-CTO and DECISION-CTO studies are eagerly anticipated to shed further light on the safety and efficacy of CTO PCI in patients with stable coronary artery disease. And even when these two ongoing trials will be published, the answers to many clinical questions regarding CTO PCI will remain to be explored.

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Five factors and three characteristics of coronary in-stent restenosis

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Provenance: This is a Guest Editorial commissioned by the Section Editor Yue Liu (Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China).

Abstract: In the field of interventional cardiology, several patient subsets still present with poor clinical and angiographic outcomes after drug-eluting stent (DES) implantation. The author of this editorial comment supports the idea that in-stent restenosis (ISR) includes three characteristics (severity and extent of stenosis, and tissue characteristics) that are caused by five factors (device, patient, anatomy, procedure, and history). To reduce further revascularization, a tailor-made strategy may be considered in accordance with the factors and characteristics of the individual ISR lesion.

Keywords: Coronary artery; coronary intervention; stent; restenosis; intravascular ultrasound (IVUS); optical coherence tomography (OCT)

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In the field of interventional cardiology, the emerging drug-eluting stent (DES) has markedly reduced the number of patients requiring repeat revascularization. Nevertheless, several patient subsets still present with poor clinical and angiographic outcomes after DES implantation (1). It cannot be overlooked that the main reason for a poor clinical outcome after percutaneous coronary intervention (PCI) in comparison with after coronary artery bypass grafting for multivessel disease is still restenosis, even in the DES era (2). Although drug-coated balloon angioplasty is known as a safe and effective remedy for in-stent restenosis (ISR) (3), additional DES implantation provides superior long-term clinical and angiographic outcomes (4). However, additional DES implantation causes multiple layers of stent in the coronary artery (5). A better therapeutic strategy for ISR still needs to be investigated.

Intravascular ultrasound (IVUS) remains the gold standard to elucidate coronary artery disease (6). The utility of IVUS for exploring the mechanism of ISR has already been reported (7,8). Goto *et al.* used IVUS to identify the difference between the mechanism of ISR in various types of stents: bare metal stent (BMS) and first- and second-generation DES (9). Although reference lumen areas were similar in BMS and first- and second-generation DES, restenotic DES was significantly longer and stent areas were significantly smaller. Stent fracture was seen only in DES, whereas there was no difference between first- and second-generation DES. This paper concluded that restenotic first- and second-generation DES were characterized by less neointimal hyperplasia, smaller stent areas, longer stent lengths, and more stent fractures compared with restenotic BMS (9).

The author of this editorial comment supports the idea that ISR includes three characteristics that are caused by five factors (*Figure 1*). Goto's study investigated four of five factors and two of three characteristics (9). This paper explored the impact of fracture on ISR, whereas baseline calcification (10), stent edge injury, and underexpansion, etc., which are visually and quantitatively identifiable on IVUS just after stent implantation, were not investigated. Serial findings should demonstrate the mechanism of ISR more clearly (11). This paper failed to show the difference in ISR tissue characterization. Smooth muscle migration is known as a major factor of ISR (12). However, a previous study showed that thrombus and inflammatory cell infiltration can be observed in DES-ISR tissue (8).

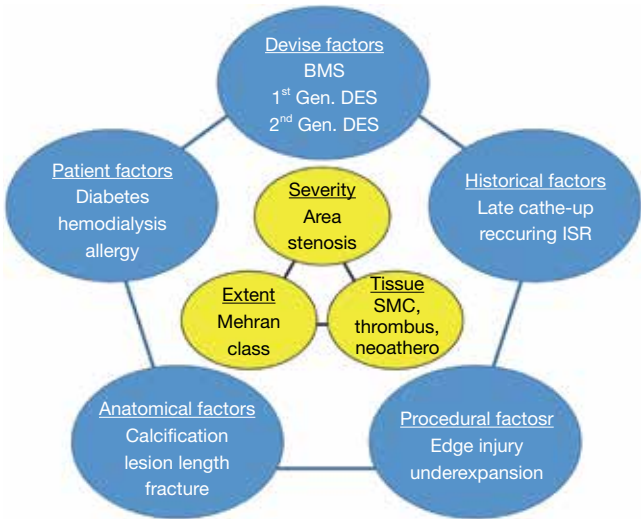

Figure 1 Five factors and three characteristics of coronary ISR. BMS, bare metal stent; DES, drug-eluting stent; ISR, in-stent restenosis; SMC, smooth muscle cell.

Neoatherosclerosis is a known factor of ISR, which appears more than 1 year after DES implantation (13). Optical coherence tomography (OCT) has the potential to reveal more subtle features in restenotic tissue (14-16). Notably, previous investigations using OCT revealed that the neointima of diabetic patients frequently shows microvessels (16,17). The suppression of microvessel proliferation may be a key to reducing ISR in diabetic patients. Additionally, we reported that coexistence of eccentric tissue proliferation and strong signal attenuation detected in OCT images of ISR is related to TLR after PCI for DES-ISR especially in patients undergoing maintenance hemodialysis (18). To reduce further revascularization, a tailor-made strategy may be considered in accordance with the factors and characteristics of the individual ISR lesion.

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Mechanism of in-stent restenosis after second-generation drug-eluting stents (DES): is it different from bare-metal stents and first-generation DES?

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First-generation drug-eluting stents (DES) have dramatically reduced the rate of in-stent restenosis (ISR) and subsequent target lesion revascularization (TLR) compared with bare-metal stents (BMS) (1). However, widespread use of first-generation DES has drawn attention to several unresolved, clinically relevant issues such as late stent thrombosis (ST) and late restenosis (2). Histopathological studies of first-generation DES have revealed that a chronic reaction to components of the permanent polymer reaction may lead to the delayed arterial healing, which is associated with increased risks of late DES failure (3,4). In addition, neoatherosclerosis is suggested as another cause of very late ST and late TLR (5). To overcome these limitations, biocompatible and biodegradable polymers have been developed and equipped with second-generation DES. Recent clinical trials demonstrated that second-generation DES has the improved efficacy and safety compared with those of first-generation DES (6,7). Nevertheless, second-generation DES, as well as first-generation DES, are not immune to ISR. In fact, Cassese *et al*. reported a large cohort of patients with angiographic surveillance that ISR rate of second-generation DES remains higher than 10% (8). Therefore, it is important to elucidate the mechanism of ISR after second-generation DES compared with that of BMS and first-generation DES, which may play a crucial role in the newly developed DES.

In recent issue of *American Journal of Cardiology*, Goto *et al*. retrospectively analyzed intravascular ultrasound (IVUS) data in 298 ISR lesions (52 BMS, 138 first-generation DES, and 108 second-generation DES) to compare the mechanisms of ISR after second-generation DES implantation with those of BMS and first-generation DES implantation (9). The main findings of this study was that (I) both neointimal hyperplasia (NIH) and stent underexpansion were the mechanisms of ISR even in the second-generation DES era; (II) NIH was dominant in 69% of BMS-ISR and 59% of DES-ISR; (III) stent underexpansion was greater in DES-ISR than BMS-ISR; (IV) stent fracture (SF) was found only in DES-ISR.

NIH has emerged as the main cause of ISR in both BMS and first-generation DES (9-11). However, histopathological studies demonstrated considerable differences in the tissue characteristics of ISR between BMS and first-generation DES. BMS-ISR is typically characterized by NIH consisting of a proteoglycan matrix and high proportion of vascular smooth muscle cells. Conversely, DES-ISR is typically characterized by a proteoglycan-rich NIH with relatively few smooth muscle cells. Furthermore, neoatherosclerotic change within the restenostic tissue is seen earlier and more frequently in DES-ISR (5). In fact, an optical coherence tomography (OCT) study demonstrated that homogeneous and lipid-laden neointima were frequently observed in the BMS early phase (≤1 year) and late phase (>1 year), respectively; heterogeneous neointima was observed more frequently in the DES early phase (≤1 year) compared with the BMS early phase (44% *vs*.

9%, P<0.05) (12). Habara *et al*. reported that homogeneous neointima was frequently observed in the early BMS-ISR (≤1 year) than in the late ISR (>5 years, without restenosis ≤1 year), whereas heterogeneous neointima was frequently observed in the late ISR (13). Furthermore, Habara also reported morphological differences of neointimal characteristics between early (<1 year), late (1–3 years), and very late (>3 years) restenosis after first-generation DES implantation using OCT that thin-cap fibroatheroma-like and heterogeneous neointima were increased from early to very late phase (14). These findings are consistent with pathological findings. Therefore, NIH is the main cause of ISR in both BMS and first-generation DES, but the detailed mechanism of NIH may be different according to stent type and restenotic phase.

Stent underexpansion is another mechanism of ISR in both BMS and first-generation DES. Previous IVUS studies showed that the cutoff of minimum stent area (MSA) to predict freedom from ISR was 6.5 mm^2 for the BMS, 5.0 mm^2 for sirolimus-eluting stent, and 5.7 mm^2 for the paclitaxel-eluting stent (15,16). Recently, Song *et al*. reported the cutoff of MSA for the second-generation DES, demonstrating 5.4 mm^2 for the everolimus-eluting stent and 5.3 mm^2 for the zotarolims-eluting stent (17). These findings suggested that the cutoff of MSA for the second-generation DES was similar to that for the first-generation DES. Interestingly, Kang *et al*. showed that NIH was the dominant mechanism of ISR, whereas stent underexpansion associated with longer stent length (>28 mm) remained an important mechanism of ISR (11). In previous studies, stent underexpansion (NIH <50% and MSA <5 mm^2) was seen in approximately 20%–30%, which were consistent with the current study. Although NIH may be unavoidable mechanism of ISR in the second-generation DES, stent underexpantion is a preventable mechanism of ISR. Nevertheless, stent underexpansion still contributed to ISR even in the second-generation DES era. Therefore, we should recognize the clinical implication of stent underexpansion as a residual mechanism of ISR in the second-generation DES era. In addition, we should make effort to obtain an optimal final MSA in each DES using IVUS or OCT-guidance percutaneous coronary intervention (PCI) during the procedure.

SF after DES implantation has recently become an important concern because of its potential association with ISR, TLR, and ST. The incidence of SF in clinical setting has been reported to be 0.84% to 8.4% in first-generation DES (18). Recently, we reported the SF after second-generation DES implantation occurs in 1.7% to 4.1% of lesions and is associated with a higher incidence of major adverse cardiac events, mainly driven by higher rates of TLR or ST (19-21). These findings suggested that SF is still one of the causes of ISR in the second-generation DES. As reported previously, there are some differences in the predictors of SF among the second-generation DES (19-21). Therefore, we should make effort to learn the feature of stent platform and to select current DES appropriately on the basis of lesion characteristics.

In the second-generation DES era, the incidence of very late ST continued to be much lower up to 5 years after the index procedure, which was quite different from that of first-generation DES (8,22). These findings supported the improved safety of second-generation DES compared with first-generation DES. In contrast, late TLR beyond 1 year occurred constantly without attenuation up to 5 years, which was similar to first-generation DES (8,22). The reason why this discrepancy occurred remains unclear. In fact, there is limited data regarding the mechanism of ISR after second-generation DES implantation. Goto *et al*. confirmed the importance of NIH and stent underexpansion as the cause of ISR after second-generation DES, which were similar to BMS and first-generation DES (9). In addition, SF was seen only in DES-ISR. The authors should be congratulated for providing the IVUS data on mechanisms of ISR after second-generation DES implantation. However, a number of limitations need to be addressed. As authors mentioned in study limitations, grayscale IVUS could not identify the presence of neoatherosclerosis and thrombus within the stent. Recently, Otsuka *et al*. reported that the observed frequency of neoatherosclerosis did not differ significantly between first-generation DES and second-generation everolimus-eluting stent in human autopsy (23). Although these findings suggested that neoatherosclerosis was associated with ISR, TLR and ST after second-generation DES implantation, it remains unclear how often neoatherosclerosis contribute to these events. In addition, the duration between index and stent failure was significantly shorter in the second-generation DES than in the BMS and first-generation DES. To date, the mechanism of late TLR after second-generation DES has not been fully evaluated. Compared with IVUS, OCT is a high resolution intravascular imaging modality to evaluate neointima tissue such as in-stent neoatherosclerosis and thrombus adequately *in vivo*. Therefore, further long-term follow-up OCT studies are required to compare the mechanism between early and late

ISR after second-generation DES implantation.

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Footnote

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Use of intravascular ultrasound *vs*. optical coherence tomography for mechanism and patterns of in-stent restenosis among bare metal stents and drug eluting stents

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Abstract: This article is a perspective responses to the "Mechanisms and Patterns of Intravascular Ultrasound In-Stent Restenosis Among Bare Metal Stents and First- and Second-Generation Drug-Eluting Stents" by Goto *et al*., The above mentioned article outlines the use of intravascular ultrasound (IVUS) in visualizing the patterns and mechanisms of in-stent restenosis (ISR) post percutaneous coronary intervention (PCI). Although IVUS is an appropriate method of choice for this scenario, IVUS has certain limitations which can be overcome by using optical coherent tomography (OCT). OCT is not only able to overcome IVUS's limitations but is also able to provide additional information to enhance the understanding of in-stent restenotic lesions. This article also outlines the future directions for OCT both in clinical and investigation settings.

Keywords: Intravascular ultrasound; optical coherent tomography (OCT); in-stent restenosis (ISR)

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Introduction

In-stent restenosis (ISR) is a histologically distinct pathological process after balloon angioplasty with bare metal stents (BMS), first generation drug-eluting stents (DES), second generation drug-eluting stents (DES), occurring through various mechanisms such as: neointimal hyperplasia, neoatherosclerosis, stent under expansion, and other complications. "Mechanisms and Patterns of Intravascular Ultrasound In-Stent Restenosis Among Bare Metal Stents and First- and Second-Generation Drug-Eluting Stents" by Goto *et al*., demonstrates the value of intravascular ultrasound (IVUS) in visualizing the mechanisms and patterns of ISR after implanting BMS and first and second generation DES. Although presented through this paper that IVUS is suitable for evaluating and inspecting in stent restenosis, optical coherence tomography (OCT) may provide greater benefit and insight in inspection, and understanding of the mechanisms of ISR.

History of ISR visualization

Coronary angiography has been a gold standard investigation for ISR lesions, especially in providing angiographic classifications for prognostic importance, and therefore can provide appropriate and early patient triage for clinical and investigational purposes (1). Although coronary angiography is commonly used to evaluate ISR lesions, it is limited in its ability to assess ISR in detail. It fails to show differences in the lumen, stent or restenotic tissue area and restenotic tissue. Use of CT coronary angiography allowed reliable detection and quantification of ISR with low radiation exposure (2). Although the results showed high overall diagnostic accuracy, the CT coronary

angiography is compromised by several factors; severely calcified arteries, high body mass index, and high heart rates decrease diagnostic accuracy of multidetector CT because of beam-hardening artifacts, excessive image noise, and limited temporal resolution (3). The visualization of the in-stent neointimal hyperplasia with multidetector CT is additionally slowed down by metallic stent struts, because of their high attenuation characteristics and limited spatial resolution of standard-resolution multidetector CT scanner, coronary artery stents are susceptible to partial volume and beam-hardening artifacts. Although decreased collimator width and use of dedicated convolution kernels have been shown to improve stent visualization at multidetector CT, these advances did not overcome artifacts owing to multidetector CT limitations in spatial resolution.

IVUS for ISR

According to the article by Goto *et al.*, IVUS was performed after 0.1–0.2 mg intracoronary nitroglycerine, followed by quantitative IVUS analysis performed using computerized planimetry (4). The IVUS measurements included cross-sectional areas of the external elastic membrane, lumen, stent and NIH. The study was able to confirm the importance of both NIH and chronic stent under expansion as the mechanisms of ISR. The main limitation to the study included inability to evaluate the frequency of neoatherosclerosis because grayscale IVUS is not the technique of choice to assess this phenomenon.

IVUS can be compared to black-and-white TV, where definite imaging is not present therefore does not show as much detail. A situation where IVUS is a suitable choice is a patient with very severely compromised renal function, PCI is planned and aim is trying to minimize contrast usage. Especially if multiple OCT runs are required for vessel sizing or to assess stent expansion then IVUS is a great choice.

OCT for ISR

OCT provides high-definition color images and is a leap forward in assessing coronary vessels from an anatomic standpoint. It has much better resolution, with 10× the axial and lateral resolution of IVUS. OCT has a much faster rotational and pullback speed, and data acquisition only takes 2.5 seconds. This results in obtaining necessary images, and interpreting them with confidence. OCT is easier and faster to set up and use as well. However, OCT requires additional contrast use which is not suitable in case of patients with severe renal dysfunction.

OCT is also superior for guided stent implantation (5). The ILUMIEN system is the first integrated diagnostic technology that combines OCT and FFR in one platform. physiologic and anatomic assessment all in the same system. Reports also show a clear advantage over FD-OCT guided PCI in randomized study (6). OCT provides a 15 um axial resolution, yielding detailed images of his vessel lumen, neointimal tissue and strut distribution (7-12).

OCT patterns of ISR

The high resolution imaging is able to show clear layered appearance of the restenotic tissue, suggesting that the restenosis may be composed of different tissues (13). Pathologic examinations of human atherectomy specimens have demonstrated that restenosis is DES can consist of heterogeneous components including proteoglycan-rich tissue, organized thrombus, atheroma, inflammation and fibrinoid (14). The inner luminal border, the smooth muscles are more compact therefore show a homogeneous concentric orientation, whereas the cell density decreases and appears heterogeneous in the tissue located far from the lumen. Atheromatous material, organized thrombus and inflammatory cells can be observed around the stent struts where the smooth muscle cells are usually oriented in a longitudinal fashion (15). These differences in tissue composition, cell density and orientation comprise in the layered appearance observed. OCT is also successful at identifying structures suggestive of micro vessels in the restenosis, which corresponds to postmortem histology data where the presence of neovascularization in DES restenosis has been described (16,17). The presence of neoatherosclerosis as a cause of late stent failure (18-20) and observation regarding the relationship between lack of stent strut tissue coverage and late/very late stent thrombosis, can be indicted by OCT (21). OCT findings in stent thrombosis may however depend on whether aspiration thrombectomy is performed before or after OCT imaging, due to aspiration's effect on removing not only thrombus but also fragments of atherosclerotic plaques such as foamy macrophages, cholesterol crystals and thin fibrous cap (22).

IVUS and OCT in comparison

Both systems offer an anatomic assessment of the vasculature and allow visualization into the living, beating hearts. Both of these techniques are used to make

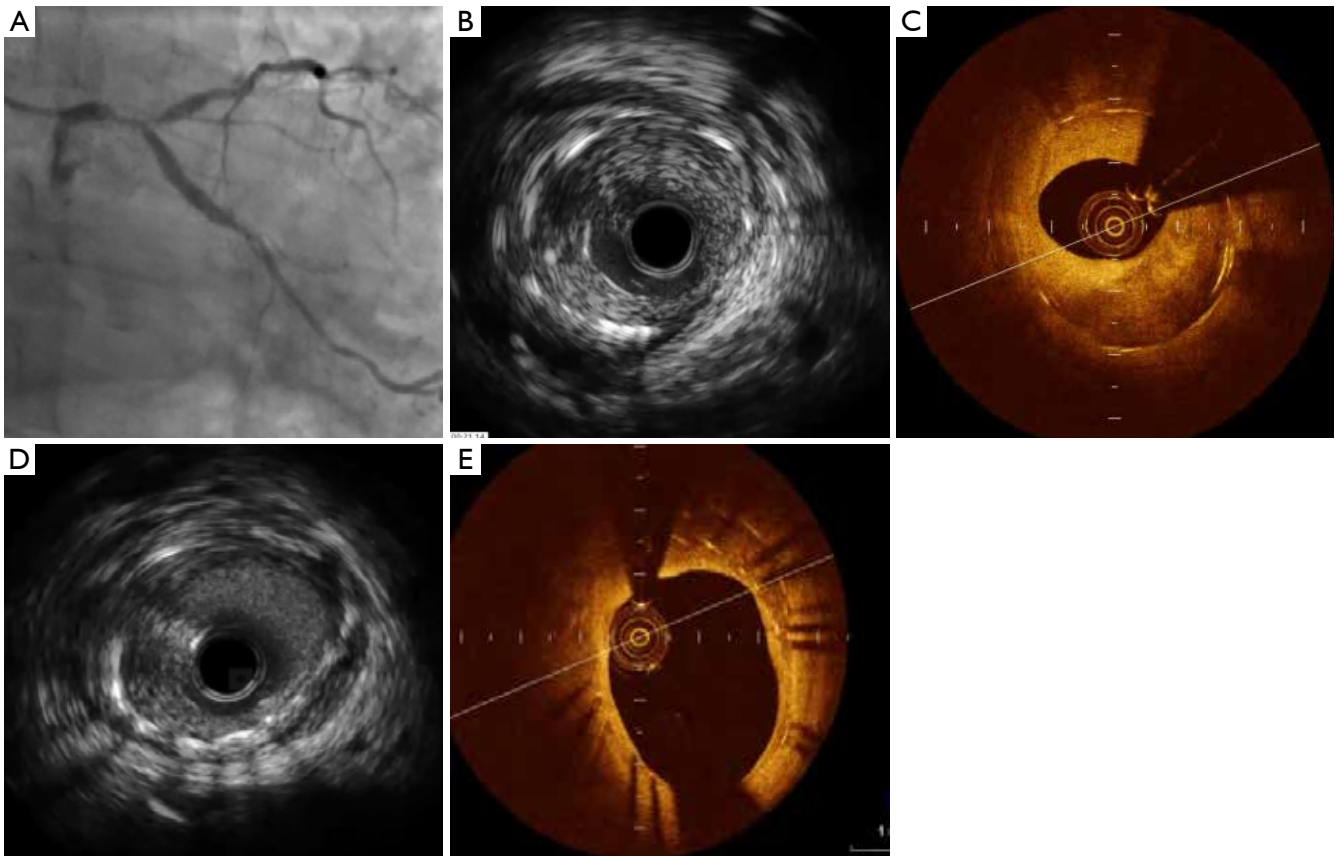

Figure 1 Common presentations of in-stent restenosis by IVUS and CTO. (A) Coronary angiogram shows LM instent restenosis, previously a culottes two stents technique was performed for left main bifurcation lesions; (B) IVUS shows instent tissue growth; (C) OCT shows two layers of stents and homogenous instent fibrosis lesion; (D) IVUS shows that two layer stents are not clearly visible; (E) OCT shows tissue growth between the two layers of stents. LM, left main; IVUS, intravascular ultrasound; OCT, optical coherent tomography.

measurements for lesion length and lumen size, but OCT is being shown in studies to be more accurate. Intravascular ultrasound (IVUS) is a useful technique to evaluate the extent and distribution of the neointima tissue within the stented segment but is limited to visualize its complex tissue structure as can be documented by histopathology (1,23). Both technologies are analogues as they send out energy waves, OCT uses light and IVUS emits sound waves into the vessel wall and that energy is sent back to the catheter to reconstruct an image, the wavelength of light is much shorter and much faster than sound waves. For this reason, the OCT is able to produce a resolution 10 times greater than IVUS and is able to show much more information. OCT allows us to determine vessel sizing, stent under-expansion, dissection, thrombus, and gives us a good look at intermediate lesions, which on coronary angiography sometimes are hard to determine.

FD-OCT generates similar reference lumen dimensions but higher degrees of disease severity and NIH, as well as better detection of malapposition and tissue prolapsed compared with IVUS (*Figure 1*). First-generation TD-OCT was associated with smaller reference vessel dimensions compared with IVUS (24). However, an advantage of IVUS is its penetration of 4–8 mm inside the vessel wall. The light-based OCT technology can only penetrate about 2–3 mm. As well as IVUS superior role in contrast limitations and to assess aorto-ostial lesions. The resolution of OCT is far better than IVUS for determining the vessel's luminal diameter and cross-sectional area. The ability of OCT to provide more detailed visualization of intrastent tissue opens new avenues for tissue characterization and permits establishment of new classification systems for ISR. Moreover, OCT-derived FCT is a good discriminator between ruptured plaque and nonruptured TCFA, while

IVUS-derived plaque burden and lumen area had good performance in discriminating RCP from RNCP and TCFA (25). The high-resolution imaging technique is able to evaluate the hyperplastic tissue, demonstrating variation in structure, backscatter and composition (13) that is missed by IVUS in the past (26).

Future of intracoronary imaging

OCT has become a key intracoronary imaging modality capable of overtaking some of the limitations of angiography and intravascular ultrasound. OCT's imaging with high resolution has given unique insight into not only atherosccl erotic plaque, but also to understanding of tissue responses underlying stent implantation. Further developments with faster OCT pullback speeds will further simplify the procedural requirements and eventually eliminate the need for proximal vessel balloon occlusion during image acquisition. The future developments in OCT technology will see this unique imaging modality become a key player in both the clinical and research arena for the interventional cardiologist. Firstly, an area requiring further exploration, includes widening the clinical indications; for example settings of increased neointima (NI) formation, such as pulmonary hypertension (27), or post-transplantation vasculopathy. Secondly, technological advances currently under investigation are expected to yield improved imaging times and image quality for intravascular OCT. Moreover, the use of various macrophage or other cellular targeting agents labeled with fluorophore, such as annexin A5 and other compounds, may allow better characterization of fibrous cap characteristics using hybrid optical systems (28). However, routine clinical use of OCT will require further clinical trials to validate the technology, establish standard definitions/measurements, and to test its safety and utility in improving clinical outcomes.

Conclusions

Although IVUS is an appropriate choice for assessment of ISR post PCI, IVUS faces certain limitations when comparing the images to OCT; which is able to produce images with higher definition and therefore show more detail. With this evidence, the physician is able to gain a better understanding of the pattern and mechanism of the in-stent restenotic lesions. Moreover, any physician who uses IVUS at the present time has no problem placing the OCT Dragonfly catheter (St. Jude Medical). It's very small, 2.7 French at the tip, and is very flexible. It is easy to move around curves and significant angulation. Placing the device is not a problem for any interventional cardiologist. Only learning curve is with image interpretation. Interventionalists have to learn how to interpret edge dissection, stent malapposition, vessel sizing, and identify different types of plaque. Although OCT is able to identify differential patterns of restenotic tissue after stenting. This information is helpful in understanding the mechanism of stent restenosis and is useful in further studying of the ISR in the future.

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Footnote

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In-stent restenosis and thrombosis due to metal hypersensitivity: implications for Kounis syndrome

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The metal platforms used in interventional cardiology can prevent the late luminal enlargement and induce advantageous vascular remodeling, but have failed to prevent restenosis which remains a problem due to neointimal hyperplasia. Therefore, the first and the second generation drug-eluting stents have been developed in an effort to prevent vessel restenosis. Indeed, drug-eluting stents have significantly reduced in-stent restenosis and target lesion revascularization rates compared with the bare metal stents, but a very dangerous and lethal side effect has emerged with these stents that is acute, late and especially very late stent thrombosis. The thrombus formation inside the stent lumen is the result of platelet adhesion, platelet activation by activating factors that is followed by platelet aggregation (1). This occurs because stented regions constitute an ideal substrate for foreign body reaction due to endothelial damage and dysfunction, hemorheologic changes and turbulence as well as platelet dysfunction, coagulation and fibrinolytic disturbances, at least until re-endothelialization will have been completed (2). Several important papers have been published concerning hypersensitivity toward metallic stent failure such as restenosis-thrombosis, with their authors urging for further studies to be carried out in an effort to prevent, diagnose and treat such dangerous complications. Indeed, in a recent report (3) concerning atopic patient sensitized to nickel, in-scaffold thrombosis had occurred at the mid segment of the absorb bioresorbable vascular scaffold (Abbott Vascular, Santa Clara, California, USA) implanted in-ZES (Resolute Integrity zotarolimus-eluting stent, Medtronic, Santa Rosa, California, USA) for in-stent restenosis. Furthermore, reports that have been published recently have raised important questions about the pathophysiology of allergy-associated in-stent restenosis and thrombosis, as well as their prediction, prevention and treatment (4). The general plea, therefore, for efforts to prevent hypersensitivity-associated complications and especially stent restenosis-thrombosis should take into account the followings:

(I) The factors for stent restenosis include (5) stent underexpansion, overexpansion, malapposion, vessel tortuosity, calcification, total occlusion drug resistance, uncontrolled hypertension, diabetes, insulin resistance, genetic factors, such as the PIA polymorphism of glycoprotein IIIa, insertion/deletion polymorphism, plasma activity of angiotensin I-converting enzyme and allergy to stent components. These causes should be searched and be considered before any stent insertion;

(II) In susceptible patients following the stent implantation, blood-implant interactions are taken place and lead to complement system activation. This triggers the body's innate immune system, which

leads to white blood cells infiltration (primarily neutrophils and monocytes) at the implantation site and to tissue edema. Following this, collagen fibers are deposited around the implant to form a dense, acellular, fibrous capsule that induces rapidly progressive neointimal hyperplasia and in-implant restenosis (6). On a molecular level, acute inflammation takes place with increased levels of pro-inflammatory cytokines (7). Such cytokines are excreted by neutrophils and macrophages and in the case of hypersensitivity by eosinophils and mast cells that constitute the pathophysiological basis of Kounis hypersensitivity-associated coronary syndrome (8);

(III) The zotarolimus stent platform is made of stainless steel that is an alloy of nickel, chromium, titanium, manganese, and molybdenum. Furthermore, the so-called "cobalt chromium" and "platinum-chromium" stents have platforms that contain nickel and other metals and seems that these terms are inappropriate. The information we have obtained from the manufacturers indicates that the alloy composition of zotarolimus stent is 35% nickel, 20% chromium, 10% manganese and 35% cobalt and of everolimus stent is 55% cobalt, 20% chromium, 15% tungsten, and 10% nickel. Indeed, in the US nickel, chromium and cobalt induce allergic skin reactions in about 14%, 4%, and 9% while in Europe in about 20%, 4%, and 7% respectively (9);

(IV) The metallic scaffolds used in the bare metal and drug eluting stents counteract the main event that can occur and progress in a set frame of time, namely coronary artery restenosis. Since the majority of restenotic events occur within the first 6 months (10) and the most feared thrombotic complications of the permanent stents occur very late (beyond 1 year after implantation), the question which arises is: has any clear function a permanent stent prosthesis to be in place beyond this initial period? The bioresorbable and bioabsorbable stents have a lot advantages over the previous types of stents but have also many limitations. Recent reports have shown that bioresorbable scaffold components can induce local foreign body reactions and hypersensitivity reactions (11);

(V) Metals are ubiquitous in the surrounding environment because they are normally present in water, food and generally in the earth's crust and individuals could be easily sensitized to these. Metals can release metal ions while are embedded in the arterial orifice and are directly or indirectly in touch with the blood stream. Such anions can react with high affinity and low affinity IgE antibody receptors FCγRI, FCγRII, FCεRI and FCεRII, on platelet surface and trigger the Kounis syndrome (8). The Kounis hypersensitivity-associated acute coronary syndrome is manifesting as coronary artery spasm that can progress to myocardial damage, as acute myocardial infarction following plaque erosion of rupture and as stent thrombosis with thrombus infiltrated by eosinophils and/or mast cells. Fatal cases of Kounis syndrome have been already reported (12,13).

In order to prevent and treat all above serious consequences, it has been suggested that the FDA recommendations for coronary stent implantation should be applied to all kinds of stents including bioresorbable scaffolds (11). In order to predict and prevent such dangerous consequences these recommendations which emphasize clearly that careful history of hypersensitivity reactions with monitoring of inflammatory mediators as well as lymphocyte transformation studies to detect material hypersensitivity, before implantation, should be always considered (14).

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Contemporary drug-eluting stents and companion polymers: durable is not synonymous with harm

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On September 3, 2006 during the annual European Society of Cardiology meeting in Barcelona, two independent meta-analyses revealed for the first time that the superior efficacy of early-generation drug-eluting stents (DESs) as compared with bare metal stents (BMSs) came at the expense of increased mortality due to very late stent thrombosis (ST) (1). Subsequently, the main DESs components (supportive backbones, polymer coatings or carriers and antiproliferative drugs) underwent a systematic investigation to rule-out the underlying reasons of early-generation DESs failure. Preclinical and necropsy studies showed that, among other factors, the methacrylate-based polymers, responsible for drug-release modulation in a large part of early-generation DESs, persisted in the implanted vessel wall long after their function was duly served (2). This kind of durable carriers caused chronic inflammatory response and delayed arterial healing at the stented site, which have been associated with neoatherosclerosis, restenosis and ST over the long term (3).

Ten years later, contemporary DESs have definitely proved to be safer than preceding coronary prostheses. This achievement arises from the iterations to which DES technology has been subject during this interval (4). In this scenario, the development of coronary implants with transient components (either polymers or backbones) has attracted considerable interest. Currently, biodegradable-polymer DESs and fully bioresorbable DESs are promoted as valuable alternative to durable-polymer metallic DESs.

The peculiarity of biodegradable-polymer DESs is that once the antirestenotic drug is eluted and the carrier completely degraded, the stent platform left behind is comparable to that of a BMS. By virtue of the temporary nature of the carrier, these modern devices should reduce the thrombotic risk and the need for long-term antiplatelet therapy, two intrinsic disadvantages of early-generation DESs (5). Although previous investigations displayed that stents eluting antirestenotic drugs from a biodegradable polymer have superior safety in comparison with early-generation DESs (6,7), the utility of these platforms against contemporary biocompatible durable-polymer DESs is not so easily discounted. At the opposite, biodegradable-polymer DESs showed a higher risk for ST out to 1 year as compared to the benchmark everolimus-eluting stent (EES) with a fluorinated durable-polymer coating (Xience; Abbott Vascular, Santa Clara, California, USA) (8). This latter platform appears the safest among contemporary DESs, notwithstanding the durable nature of both carrier and metallic frame (9).

Fully bioresorbable DESs aim at providing a temporary scaffold for the vessel until the elution process is completed and then self-degrade into inert breakdown products after about 3 years (10). In consideration of initial positive reports in highly selected patients populations, the everolimus-eluting bioresorbable vascular scaffold (Absorb/BVS, Abbott Vascular, Santa Clara, CA, USA) has been the first of such devices deserving CE-mark approval. Preclinical and imaging-based clinical studies reported a favorable behavior of this platform in terms of healing, vasomotricity and

late remodeling of the treated segment. However, recent investigations suggest a between 2- and 3-fold higher risk of ST out to 1-year follow-up with BVSs compared to the benchmark metallic EES with a durable fluoropolymer (11).

Notably, in the fall of 2015, the first DES with a bioresorbable polymer has received US Food and Drug Administration (FDA) approval for use in the United States. Similarly, the BVS represents the only fully bioresorbable DES approved for clinical use from FDA since July 2016. Nonetheless, the creeping skepticism surrounding these two new technologies depends on whether the temporary nature of either polymers or backbones contributes to improve their safety against contemporary DESs with biocompatible durable coatings and thinner metallic frames. Intuitively, the plethora of randomized studies comparing different platforms results largely underpowered to investigate rare outcomes, as in the case of ST. In this respect, an interesting report, which was published in *JACC Cardiovasc Interv* in 2016 has to be highlighted (12).

Kang and colleagues combined in the form of network meta-analysis direct and indirect evidence concerning the safety of early- and new-generation DESs, as well as of BMSs. The primary objective was to investigate the risk of definite/probable ST across a wide spectrum of DESs and BMSs out to 1-year follow-up. With a total of 110 randomized controlled trials and 111,088 patients available for risk estimation of primary outcome, the final messages of this study were as follows: at 1-year follow-up (I) contemporary DESs have a lower risk for ST as compared to earlier stent platforms (both DESs and BMSs); (II) among contemporary metallic DES platforms, the safety of those with a fluorinated coating is superior to that of DESs with biodegradable-polymer and thicker strut design and similar to that of biodegradable-polymer DESs with thinner metallic frames; (III) fully bioresorbable DESs have inferior safety as compared to fluoropolymer-based DESs and biodegradable-polymer DESs with thinner metallic frames. These results deserve an in-depth discussion.

First, the findings of a network meta-analysis should not be over-interpreted. Those who are familiar with this statistical method are aware that a low degree of inter-study variability and balanced nodes (each one reflecting the actual number of patients available for a certain comparison) are prerequisite for a credible estimation of treatment effects. These premises were not rigorously fulfilled in this report, especially in those comparisons involving biodegradable-polymer DESs with thinner metallic frames.

Second, the meta-analysis of Kang and co-workers remarks that the restraint of DES platforms and coatings within approximate categories (durable, biodegradable, bioresorbable etc.) appears more manufacturers-guided than scientifically-based. Indeed, the safety of contemporary durable-polymer DESs with fluorinated coatings cannot be assimilated to that of early durable-polymer DESs with metacrylate-based coatings. Similarly, the performance of biodegradable-polymer DESs cannot be handled as a "class effect". For example, the complete degradation of the polymer coating of the Nobori stent (Terumo, Tokyo, Japan), one of the first biodegradable-polymer DESs receiving CE-mark approval, occurs in 6 to 9 months and its metallic frame is based on a thicker-strut design (150 μm). In contrast, a recently marketed stent eluting sirolimus from a biodegradable coating (Orsiro; Biotronik, Bülach, Switzerland) has complete degradation of the carrier after 12 to 24 months and a thinner-strut design (60 μm). These two biodegradable-polymer DES platforms subtend a different thrombotic risk, as highlighted in the report from Kang and co-workers and in a recent randomized head-to-head comparison (13).

Third, Kang and co-workers reinforce the common concern that the thrombotic risk within 1 year after BVS implantation is higher than we have accustomed to with contemporary metallic DESs (14). The fact that the performance of current BVSs does not reflect initial enthusiastic expectations should not preclude further investigations of this technology. Researchers should define procedural protocols for proper selection and implantation specific to these devices, including a more liberal use of intracoronary imaging. Manufacturers should profit from the awareness of intrinsic limitations of this immature technology to pursue meaningful ameliorations, replicating the virtuous process, which guided the transition from early- to new-generation DESs.

Finally, although the study of Kang and co-workers focused on ST at 1-year follow-up, long-term data is needed to properly address the relative safety of different DESs. This aspect is of paramount importance for DES technologies with transient components for which the main benefit is expected to accrue time after implantation. For example, the direct comparison of biodegradable-polymer DES with thicker-strut design and fluoropolymer-based EESs revealed a similar safety out to 5-year follow-up (15). This may suggest a negligible impact of contemporary biocompatible durable coatings on long-term outcomes. In contrast, long-term safety data from large-scale clinical trials investigating fully bioresorbable DESs are not

expected before 2020 or 2021, leaving a sense of uncertainty regarding the possible late benefits of this technology.

As long as biodegradable-polymer DESs and fully bioresorbable DESs will undergo continuous technological improvements, comparative studies and long-term follow-up data are fundamental to disclose possible advantages of these technologies in comparison with contemporary high-performance metallic DESs. Until further data will be available, the fluoropolymer-based EES with its durable components represents an appropriate comparator for studies investigating the relative safety of different DES platforms for patients undergoing percutaneous revascularization because of obstructive disease of coronary arteries.

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Treatment of coronary in-stent restenosis—evidence for universal recommendation?

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Coronary artery disease, clinically evident as stable angina, acute coronary syndrome (ACS) or ischemic cardiomyopathy is the leading cause for mortality in Western population. With widespread use of coronary revascularization the rate of death from myocardial infarction (MI) has decreased, whereas mortality from heart failure is rising. Percutaneous coronary intervention (PCI) initially performed as "plain old balloon angioplasty" (POBA) has established standards over the last 25 years with the introduction of bare-metal stents (BMS), drug-eluting stents (DES), drug-coated balloon (DCB) and scaffolds with concomitant antiplatelet therapy (1,2). However, despite the introduction of these innovations, restenosis remains the Achilles' heel of any PCI. Traditionally, coronary restenosis is defined as an angiographically detected reduction of ≥50% of vessel diameter at the site of a previously treated segment or its edges. Several surrogate parameters, like late lumen loss (LLL), minimal lumen diameter (MLD), target lesion revascularization (TLR), and target vessel revascularization (TVR) were introduced to better describe the nature of restenosis. With POBA the rate of restenosis, mainly driven by recoil and proliferative remodelling, was up to 30%–60% at 6 months (3). BMS eliminated the issue of recoil but induced neointimal hyperplasia, and the term in-stent restenosis in 16%–44% of cases (4). Detailed analyses revealed that restenosis after placement of BMS occurred in 42%, 21%, 30%, and in 7% as focal, diffuse, proliferative and total, respectively (5). The introduction of first-generation DES has substantially reduced both angiographic and clinical appearance of restenosis both in randomized clinical trials and in large-scale registries over 4 years (6). Second-generation DES are typically coated with new polymers and drugs resulting in fewer side-branch occlusion, less periprocedural infarction and restenosis rates (7). However, with widespread use of newer generation DES in complex lesions and "off-label" use rates of restenosis are still high at 12% (8). In-stent restenosis has traditionally been considered benign with recurrent symptoms but without any prognostic impact. However, several analyses revealed that 30%–60% of patients develop ACS, predominantly with unstable angina and in 5% with ST-elevation myocardial infarction (STEMI) (9). The treatment strategy for restenosis has changed over 25 years and included conventional POBA, cutting or scoring balloon, BMS, vascular brachytherapy, same DES ("homo-DES"), different DES ("hetero-DES"), drug-eluting balloon (DEB) and even bypass surgery. POBA, with compliant or non-compliant balloons, was one of the first strategies used in patients suffering from restenosis. Despite reasonable outcomes in "focal" restenosis, long-term results of patients with diffuse pattern were less favourable. The use of a cutting balloon preventing slippage, ensured higher luminal gain and led to better clinical outcomes. The use of BMS for BMS restenosis ("sandwich technique") was supported by the fact of larger acute luminal gain. In RIBS I, comparing balloon angioplasty with BMS implantation for BMS restenosis, patients revealed better acute angiographic results as well as better long-term clinical

outcomes in the subset of large vessels (>3 mm) and in the setting of restenosis affecting the stent edge (10). Clinical and angiographic results with DES for BMS restenosis were superior to those with balloon angioplasty, BMS or brachytherapy in several randomized trials (11). Treatment of in-stent restenosis after DES is very challenging and is gaining momentum with the widespread use of DES in primary stenting. Initial experience revealed that the use of DES is associated with better outcomes than other techniques (12). The question whether the same stent or another stent will be superior was addressed in the ISAR-DESIRE 2 trial which not only confirmed that repeat DES implantation is safe for DES restenosis up to 1 year but also showed that using either SES or PES for DES restenosis has similar anti-restenotic efficacy (13). More recently, the concept of DCB for restenosis have been proven to be very effective in patients with both BMS as well as DES in-stent restenosis (14) with the advantage of avoiding multiple stent layers; DCB are noninferior to paclitaxel-DES and both DCB and paclitaxel-DES are superior to POBA (15).

Recently, the largest Bayesian network meta-analysis including 2,059 patients compared the effects of POBA, DES and DEB for the treatment of in-stent restenosis (BMS 42% and DES 58%) and revealed that surrogate endpoint parameter TLR was lowest in DEB and DES as compared to POBA without any significant difference between DES and DEB and without any significant difference between all three groups according to clinical endpoints for MI and mortality. On angiographic outcome analysis, DEB or DES also showed a significantly lower risk of binary restenosis at 6- to 9-month follow-up angiography than POBA (16).

Current literature reveals superiority of DES and DEB for the treatment of BMS in-stent restenosis, which is pointed out in the Guidelines by a recommendation, Class I, Level of Evidence A (1,2). However, in the future, the main issue will be how to deal with DES in-stent restenosis considering a penetration rate of 90%. The main limitation of trials addressing in-stent restenosis is the solely angiographic view on restenosis without a holistic perspective on this vexing problem. Underlying mechanisms of restenosis are complex and can be divided into lesion-specific, procedure-related and patient-related. There is evidence that high-risk patients (e.g., diabetics, end-stage renal failure, previous bypass graft surgery, arterial hypertension) ware prone to higher restenosis rates and that these factors should be taken into considerations when choosing a revascularization strategy (1,2). Regardless of treatment strategy these modifiable patient-related factors should be considered in the context of secondary prevention. Similarly, there is evidence that procedure-related factors are of utmost importance to avoid restenosis and stent thrombosis. Also anatomic features are important with increased likelihood of re-stenosis in the setting of saphenous vein graft disease, small vessel diameter, long lesions, bifurcation lesions, left main lesions and chronic total occlusion. Evaluated methods for prevention of in-stent restenosis and its recurrence consist of optimized implantation techniques, better stent design, improvements in reservoir design, development of bioabsorbable polymers, polymer-free drug delivery, fully biodegradable stents, stents eluting new pharmaceutical agents, and finally, gene therapy and prohealing therapy. Technical failure of the implantation with small post-procedural diameter, higher residual percent diameter stenosis, underexpansion, overexpansion, stent fracture, non-uniform distribution of stent struts and malapposition have all been associated with DES restenosis. Such shortcoming can be reduced with use of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) for procedure optimization (17). Advanced techniques such as fractional flow reserve (FFR), IVUS and OCT have greatly improved the ability to visualize re-stenosis and make quantitative assessments of functional relevance, neointimal thickness, neointimal volume, and MLD. Conversely, as the natural history of "asymptomatic" patients with angiographic restenosis with no ischemia is favorable (18), the so-called "oculostenotic reflex" should be avoided whenever possible. However, analysis of data on treatment strategies of in-stent restenoses with DES is characterized by small studies having variable results with "old-fashion" stents for first generation DES. To date, there have been no reports on the use of newer-generation DES for DES-restenosis. Subanalysis of RIBS III suggested that the use of second-generation DES was superior to first-generation DES, and that guidance with intracoronary imaging was associated with better long-term results (19,20). Recently, the RIBS V and RIBS IV trials reported superiority of DES for the treatment of BMS and DES restenosis as compared to DCB in terms of angiographic endpoints, but without a clear signal of clinical benefit over one specific DCB using iopromide as a hydrophilic spacer used in all comparing trials. It is important to note that any of these therapeutic strategies offer solutions for the failure of initially implanted opzimized stents. Thus, the treatment of restenosis is always associated with a natural delay of a success of the initial treatment. To optimize the dynamic process of restenosis treatment, there will be ongoing need

to conduct studies on restenoses therapy with adaptable innovations. Current evidence should always be challenged by newer strategies and revolutionary treatment strategies. Apart from stents and scaffolds it seems that better understanding of the biological nature of restenosis, specific drugs may be key to successful tackling of restenosis rather than placement of local devices such as stents. Whether drug delivery will be local or systemic needs to be shown in future trials, but regardless of any innovation and a motion towards personalized medicine an honest comparison to current standards remains the benchmark for new treatment to become standard.

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Treatment for in-stent restenosis: patient-specific decision rather than universal recommendation

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The development of the drug-eluting stent (DES) created a milestone in the field of percutaneous coronary intervention (PCI) by markedly reducing the rates of in-stent restenosis (ISR) compared to the bare metal stent (BMS). The development of a thinner strut and biocompatible or bioresorbable polymer coating in newer generation DES has enhanced the efficacy and safety of DES. However, along with the widespread use of this newer generation DES in most clinical conditions, including high-risk patients with more complicated lesion profiles, ISR has continued to be a major concern, even in the era of newer generation DES (1). The incidence of ISR ranges from 3% up to 20% of patients (1). The clinical importance of ISR should be further emphasized, since more than half of ISR patients present with acute coronary syndromes (ACS) such as unstable angina or acute myocardial infarction (1), and patients who have been treated for ISR consistently show higher rates of future adverse cardiovascular events compared to those without ISR (2). In this regards, decision regarding optimal treatment option for ISR lesion should be considered even in contemporary era of PCI using newer generation DES. In order to address this issue, our group recently published the first network meta-analysis which compared clinical and angiographic outcomes among DES, DEB, and plain old balloon angioplasty (POBA). As specifically discussed in the previous editorials (3-6), our group firstly presented the superior efficacy and safety of DEB and DES, compared with POBA, and comparable efficacy and safety between DEB and DES to treat BMS or DES ISR lesion. Although DEB and DES showed similar risk of MI, DEB tended to show lower risk of MI during follow-up period, compared with DES. Although the network meta-analysis by our group comprehensively summarized previous evidences from 11 randomized controlled trials (RCTs) with 2,059 patients with BMS or DES ISR, some unsolved issues are worth to be discussed.

First, it should be considered that there has been relatively scarce evidence which evaluated newer generation DES as treatment option for ISR. Current European Society of Cardiology/European Association for Cardiothoracic Surgery (ESC/EACTS) guidelines recommend drug-eluting balloon (DEB) and DES as class IA recommendations for the treatment of BMS or DES-ISR (7). However, most previous studies, which evaluated DEB as a treatment option for ISR, compared its safety and efficacy to first generation DES, which is no longer used in daily clinical practice (1,8-12). Our network meta-analysis also shared the common limitation. Among the included trials, 6 out of 7 RCTs which had a DES arm to treat ISR in the previous network meta-analysis, actually used old-fashioned 1st generation DES such as sirolimus-eluting or paclitaxel-eluting stents. Among the included RCTs, only the RIBS-V trial used 2nd generation

everolimus-eluting stent (Xience Prime, EES) which has been proved to be superior to 1st generation DES (13). In the RIBS-V trial, DES was comparable to DEB both in the rates of MI and TLR for BMS ISR (14).

After publication of our meta-analysis, RIBS IV trial (15), which randomly compared DEB versus EES in DES-ISR patients, firstly demonstrated the superior efficacy of EES group in terms of MACE (18.0% *vs.* 10.0%, HR 0.58, 95% CI, 0.35–0.98, P=0.042) and TVR (16.2% *vs.* 8.4%, HR 0.33, 95% CI, 0.14–0.79, P=0.035). The pooled analysis using RIBS V and RIBS IV trial population further strengthen the superior efficacy and safety of newer generation EES for treatment of BMS or DES ISR patients, compared with DEB (16). Furthermore, more recent network meta-analysis by Siontis *et al.* consistently showed that EES was the most effective treatment, compared with DEB, sirolimus-eluting stent, paclitaxel-coated stent, vascular brachytherapy, BMS, rotablation, or POBA (17). However, it should be noted that all these previous evidences which favored EES as best treatment option were derived from the only 2 RCTs (RIBS IV and V). Except EES, other types of newer generation DES, for example, bioresorbable polymer coated DES or drug-coated polymer free DES have never been tested in this clinical setting.

Second, although EES showed clear benefit over DEB in the previous 2 RCTs (RIBS IV and V) (14-16), and recent network meta-analysis incorporating these two RCTs (17), it should be noted that these two RCTs excluded several high-risk patients and lesion subsets such as acute MI, small vessel lesions (≤2.0 mm in diameter), long lesions (>30 mm in length), or ISR with thrombotic total occlusion. Therefore, there has been no further evidence for safety and efficacy of newer generation DES or DEB in patients with high-risk patients or lesional characteristics. Our group currently preparing the patient-level pooled analysis comparing the clinical outcomes between newer generation DES (including bioresorbable polymer coated DES) and DEB in all-comers ISR population. This study will more clarify the clinical outcomes after DES or DEB treatment in high-risk population with ISR.

Third, all the previous RCTs have never compared the incidence of bleeding and the impact of duration of dual antiplatelet therapy (DAPT). The optimal duration of DAPT to maximize clinical outcome after DEB angioplasty remains uncertain. Further RCTs might be warranted regarding this subject.

Since the DEB possesses a fundamental difference from DES implantation in ISR lesions, the treatment strategy for ISR should be individualized with careful assessment of the balance between the benefits and risks of additional DES implantation including the risk which inevitably following the maintenance of long-term DAPT, especially after DES implantation. Considering insufficient evidences and heterogeneous results across all the previous studies warranted "individualized approach" in deciding the treatment option for ISR lesion, rather than universal recommendation of DES or DEB for all the ISR patients.

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Footnote

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In-stent restenosis: local drug delivery with a stent or balloon?

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The emergence of drug-eluting stents (DES) has led to a significant reduction in in-stent restenosis (ISR) rates, one of the major limitations of bare-metal stents (BMS) (1). Consequently DES have become the preferred strategy in contemporary percutaneous coronary intervention (PCI) (2). Although rates of ISR are at historical low levels, optimal management remains an important issue as PCI for ISR is associated with a worse prognosis than *de novo* coronary interventions (3).

In this issue of *JACC Cardiovasc Interv*, Lee *et al*. attempt to identify the optimal management of ISR through their Bayesian network meta-analysis comparing local drug delivery, either with a stent or a balloon, and plain balloon angioplasty (POBA) for the treatment of ISR (4). Other treatments for ISR such as vascular brachytherapy, cutting balloon and rotational atherectomy were not included in this analysis.

An advantage of a network analysis is that it allows the authors to compare the effectiveness of DES, drug-eluting balloon (DEB) and POBA with each other, although only one trial compared the three arms directly. A traditional meta-analysis would not have allowed adequate assessment of the comparative effectiveness of the three treatment options. Further, it allows the treatments to be ranked in order of effectiveness.

In this analysis, 11 trials with 2,059 patients were included with a heterogenous population of ISR of both BMS and DES. The primary endpoint was target lesion revascularisation (TLR), which emphasises a clinical rather than angiographic endpoint. This is relevant as the individual randomised controlled trials were not powered to detect a clinical difference.

Several findings have arisen from this meta-analysis. Firstly, at 6-month follow-up, both DES and DEB were associated with lower risk of TLR than POBA. Compared to POBA, DEB treatment had an odds ratio of 0.22 (95% credible interval of 0.10-0.42) and DES treatment had an odds ratio of 0.24 (credible interval of 0.11-0.47). Second, when compared against each other the risk of TLR was similar between DEB and DES (odds ratio 0.92, 95% credible interval 0.43-1.9). Third, there was no significant difference between treatment arms in mortality or myocardial infarction, though both DES and DEB were superior to POBA in reducing major adverse cardiovascular events. Fourthly, DEB and DES were equivalent but superior to POBA in reducing the risk of binary stenosis (≥50% stenosis) on angiography follow-up at 6-9 months. Lastly, DEB has the highest probability of being ranked as the treatment of choice for ISR.

The results of this meta-analysis reinforce the latest international guidelines which give DES and DEB (without differentiation) a class I (level of evidence A) recommendation for the treatment of ISR (2). We believe the suggestion that DEB technology may be the preferred treatment option in ISR is premature. A network analysis can result in a coherent ranking of treatment strategies, however in Lee's analysis DEB and DES treatment could not be differentiated, even if DEB had a higher probability of being "ranked first".

We believe the technology of DEB should be named drug coated-balloon (DCB) since the balloons are not

eluting drug, rather, they are coated with drug and the mechanism of action is different to DES. Theoretically the use of DEB technology in the treatment of ISR is appealing as an extra layer of stent is avoided and dual antiplatelet duration may be shorter.

Second generation DES are the gold standard of contemporary PCI (5). The analysis included first generation DES like TAXUS that are inferior to second generation DES as was demonstrated in Ribs IV, a randomised trial showing superior clinical and angiographic outcomes in patients with ISR treated with everolimus-eluting stents compared to DEB (6). Two contemporary studies involving second-generation stents were not included in this analysis (7,8). Late catchup at 18 months was seen with the paclitaxel-coated balloon (8).

A recent published comprehensive network meta-analysis included the RIBS IV trial as well as therapies for ISR (9). It showed that POBA, vascular brachytherapy, rotational atherectomy and BMS were not suitable treatments for ISR. Furthermore, its conclusion was consistent recommending either DES or DEB for the management of ISR. However, these meta analyses are an exercise in statistics for a complex biological process mixing technologies and mechanistic situations. A heterogeneity array of studies may point to a wrong conclusion.

In summary, Lee's analysis adds evidence supporting the use of either DEB or DES for the management of ISR from previously inserted bare-metal or DES. With the thinner struts of second generation DES, most patients can be treated with a second DES; the DEB probably falls short. The BVS (bioabsorbable vascular stent) offers promise with the capability of eliminating the stent layer. We must await needed randomised trials to ascertain the optimal management of ISR.

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Network meta-analyses on in-stent restenosis treatment: dealing with complexity to clarify efficacy and safety

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Major advances have occurred during the last decade in the prevention of in-stent restenosis (ISR). Notably, drug-eluting stents (DES) drastically reduced the incidence of ISR as compared with that seen with bare-metal stents (BMS) (1). However, DES-ISR still occurs especially when these devices are used in adverse clinical and anatomic scenarios (1). In addition, BMS are frequently used in selected patient subsets, including those unable to maintain a prolonged dual antiplatelet regimen and those at high bleeding risk (1). Therefore, nowadays treatment of ISR still represents a real challenge in every day clinical practice (2-4). Although the acute results obtained by repeated interventions are largely favorable the long-term outcome of these patients is frequently shadowed by clinical recurrences (2-4). Of concern, the underlying anatomic substrate of DES-ISR appears to be particularly complex and prone to recurrent ISR (2). Furthermore, recent evidence suggest that ISR presentation, formerly considered a benign phenomenon, is frequently associated with unstable symptoms, including a significant number of patients fulfilling current criteria for myocardial infarction (2). Many randomized clinical trials have compared different therapeutic strategies in patients with ISR (2-4). These include plain balloon angioplasty (BA), cutting balloon angioplasty, BMS, ablative devices, brachytherapy, DES and drug-coated balloons (DCB). Recent clinical practice guidelines suggest that both DES and DCB are effective (recommendation/evidence IA) for patients suffering from ISR (5). Nevertheless, the therapy of choice for these patients currently remains unsettled. Indeed, most randomized trials used surrogate late angiographic parameters (including percent diameter stenosis, binary restenosis, minimal lumen diameter and late lumen loss) as a measure of efficacy (2-4). This was a reasonable strategy to ensure an adequate enrollment of the required number of patients presenting with this relatively rare condition within a short time frame. Indeed, these trials provided major evidence on relative efficacy of these interventions. However, most randomized studies eventually enrolled a limited number of patients and, therefore, additional evidence is still warranted in order to establish the relative clinical efficacy and safety of these competing interventions.

Rigorous, methodologically sound, and carefully-performed network meta-analyses are powered to unravel additional information from the existing studies further informing the clinical decision-making process.

Current study

Very recently Lee *et al*. (6) performed an interesting Bayesian network meta-analysis of all available randomized clinical trials comparing BA, DES and DCB in patients with ISR. Eventually, a total of 2,059 patients from 11 randomized clinical trials were included in the final analysis [808 patients (39%) treated with DES, 694 (34%) with DCB, and 557 (27%) with BA]. Three trials compared DES with DCB, four compared DCB with BA and one study, with three arms, compared DES with DCB and BA. Four trials exclusively enrolled patients with BMS-ISR, five exclusively patients with DES-ISR whereas two studies included patients with either DES-ISR or BMS-ISR. Actually, many of the randomized trials included in this

meta-analysis were part of systematic ongoing multicentric strategies addressing the treatment of patients with ISR [the PEPCAD (three trials), ISAR-DESIRE (two trials) and RIBS (two trials) programs] (6).

As expected, trials that used DES obtained larger minimal lumen diameter and lower residual diameter stenosis immediately after the procedure than the corresponding DCB and BA arms. The primary outcome measure of this study was the rate of target lesion revascularization (TLR) at late follow-up [presented as OR with 95% credible intervals (CrI)] although target vessel revascularization was considered when TLR results were not available. Using a random-effects model the risk of TLR at late follow-up was significantly lower in patients treated with DCB (OR 0.22, 95% CrI: 0.1-0.42) or DES (OR 0.24, 95% CrI: 0.11-0.47) than in those treated with BA. However, the risk of TLR was similar for DCB and DES. Likewise, the risk of binary angiographic restenosis was significantly lower in the DCB and DES groups than in the BA group. Interestingly, the risk of myocardial infarction and all-cause mortality was lowest in patients treated with DCB. Finally, the risk of major adverse events—mainly driven by TLR—was also lower in the DCB and DES groups compared with the BA group. In addition, the probability of being ranked as the best treatment regarding TLR was 59.9% for DCB followed by 40.1% for DES. Alternatively, the probability of being ranked as the best therapy considering freedom from myocardial infarction was 63% for DCB followed by 35.3% for BA. Authors concluded that DCB and DES are markedly better than BA in preventing TLR. In addition, of the two active drug-therapies, DCB showed a trend to a lower risk of myocardial infarction compared with DES.

This represents a methodologically sound, comprehensive, network meta-analysis comparing safety and efficacy of BA, DES and DCB in patients with ISR. Some issues however, deserve further discussion. The results were consistent in different sensitivity analyses that included: (I) a fixed-effects model for statistical assessment, (II) the analysis of events occurring during the first year only (instead of those seen at last follow-up available), (III) including only trials with DES-ISR or BMS-ISR, and (IV) accounting for the different duration of dual antiplatelet therapy in the diverse trials using independent analyses. Reassuringly, the pooled effect estimates provided by direct and indirect comparisons were also very consistent.

The comparison of DCB with DES regarding myocardial infraction showed a trend in favour of the DCB treatment (OR 2.0, 95% CrI: 0.89-6.1), whereas the comparison of DCB with BA regarding all caused mortality showed a trend in favour of DCB (OR 2.5, 95% CrI: 0.86-7.7). Although this would suggest that treatment with DES might be associated with a higher incidence of procedural related myocardial infarction (likely resulting from side-branch occlusion), stent thrombosis or actually occur during the treatment of recurrent ISR, detailed results on the cause and timing of myocardial infarction were not available. In fact, the risk of stent thrombosis was no different in the three treatment groups. Notably, the long-term follow-up of two recent randomized trials comparing DCB with DES also suggested a safety advantage with the use of DCB (7-9). Nevertheless, further studies, with longer clinical follow-up, are warranted to definitively address this intriguing possibility.

On the other hand, before extrapolating these results to everyday clinical practice we should keep in mind that most randomized clinical trials exclude very complex ISR cases (small vessels, total occlusions, very diffuse lesions, left main stent location) and, as a result, the generalizability of current findings to these complex anatomic scenarios is probably not justified (2-4).

Finally, of the included trials, only RIBS V (10) had an arm treated with a second-generation everolimus eluting stent whereas the remaining trials included in this meta-analysis used first-generation DES. This is important as recent studies strongly suggest the value of second-generation DES in this challenging setting (2,10,11).

Incremental value of "network" meta-analysis

The publication of meta-analyses has increased exponentially in recent years. Systematic reviews examining the comparative effectiveness among competing interventions take into account all available evidence. This primarily stems from head to head comparison studies that provide direct evidence. However, the number of head to head studies tends to be limited, especially when multiple competing interventions are available. Therefore, there is also a major need to ascertain the evidence resulting from indirect comparisons of each intervention against a common comparator (12-15). This indirect evidence complements that provided by the direct comparisons but its analysis is challenging and requires a rigorous methodology to ensure validity. These indirect comparisons rely on several assumptions and may suffer from potential biases (12-15). The risk of bias in pairwise comparisons is well known and different tools are available to address its effects and

potential implications. However, the potential risk of bias is greater and more elusive when the evidence is gathered from multiple direct and indirect comparisons of competing interventions (12-13).

Recently, an extension of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement focussing precisely on the methodological aspects of the "network" meta-analysis, has been published (12). A modified 32-item PRISMA extension check list was developed to address all relevant issues that should be reported in network meta-analysis. A key element is the "network graph" that consists of nodes (points representing the competing interventions) and edges (lines connecting the nodes that have been directly compared). Sizes of nodes and thickness of edges illustrate the number of patients and studies analyzed and, therefore, visually depict the amount of available evidence (12). The meaning and implications of the geometry of the resulting network graph should be discussed and clarified. Sometimes lumping of interventions is required. However, lumping requires a clear rationale and should only include interventions that are closely related and provide similar treatment effects. Inconsistency addresses the problem of differences between the treatment effects provided by direct and indirect comparisons. Poorly connected networks depend excessively on indirect comparisons and are less reliable than networks where most treatments have been compared against each other therefore increasing the strength of the generated evidence (12).

Results of relevant studies should be described using a tabulated presentation of relevant baseline characteristics. Importantly, the PICOs (Population, Intervention, Comparators, Outcome) criteria must be observed in the presentation of the results. These baseline characteristics are potential effect modifiers. Notably, a balanced distribution of most relevant potential effect modifiers increases the plausibility of obtaining reliable findings from indirect comparisons. Transitivity refers to the existence of comparable distribution of patient characteristics across the studies. When treatment networks contain closed loops of interventions it is possible to analyze the agreement between direct and indirect estimates of intervention effects. Forest plot summarizing treatment effects should be presented in a clear and comprehensive manner (12).

Network meta-analyses may be performed with a Bayesian (assuming an expected prior probability distribution) or frequentist approach. Bayesian approaches are commonly utilized as they ensure more flexibility of the statistical models. Carefully constructed Bayesian models may address the problem of low events rates, but analysis of studies with a low event rate should be interpreted with caution (12-15).

Finally, network meta-analyses provide the attractive additional feature to readily summarize the available evidence, namely relative rankings on effectiveness among the competing interventions. In general, these rankings should be only offered as secondary outcome measures. The central stage should be reserved to the actual effects estimates with the corresponding 95% confidence or credible intervals for the primary outcome measure. Last but not least, a general interpretation of the results in the context of prior evidence and the implications for future research should be provided in network meta-analyses (12-15).

A careful scrutiny of the elegant study of Lee *et al*. (6) unravels a robust methodology with detailed description of most of the relevant methodological issues described above even though the study was published months before the extended statement of the PRISMA recommendations (12).

Too many meta-analyses on ISR?

A large number of previous meta-analyses has focused on ISR treatment (*Table 1*) (6,15-33). Some of them were very early studies whereas other concentrated in evaluating selected therapies. Some initial meta-analyses were performed to gain further insights on the role of brachytherapy compared with conventional interventions. Other meta-analyses concentrated in assessing the results of first-generation DES. Most recent analyses tried to elucidate the relative value of DCB (*Table 1*). Anyhow, this would appear to be an excessive number of meta-analyses and, in fact, some of them represent nearly simultaneous analyses of the same trials, therefore yielding redundant results. Actually, any novel late breaking clinical trial provides the temptation for performing a new meta-analysis. In general, this temptation should be resisted unless the information provided by the new meta-analysis is expected to be of real value to advance the field. Otherwise, planning a brand new randomized clinical trial should be preferred to address gaps in knowledge. Notably, "patient-level" meta-analyses allow for additional insights yet they demand much work requiring true collaboration among different investigators and, unfortunately, they are scarce. Before a meta-analysis is performed the rationale of the review should be clarified in the context of what is already known. Overall, a strong suppression of neointimal hyperplasia proved to be required to prevent ISR recurrences (6,15-33). Indeed, early studies confirmed the superiority of brachytherapy over

Table 1 Meta-analyses on in-stent restenosis treatment

Author	Date	Patients/ trials	Network meta-analysis	Interventions	1ry end-point	Main result (Better > Worse)	OR (95% CI)
Radke *et al*. (16)	2003	3,012/28	–	VBT *vs.* BA	MACE	VBT > BA	–37.7±4.0*
Costantini *et al*. (17)	2003	133	–	VBT *vs.* Placebo	BR	VBT > Placebo	0.06 (0.02-0.17) (+)
Uchida *et al*. (18)	2006	1,310/5	–	VBT *vs.* Placebo	MACE	VBT > Placebo	0.19 (0.09-0.29)
Dibra *et al*. (19)	2007	1,230/4	–	DES *vs.* VBT	TLR	DES > VBT	0.35 (0.25-0.49)
Oliver *et al*. (20)	2008	3,103/14	–	DES *vs.* VBT *vs.* BA	MACE	DES = VBT > BA	0.72 (0.61-0.85)
Alfonso *et al*. (21)	2008	300/2	–	DES *vs.* BMS	BR	DES > BMS	0.11 (0.03-0.36) (+)
Lu *et al*. (22)	2011	1,942/12	–	DES *vs.* VBT	TVR	DES > VBT	0.44 (0.23-0.81)
Yu *et al*. (23)	2013	349/5	–	DCB *vs.* DES/BA	TLR	DCB > DES/BA	0.17 (0.07-0.38)
Navarese *et al*. (24)	2013	399/4	–	DCB *vs.* DES/BA	TLR	DCB > DES/BA	0.20 (0.11-0.36)
Indermuehle *et al*. (25)	2013	801/5	–	DCB *vs.* PES/BA	MACE	DCB > PES/BA	0.46 (0.31-0.70)
Sun *et al*. (26)	2014	6,330/28	–	DES *vs.* Other	TLR	DES > BMS > Other	0.46 (0.34-0.62)
Vyas *et al*. (27)	2014	1,680/10	–	SameDES *vs.* DifDES	TLR	DifDES > SameDES	0.73 (0.45-0.93)
Piccolo *et al*. (28)	2014	1,586/7	Yes	DCB *vs.* DES *vs.* BA	%DS	DCB = DES > BA	–17.7 (–25- –11)**
Mamuti *et al*. (29)	2014	864/5	–	DCB *vs.* DES/BA	MACE	DCB > DES > BA	0.49
Mamuti *et al*. (30)	2015	803/4	–	DCB *vs.* DES	MACE	DCB = DES	1.04
Li *et al*. (31)	2015	1,448/9	–	DCB *vs.* DES *vs.* BA	MACE	DCB = DES > BA	0.21 (0.13-0.33)
Benjo *et al*. (32)	2015	1,375/5	–	VBT *vs.* DES	TLR	DES > VBT	2.4 (1.5-3.6)
Siontis *et al*. (33)	2015	5,923/27	Yes	Multiple	%DS	EES > DCB > Other	–9 (–15.8- –2.2)**
Lee *et al*. (6)	2015	2,059/11	Yes	DCB *vs.* DES *vs.* BA	TLR	DCB = DES > BA	0.22 (0.10-0.42)

(+), Simple pooled analysis of randomized clinical trials. Other, more than 2 different interventions; *, Probability of MACE (in %); **, %DS, percent diameter stenosis. EES, everolimus eluting stent; DCB, drug coated balloon; VBT, vascular brachytherapy; TLR, target lesion revascularization; DES, drug eluting stent; MACE, mayor adverse cardiac events; DifDES, different (hetero) DES; SameDES, similar (homo) DES; TVR, target vessel revascularization.

classical mechanical strategies. More recently, the superior role of pharmacoactive interventions, namely DES and DCB, over isolated mechanical interventions, became established (*Table 1*).

As compared with most of these previous reports, the current study by Lee *et al.* (6) includes a larger number of recent trials and, more importantly, the Bayesian network approach selected allowed for adequate direct and indirect comparisons among the studied therapies. This provided important novel insights on safety and efficacy.

Very recently we collaborated in yet another network meta-analysis (33). This aimed to synthesize both direct and indirect evidence from relevant trials in patients with any type of ISR comparing a wide array of coronary interventions. Importantly, in this network meta-analysis the results from second-generation everolimus-DES (provided by the recent RIBS V and IV randomized clinical trials), could be included. A total of 27 trials including 5,923 patients were deemed eligible and the primary outcome measure was percent diameter stenosis at late follow-up. Everolimus-DES emerged as the most effective treatment for percent diameter stenosis, with a difference of –9.0% (95% CI: –15.8 to –2.2) *vs.* DCB, –9.4% (95% CI: –17.4 to –1.4) *vs.* sirolimus-DES, –10.2% (95% CI: –18.4 to –2.0) *vs.* paclitaxel-DES, –19.2% (95% CI: –28.2 to –10.4) *vs.* brachytherapy, –23.4% (95% CI: –36.2 to –10.8) *vs.* BMS, –24.2% (95% CI: –32.2 to –16.4) *vs.* BA, and –31.8% (95% CI: –44.8 to –18.6) *vs.* rotational atherectomy. Everolimus-DES were ranked as the most effective strategy and DCB were ranked as the second most effective treatment without significant differences from sirolimus-DES or paclitaxel-DES.

Conclusions

No clear consensus exists for the treatment of ISR and this explains the variability seen in real world clinical

practice. Randomized clinical trials and meta-analyses are consolidated as key elements of the evidence based medicine to inform clinical practice. Network meta-analyses are particularly useful to address evidence gaps by fully exploiting all the available scientific information. The lack of head to head studies comparing treatments of interest, the absence of comparisons powered for most hard clinical outcomes and, finally, the need for unravelling further insights into the relative effectiveness and harm of the different treatment modalities available, remain powerful drivers in this never ending research. The network meta-analyses by Lee *et al.* (6) and by Siontis *et al.* (33) provide unique and complementary insights for the treatment of patients with ISR. Both DES and DCB are very attractive in this setting. However, the particular efficacy of second-generation everolimus-DES in this adverse anatomic scenario (demonstrated in the RIBS V and VI studies) should be keep in mind during the decision making process used in every day clinical practice. Further studies, however, should confirm the very long-term efficacy of new-generation DES in patients with ISR and also establish whether comparable results may be obtained with other new-generation DES.

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Footnote

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Optimal interventional strategy for the treatment of coronary in-stent restenosis

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In-stent restenosis (ISR) has been an important issue in the era of percutaneous coronary intervention (PCI) since the first bare metal stent (BMS) was applied to clinical settings. BMS substantially reduces acute vessel closure and restenosis after PCI by attenuating early arterial recoil and contraction, two major limitations of plain old balloon angioplasty (POBA). Thereby, it has been considered as a major advancement over POBA. However, ISR caused by neointimal hyperplasia after stent implantation hampers the benefit of BMS by increasing the rate of target lesion revascularization (TLR) or target vessel revascularization (TVR). With the innovation of stent technology, drug-eluting stents (DES) designed to inhibit excessive neointimal growth was produced and anticipated to reduce the incidence of ISR. Indeed, the RAVEL trial (1), a double-blind randomized study comparing sirolimus-eluting stent with its non-coated counterpart, reported no restenosis in the sirolimus stent group, and 23.4% of the patient in the BMS group developed binary restenosis ($P<0.001$) at 6-month follow-up. Despite of these promising results, there's still a certain proportion of ISR occurring after DES implantation due to the expansion of indications for PCI to complex coronary lesions in high-risk patients. Meanwhile, the advent of DES brought new challenges for the interventional cardiologists, such as the higher rate of late stent thrombosis and more bleeding events due to prolonged duration of dual anti-platelet therapy (DAPT). According to the type of stents previously implanted, ISR is classified as BMS ISR and DES ISR. As the literature (2,3) mentioned, 20% to 53% BMS ISR present as unstable angina and 3.5% to 20% as myocardial infarction (MI); The proportion of DES ISR manifesting as unstable angina and MI is 16% to 66% and 1% to 20% respectively. Given the clinical and prognostic importance of ISR, the debate on the optimal strategy to prevent and treat ISR is far from over.

The current treatment options for ISR include POBA, drug-eluting balloon (DEB), repeated DES implantation, radiation therapy and local drug delivery. Among these modalities, POBA, DEB and DES are widely studied. To date, the most appropriate therapeutic strategy for ISR remains poorly identified. In recent issue of *JACC: Cardiovascular Interventions*, Lee *et al*. (4) performed a network meta-analysis of 11 randomized, controlled trails, trying to comprehensively compare among POBA, DEB and DES for the treatment of ISR. Their study enrolled 11 RCTs including 2,059 patients with BMS ISR or DES ISR.

There are several important points of this meta-analysis. First, it showed that both DEB and DES are superior to POBA in the prevention of TLR or major adverse cardiovascular events (MACE). On angiographic outcome analysis, the rate of binary restenosis for DES or DEB is significantly lower than POBA. Second, the efficacy of DEB and DES is comparable, whereas in terms of safety, DEB showed a nonsignificantly lower risk of MI or all-cause mortality when compared with DES. Third, DEB had the highest probability of being ranked as the first treatment option for ISR with the lowest risk of TLR, MI, all-

cause mortality and MACE. While, DES had the highest probability of being ranked as the second option for the treatment of ISR in terms of TLR, all-cause mortality and MACE. In terms of MI, DES showed the lowest probability to reduce the risk of MI after treatment for ISR. Overall, these results are in agreement with our previous analyses that have compared DEB angioplasty with conventional balloon angioplasty or DES implantation for the treatment of coronary ISR (5,6).

Two factors should not be ignored when we interpret the results of this study. First, the trails enrolled in the analysis include two types of ISR population: BMS ISR and DES ISR. Can we simply compare the efficacy and safety of different treatment options without considering the type of ISR? A multicenter randomized trial (7) comparing DEB with POBA in patients with BMS ISR and DES ISR found that in DEB treated group, recurrent restenosis occurred in 1.1% of patients with BMS-ISR and in 9.1% of patients with DES ISR (P=0.04). Late lumen loss was lower in patients with BMS ISR than in patients with DES ISR (0.05±0.28 *vs*. 0.18±0.38 mm; P=0.03). These results suggest that DES ISR is associated with poorer outcomes compared with BMS ISR. Therefore, it may not be appropriate to take BMS ISR and DES ISR as an undistinguished ISR population to compare different ISR treatment modalities. Second, DES studied in the enrolled trials includes sirolimus-eluting stent, paclitaxel-eluting stent and everolimus-eluting stent (EES). As we know, stents coated with different drugs have different properties with regard to the prevention and treatment of ISR. As Kastrati *et al*. (8) demonstrated in their randomized trials, sirolimus-eluting stent had an insignificantly lower rate of angiographic restenosis (P=0.19) and a significantly lower rate of TVR (P=0.02) compared with paclitaxel-eluting stent. Another clinical trial (9) comparing the efficacy of EES with that of DEB in patient with BMS-ISR revealed that both EES and DEB provide excellent clinical outcomes with a very low rate of clinical and angiographic recurrence. However, in late angiographic findings, EES was shown to be superior to DEB. For this reason, exclusively concluding DES as the second option for the treatment of ISR without considering the type of DES is likely to mislead real-world clinical practice, especially when the new generation stents are showing promising prospect in term of prevention and treatment of ISR (10,11).

It has been widely recognized that ISR and stent thrombosis are two major reasons for revascularization failure. Therefore, reducing the incidence of ISR after stent implantation without increasing the rate of late stent thrombosis has been a great challenge for today's interventional cardiologists. As DES has developed from the first generation to the third generation, it is quite promising that the rate of ISR will be substantially reduced without compromising safety benefit. The SPIRIT trial and its subsequent trials (12,13) comparing the second generation stent EES with its bare metal counterpart and other DES demonstrated that EES was superior to its bare metal counterpart in terms of reducing ISR rate and was shown to have a significant advantage over the first generation stent PES with regard to TLR, combined cardiac endpoints and stent thrombosis. Recently, results from a multicenter Italian experience (11) revealed that the implantation of bioresorbable vascular scaffold for the treatment of coronary ISR is technically feasible and associated with favorable mid-term clinical results. As the technology of stents advances rapidly, evidence-based application of new generation DES to de novo coronary lesions may effectively prevent the occurrence of ISR in the age of the third generation DES. Choosing an optimal strategy when ISR occurred after stent implantation has been another great challenge facing interventional cardiologists. American College of Cardiology/American Heart Association/Society for Cardiovascular Intervention (ACCF/AHA/SCAI) guidelines for PCI (14) recommends BMS ISR to be treated by DES (class I, Level of evidence: A) and DES ISR by POBA, BMS or DES. However, the real-world clinical practice is far more complicated than what the guidelines recommend. A comprehensive consideration of previously implanted stent types, lesion types and patients' sensitivity and tolerance to DAPT should be made to determine the optimal therapeutic strategy for each individual patient.

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Footnote

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The appropriate use of risk scores in the prediction of atrial fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice (1). It is associated with a significant risk for several adverse cardiovascular outcomes, including stroke (2), myocardial infarction (3), heart failure (4), and mortality (5). Additionally, AF is associated with significant cost to the health care system, with annual projected costs between $6 and $26 billion dollars (6). The aforementioned complications and financial burden associated with this arrhythmia underscore the importance of accurate AF risk assessment, as this will allow for the development of targeted preventive strategies.

This need for the accurate prediction of AF has given rise to the development of several scoring systems from population-based cohort studies (7). Risk scores have been developed in the Framingham Heart Study (FHS) (8), the Atherosclerosis Risk In Communities (ARIC) study (9), and the Women's Health Study (WHS) (10). However, the risk scores developed from these individual cohorts were limited in their predictive ability, as each cohort varied widely in the diversity (e.g., age, sex, and race/ethnicity) of recruited participants. Accordingly, the Cohorts for Aging and Research in Genomic Epidemiology (CHARGE)-AF consortium derived a 5-year predictive model to address some of these limitations (11). This score used pooled data from 18,556 participants of the FHS, the Cardiovascular Health Study, and ARIC, and included the following characteristics: age, race, height, weight, systolic and diastolic blood pressure, current smoking, treatment of hypertension, diabetes, and history of myocardial infarction and heart failure. The score was then validated in a sample from the Age, Gene and Environment-Reykjavik study (AGES) and the Rotterdam Study (RS), and it demonstrated acceptable discrimination in these cohorts. Additionally, the CHARGE-AF model has been validated in the EPIC-Norfolk cohort (12), in a large multi-ethnic patient population in New York City (13), and in the Multi-Ethnic Study of Atherosclerosis (MESA) (14), providing evidence that this risk prediction tool performs well in diverse populations. The above models and risk scores were derived with the specific aim of predicting AF incidence, and the decision to include, or exclude, predictors was largely based on prior knowledge of well-known AF risk factors and the association of those predictors with AF. Furthermore, each score, particularly CHARGE-AF, has been validated in external cohorts, confirming its ability to accurately predict AF across diverse settings.

The ability of models originally derived to predict AF-related complications, particularly stroke, to predict the occurrence of AF also has been explored. The $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack) score (15), and its later version, CHA_2DS_2-VASc (Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–75 years, and sex category) (16), were originally developed to predict stroke among patients with AF. These scores aid

clinicians in the selection of appropriate anticoagulation strategies. Recent reports have suggested that the $CHADS_2$ and CHA_2DS_2-VASc risk scores also are able to predict incident AF (17,18). Notably, many of the risk factors included in $CHADS_2$ and CHA_2DS_2-VASc (older age, diabetes, hypertension, heart failure, vascular disease) are well-known AF risk factors, likely explaining their ability to predict AF. If $CHADS_2$ and CHA_2DS_2-VASc adequately identify individuals who are high risk of developing AF, this would obviate the need to use models specifically derived to predict AF.

A recent report published in the *American Heart Journal* aimed to directly compare the predictive ability and calibration of the CHARGE-AF and CHA_2DS_2-VASc risk scores for the prediction of incident AF (19). For this analysis, Christophersen *et al.* used data from 4,548 (mean age, 63.9±10.6 years, 56% women) participants form the original FHS and Framingham Offspring Cohort applying a pooled-examination approach and standard statistical techniques (Wald χ^2 statistic to assess model fit, the C-statistic to assess model discrimination, and the Hosmer-Lemeshow (HL) χ^2 statistic to assess model calibration). The authors hypothesized that the CHARGE-AF risk score would have better model performance in AF prediction than CHA_2DS_2-VASc in a community-based cohort. The results confirmed their initial hypothesis: compared with CHA_2DS_2-VASc, the CHARGE-AF model demonstrated better fit (Wald χ^2=403 *vs.* 209, both with 1 df), improved discrimination (C-statistic =0.757; 95% CI, 0.741–0.762 *vs.* C-statistic =0.712; 95% CI, 0.693–0.731), and better calibration (HL χ^2=5.6; P= 0.69 *vs.* HL χ^2=28.5; P<0.0001) in the prediction of AF. Due to the fact that women <65 years of age with lone AF have a low risk of stroke, a secondary analysis was performed assigning a CHA_2DS_2-VASc of 0 to all women <65 years who scored 0 on all other categories. When scoring these women with lone AF as CHA_2DS_2-VASc =0, the model fit (Wald χ^2=288) and discrimination (C-statistic =0.730; 95% CI, 0.713–0.747) improved, yet calibration was reduced (HL χ^2=35.5; P<0.0001). A secondary analysis also was performed in which sex was excluded from the CHA_2DS_2-VASc score, as women have been suggested to have the same or lower risk of AF compared with men (20). This resulted in improved discrimination (C-statistic =0.741; 95% CI, 0.724–0.758), but the model fit (Wald χ^2=360) and calibration (HL χ^2=28.5; P<0.0001) remained inferior to values reported for the CHARGE-AF score. Interactions were not detected by age or sex, and similar results were observed in sex-stratified models.

The results from Christophersen *et al.* (19) are consistent with those from a recent publication from the MESA cohort (14). In the MESA analysis, which included a multi-ethnic sample of 6,663 adults in the United States without prior cardiovascular disease, the C-statistic for the CHARGE-AF score was 0.779 (95% CI, 0.744–0.814), compared with a C-statistic of 0.695 (95% CI, 0.654–0.735) for the CHA_2DS_2-VASc score.

Overall, the findings from the FHS and MESA studies confirm that the CHARGE-AF risk score is superior to the CHA_2D_2-VASc risk score in the prediction of incident AF in community-based cohorts. The FHS analysis also offers insight into the use of the CHA_2DS_2-VASc score to predict AF, as the discriminative ability of the CHA_2DS_2-VASc risk score improved when sex category was removed from the model. Female sex is associated with a higher risk for stroke among patients with AF (16), yet women are less likely to develop the arrhythmia compared with men (though this sex difference disappears once differences in AF risk factors between men and women, including height, are considered) (21). Accordingly, female sex was not included in the CHARGE-AF model, as this tool was developed with the intention of predicting incident AF and not its complications. Additionally, the model fit (measured by Wald χ^2) and calibration (measured by HL χ^2) for CHA_2DS_2-VASc without sex category remained inferior to that of CHARGE-AF, highlighting the perils of using risk scores for the prediction of outcomes other than for what the score was originally intended.

An additional limitation of the CHA_2DS_2-VASc score for the prediction of AF compared with the CHARGE-AF model is the absence of information on the actual risk of AF associated with a particular value of the CHA_2DS_2-VASc score. For example, we know that, based on the original study in which the CHA_2DS_2-VASc score was developed, a CHA_2DS_2-VASc of 2 equates to a 2% annual risk of stroke (16). However, the risk of AF associated with a comparable CHA_2DS_2-VASc score is unknown, and we are unable to derive this information from the C-statistic. In contrast, the CHARGE-AF model (as well as the other AF-specific models) provides an actual estimate of AF risk over a 5- to 10-year period.

The findings of Christophersen and colleagues have relevant clinical implications, as the burden that AF places on the health care system will increase with the expected growth in individuals 65 years and older (1,22). These projections expose the urgent need for the development

of AF preventive strategies. However, before targeted screening measures or the identification of high-risk patients for clinical trial enrollment are feasible, we must be able to appropriately select those who are more likely to benefit from such efforts. The success of future research aiming to prevent AF will ultimately rely on the appropriate selection of participants who are deemed high risk. Therefore, risk scores such as CHARGE-AF that were originally developed to identify persons who are high risk for AF development are of paramount importance to aid current and future preventive research endeavors. Using the $CHADS_2$ or CHA_2DS_2-VASc scores for this purpose, though an attractive alternative due to its simplicity should be avoided since these scores have suboptimal performance in the prediction of AF. Finally, although the CHARGE-AF score has demonstrated its predictive value across a wide range of populations, additional work is needed to determine the role that other clinical factors, blood biomarkers, and genetic information have in predicting AF.

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Footnote

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A meta-analysis of left atrial appendage closure for stroke prevention in atrial fibrillation—adding to the debate but elements remain unresolved

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Background

Managing the trade off between stroke risk and bleeding risk is a key challenge in patients with atrial fibrillation (AF). In 90% of patients with non-valvular AF and intracardiac thrombus, the left atrial appendage (LAA) is thought to be the location (1). The advent of devices to occlude the LAA therefore raised the possibility that stroke risk could be eliminated in this group of patients without the need for long term anticoagulation. However, since the first reports of percutaneous LAA closure with the PLAATO device were published in 2002, progress has been somewhat limited (2). Despite the initial optimism, concerns surrounding safety and efficacy have restricted the number of devices receiving FDA approval (3) and limited commissioning of this treatment in the United Kingdom (4). Guidelines for the management AF to date have varied their advice on this technology with European Guidelines giving LAA closure devices a "IIb" recommendation (usefulness/efficacy is less well established by evidence/opinion) and this only in patients who have a contraindication to warfarin (5). North American Guidelines do not currently recommend LAA closure at all (6). In some ways the caution in recommending this technology is understandable given the paucity of data to support their use.

Holmes *et al.* publish a meta-analysis in the *Journal of the American College of Cardiology* (7) which helps to address the deficit to some degree. This individual patient meta-analysis brings together data from two randomised controlled trials and two observational studies of the Watchman LAA occlusion device. Analysing data from 2,406 patients (5,931 years of patient follow), the authors conclude that rates of haemorrhagic stroke, non-procedural bleeding, and cardiovascular/unexplained death are reduced in patients with non-valvular AF who receive LAA closure compared to patients on long term oral anticoagulation. However once peri-procedural complications are included, all cause stroke and systemic embolism were similar between the two groups, and there was no significant difference in all cause mortality nor in major bleeding complications.

They include the only two randomised trials of LAA closure: the PROTECT-AF study (8) and the more recent the PREVAIL study (9). In addition data are incorporated from registries from both these trials (CAP1 and CAP2 respectively). In terms of size, this therefore dwarfs any previous publication on LAA closure, which often have included no more than 100 participants (10).

Some important observations should be noted when interpreting the results of this analysis. Of the quoted 2,406 patients, the total number of controls treated with long term warfarin was comparatively small at 382. A total of 1,145 of the participants come from study registries and so have not been randomised. In their analysis, the authors focus mainly on a separate meta-analysis just of the two randomised controlled trials. When these randomised trials are analysed alone, Watchman device implantation was non-inferior to warfarin therapy for a primary composite

endpoint of systemic embolism, cardiovascular/unexplained death, and stroke (2.72 v 3.5 events per 100 patient years, P=0.22). There was no difference in all cause stroke (P=0.94) nor all cause bleeding (P=0.95). However, if procedure related bleeding was excluded, Watchman devices proved superior to warfarin (P=0.02) for bleeding risk.

The authors present further meta-analysis data including the patients from the linked registries from the two trials, and here some caution is also required in interpreting the data. The authors do make the point that there is little difference to the data looking at the randomised controlled trials and registries and in particular event rates in the treatment arms of the randomised trials were similar to the event rates in the registry patients.

Mortality reduction

Much is made by the authors of a tendency towards a reduction in all cause mortality in the Watchman group which did not meet statistical significance. The implication is that while non-significant, it might represent an important signal. The meta-analysis is dominated by data from the PROTECT-AF study as it is both larger and has a much longer period of follow-up than PREVAIL (2,717 patient years follow-up versus 860). PROTECT-AF had a lower risk group of patients with a lower mean CHADS2 score than PREVAIL (mean CHADS2 score 2.2 versus 2.6 respectively). One reason why PREVAIL was designed was in response to criticisms that PROTECT-AF included a relatively low risk group of patients, many of whom had a CHADS2 score of 1. If the data contributing to this meta-analysis included a greater number of patients with a higher CHADS2 score, the group might have which benefited more greatly from LAA closure, and we might have seen a significant mortality benefit.

Stroke risk

A slightly increased risk of haemorrhagic stroke in the warfarin arm was offset by an increased risk of ischaemic stroke in the Watchman group. The increased risk of ischaemic stroke persisted after strokes in the first 7 days were excluded. This suggests that warfarin continues to confer a benefit over Watchman in the longer term for ischaemic stroke, presumably because most, but not all strokes are due to emboli from the LAA and warfarin continues to offer protection in this situation. In this analysis approximately a quarter of participants had heart failure and 90% were hypertensive.

Procedural risk

This analysis further highlights the impact of peri-procedural events on the safety of Watchman implantation, but also an ongoing risk associated with late complications with Watchman implantation. The risk of pericardial effusion requiring drainage in the PROTECT AF study was substantial at 4.8%. There is clearly a learning curve associated with this procedure as this complication rate fell in the PREVAIL study to 2.2%, despite a sicker group of patients (30% had a HASBLED score >3 in PREVAIL versus 20% in PROTECT-AF), and the implant success rate similarly improved to 95% in PREVAIL compared to 88% in PROTECT-AF.

Clopidogrel as a confounder

Anti-platelet use continues to cloud our understanding of this treatment. In the Watchman group all patients received aspirin long term, and if warfarin was discontinued both aspirin and clopidogrel were given for a 6-month period. There remains the possibility that some of the benefits or non-inferiority at least, is related to clopidogrel use rather than the device. The benefits of aspirin and clopidogrel over aspirin alone have previously been demonstrated in patients with AF in the ACTIVE-A trial (11). Are these Watchman trials an unwitting comparison of a combination of aspirin and clopidogrel versus warfarin? The patients recruited to ACTIVE-A are indeed those in whom the benefits of LAA closure would be more obvious—those with a contraindication to warfarin. The benefits of aspirin and clopidogrel in this group have already been demonstrated, and this drug combination is required for LAA closure. A clinical trial of aspirin plus clopidogrel with or without LAA closure would address this uncertainty.

What this analysis adds

While this is an impressive collation of data, and a necessary publication in this field, whether it has moved our understanding of the role of the Watchman device in clinical practice is more difficult to quantify. Many of the conclusions are quite similar to the original findings of the PROTECT-AF trial. The primary composite endpoint is similar despite the additional data. However, the additional

patients and extended follow-up have certainly allowed us to analyse some of the secondary endpoints more meaningfully such the development of ischaemic versus haemorrhagic stroke. It also allows us to appreciate how the safety of this procedure has improved with the passage of time.

Unanswered questions

On balance this study confirms that LAA closure with a Watchman device is potentially a viable long term option for stroke prevention in AF. Currently some of the benefits of Watchman implantation are masked by procedure related complications but that may yet improve as the implanters progress along the learning curve. Many unanswered questions remain in this field however.

First and foremost, this analysis does not answer whether LAA closure provides what is ultimately required—stroke prevention without oral anticoagulation. In all four studies, the participants were required to take warfarin for at least 45 days. LAA closure was envisioned as a therapy where anticoagulation is not required. What are the risks associated with this procedure if warfarin is not used at all? Forty-five days however may be considered to be a short enough period for both clinicians and patients to accept the limitations of oral anticoagulant therapy.

Second, these studies will need to be interpreted differently in the era of novel oral anticoagulants (NOACs). We know that, certainly for intracranial bleeds, these have a lower bleeding risk than warfarin, and have favourable outcomes in terms of stroke and mortality (12). In contemporary practice, it may be fairer to compare LAA closure to NOAC use. There is a potential advantage that LAA closure may continue to offer over NOAC use. Unlike drug treatment, once LAA closure is achieved, the issue of compliance and discontinuation of therapy is no longer a consideration. We know that with NOACs, there is a discontinuation rate varying between 21%-24% after 1 year (10), and a similar order of magnitude to warfarin from the control arm of the PROTECT-AF trial at 16%-34% (8).

Third, there remains the question of the alternative approaches to LAA closure. While the data on the Watchman device is most extensive, alternatives exist. These include a range of different Amplatzer closure devices where only retrospective non-randomised studies have been published (13), and the Coherex WaveCrest device for which there currently are no peer reviewed data published (3). Alternative approaches also include the LARIAT suture where a combined epicardial and pericardial approach is used to lasso and occlude the LAA externally with a stitch. Again, evidence of efficacy is limited to non-randomised case series, but data on safety can be ascertained and major complications rates approaching 10% are seen with this (14). Finally a range of surgical techniques are also described (15). It remains to be seen whether over the longer term any of these alternatives prove to be better than a Watchman, or indeed oral anticoagulation, but until a randomised controlled trial is done we will never know.

Moving forward

The available data on LAA closure is evolving and emerging, and new technologies will potentially act as game changers in this field. We have seen from this analysis that many of the limitations of LAA closure relate to peri-implant complications, and as with any new procedure with the inevitable learning curve these are declining. The North American Societies, SCAI, HRS, and the ACC have recently issued joint guidance on best practices and procedures to help guide dissemination of this technology (3). So we may in the future be in a situation where we are able to demonstrate superiority over traditional warfarin anticoagulation. However the demand for an alternative to warfarin may decline with wider use of NOACs, illustrating the constant evolution of options for best care. Overall it remains hard to predict quite where we will be with this technology in the next 5 to 10 years.

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Footnote

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The case of stroke prevention by left atrial appendage occlusion in patients with atrial fibrillation—can we close the file?

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Atrial fibrillation (AF) is the most common arrhythmia and the prevalence is increasing. Future projections predict at least a doubling of AF patients by the year 2050 (1). One of the most devastating consequences of AF is stroke. The presence of AF increases the risk for thromboembolic complications 5-fold and strokes associated with AF have increased morbidity and mortality (2). For this reason stroke risk stratification and appropriate treatment in each patient with AF is of utmost importance. The last decade, the antithrombotic treatment of AF has changed significantly. Easy to use risk scores such as $CHADS_2$ and CHA_2DS_2-VASc have facilitated the use of antithrombotic agents (3). In addition, with the introduction of direct thrombin inhibitors and factor Xa inhibitors, an alternative to warfarin is available, which is at least as effective as warfarin, but with a lower incidence of intracranial bleeding (4).

One of the primary mechanisms how thromboembolic complications as a result of AF occur is believed due to dislodgement of thrombi formed in the left atrial appendage (LAA). In 90% of AF-related left atrial thrombi, they were located in the LAA (5). This was the basis for the hypothesis that systemic and intracranial embolic events in AF patients can be prevented by closure or removal of the LAA. The last decade, several devices have been developed that can occlude the LAA.

In patients with an implantable cardiac pacemaker included in the recent ASSERT study however the direct temporal link between, atrial lead-detected AF itself and cerebrovascular events was questioned (6). In only 15% of patients with AF associated embolic events, an AF episode >6 minutes duration was observed within the month before their stroke or systemic embolism (6). In the majority, the thromboembolic events occurred before or long after the AF episode. These observations suggest that there is not necessarily a direct causal relation with the AF episode itself and clot formation, and other mechanisms may be involved. AF may simply be a marker of increased stroke risk. Local endothelial coagulation and/or anatomic factors (for example trabeculae in the LAA) may be equally or even more important.

Removal of the LAA as a concomitant procedure during cardiac surgery in patients with AF can be performed safely and effectively. However, the studies evaluating the effect of LAA removal or clipping had insufficient power to provide the evidence that LAA removal during surgery reduces the risk of stroke (7,8). Theoretically, surgical or video assisted thoracoscopic removal of the LAA has potential advantages compared to endovascular devices. With epicardial removal or clipping of the LAA, no foreign body is introduced in the systemic circulation. For this reason, thrombus formation on the device cannot occur. In addition, following endovascular implantation of a device, short-term use of warfarin and long-term aspirin is recommended during endothelialisation of the device. This is not necessary following an epicardial approach. In the large Left Atrial Appendage Occlusion Study III (LAAOS III) study, the efficacy of surgical LAA occlusion will be evaluated in patients in whom an on-pump cardiac surgical procedure is performed (9).

The currently available evidence for stroke prevention by LAA occlusion devices is mainly based on data from the PROTECT AF (10) and PREVAIL study (11). Both

studies were randomized trials designed to establish non-inferiority of the endovascular implanted Watchman device versus warfarin (2:1 design). The composite primary efficacy endpoint of the trials was all cause stroke (both haemorrhagic and ischemic), systemic embolization, and cardiovascular death. Following successful implantation, the drug regime consisted of warfarin (target international normalized ratio between 2.0 and 3.0) and aspirin (81 mg) for 45 days. Thereafter warfarin was discontinued when transesophageal echocardiography revealed no device associated thrombi or residual leak >5 mm (10). The PROTECT AF study included 707 patients with paroxysmal, persistent or permanent AF with a $CHADS_2$ risk score >1. The Watchman device was successfully implanted in 88% of patients. After a mean follow-up of 18 months, Watchman device left atrial occlusion was found to be non-inferior to warfarin for the composite primary endpoint (10). Concerns were raised about adverse events (primarily peri-procedural complications) in the Watchman device group (1.1% peri-procedural stroke and 4.8% pericardial effusion requiring percutaneous or surgical drainage). To address these issues the FDA required a follow-up study. In the PREVAIL study, 407 patients with a slightly higher $CHADS_2$ score were included (mean $CHADS_2$ score 2.6±1.0 in PREVAIL, and 2.2±1.2 in PROTECT AF). Procedure-related outcomes consisted of lower adverse events rate (2.2%) and higher successful device implantation (95%). Non-inferiority of Watchman to long-term warfarin for the composite co-primary endpoint of stroke, systemic embolism, and cardiovascular or unexplained death was not reached. Importantly, more late ischemic stroke events in the Watchman arm were observed after 14 months (11).

Holmes *et al.* recently performed a meta-analysis with the combined data of the PREVAIL and PROTECT AF trials (12). In addition, outcome data from two registries (CAP and CAP 2) were included in the analysis. A total of 2,406 patients were studied (1,877 were treated with the Watchman device and 382 received warfarin) with 5,931 patient-years follow-up available.

The hazard ratio for the composite efficacy endpoint was 0.79 (95% confidence interval: 0.53-1.2; P=0.22) meeting non-inferiority of LAA occlusion *vs.* warfarin. All-cause stroke or systemic embolism rates per 100 patient-years were 1.75 for device *vs.* 1.87 for warfarin (P=0.94). There were more ischemic strokes in the device group (1.6 *vs.* 0.9 events/100 patient-years, P=0.05) but this was only the case if procedure-related strokes were included. The Watchman group had less haemorrhagic strokes (0.15 *vs.* 0.96 per 100 patient-years, P=0.004). Finally there was a significant reduction in cardiovascular and unexplained death with the Watchman device (hazard ratio: 0.48; P=0.006). This mortality benefit was believed to be the result of a reduction in haemorrhagic strokes.

The findings of the meta-analysis suggest that LAA occlusion with the Watchman device can provide stroke protection with comparable efficacy as warfarin and at the same time there is less change of haemorrhagic strokes. On the other hand remaining procedural safety concerns warrant cautious use.

In March 2015, the FDA approved the use of the Watchman in the United States for stroke prevention in patients who: "*1. are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy; 2. are deemed by their physicians to be suitable for warfarin; and 3. have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin*". The clinical reality is that LAA occlusion procedures are mainly performed in patients who are considered ineligible for anticoagulation because of (recurrent) episodes of serious bleeding. It should be mentioned however that these patients were not included in PROTECT AF and PREVAIL. In fact, all four Watchman studies excluded patients with a contraindication for warfarin. Thus, the long-term safety has not been studied properly in a sufficiently powered study. A special concern is the short-term use of both warfarin and antiplatelet agents following implantation in these high-risk patients. Although the risk of bleeding was lower in the device arm compared to warfarin in the PROTECT AF and PREVAIL trial, it remains to investigate whether this is also the case in a group of patients with a high bleeding risk. In these patients, especially those who had a previous intracranial bleeding, an alternative approach may also be a non-vitamin K antagonist anticoagulant drug.

Notwithstanding these limitations, for those patients who have an absolute contraindication for oral (novel) anticoagulation drugs but who also have a strong indication for anticoagulation, LAA occlusion is the best available alternative treatment. With further improvements in device design of the Watchman and other LAA closure devices, and increased implantation experience, safety is likely to improve in the years to come. An improved risk benefit

ratio will favour use of LAA occlusion devices and establish its role in clinical practice.

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Footnote

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Left atrial appendage exclusion for atrial fibrillation: does the protection from stroke prevail in the long-term?

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Introduction

On March 13th 2015, the approval of the Watchman left atrial appendage (LAA) closure device (Boston Scientific, Marlborough, MA, USA) by the Food and Drug Administration (FDA) introduced an important tool for stroke prevention for patients with atrial fibrillation (AF) in the United States (1). AF is the most common arrhythmia in clinical practice and afflicts approximately 33.5 million people worldwide (2). Stroke is a feared complication of AF, and systemic anticoagulation is a standard of care for stroke prevention in AF. However, systemic anticoagulation is fraught with potential disadvantages, such as bleeding, need for compliance with medication, compliance with a regular diet in case of warfarin, medication interactions, and need for temporary interruption during surgical procedures.

The Watchman device is a self-expanding nitinol structure with a porous covering that can percutaneously occlude the LAA. Its efficacy for stroke prevention was tested in randomized clinical trials PROTECT AF and PREVAIL (3-5). In the December 2015 edition of *JACC Interventions*, Wiebe *et al.* report long-term single center outcomes with the Watchman device (6). Before judging the efficacy of the Watchman device for stroke prevention, it is important to take a step back and understand the etiology of stroke in AF. Is stroke in AF due to thromboembolism from the LAA, or is AF a marker of elevated stroke risk from multiple systemic causes? Local therapy such as appendage exclusion cannot be expected to treat a potentially systemic pathophysiology. In this article we: (I) review the literature implicating the LAA in stroke in AF; (II) summarize the experience with surgical appendage exclusion; (III) discuss the article by Wiebe *et al.* in context of the PROTECT AF and PREVAIL AF trials; and (IV) provide the reader with a snapshot of future directions in appendage occlusion.

Is AF and stroke an association or causation?

While the association of stroke in patients with AF and rheumatic heart disease, especially mitral stenosis, was widely accepted, the association of non-valvular AF with stroke was established around 30 years ago by the Framingham study (7). The LAA was implicated in the pathogenesis of stroke in non-valvular AF by autopsy data. Davies *et al.* demonstrated in 1972 that 62% patients with long-term AF had thrombi in the LAA compared to 12% with short-term AF (8). In 1996, Blackshear *et al.* reviewed 23 studies and reported that thrombi, when present, extended to the left atrial cavity in 10% patients with non-valvular AF compared to 43% of patients with valvular AF (9). A previous autopsy study had also highlighted the difference in anatomical distribution of atrial thrombi between valvular and non-valvular AF patients. Among patients with atrial thrombi, valvular AF patients had left atrial main wall thrombi in 26.5% cases compared to 13.5% cases in the non-valvular AF group (10). This body

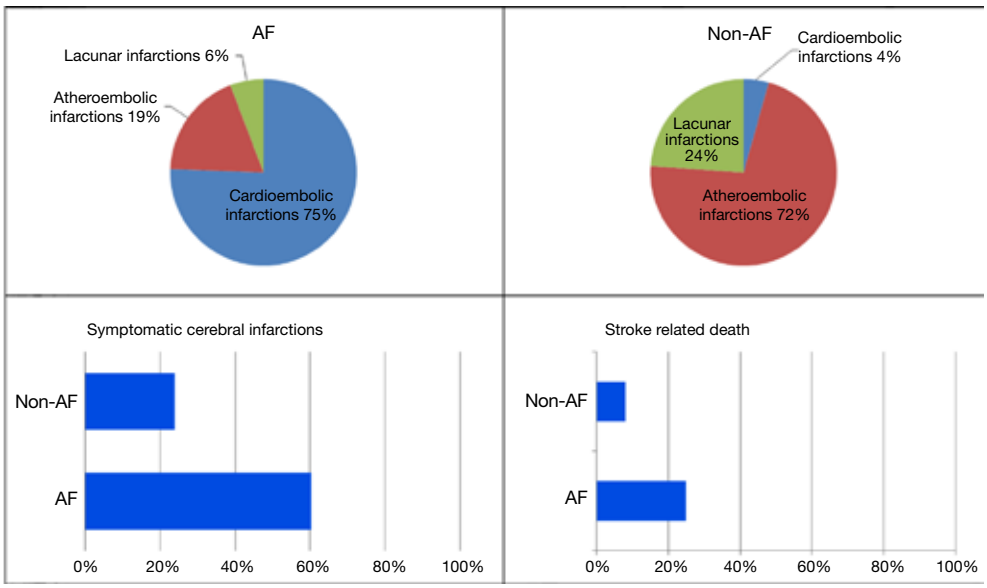


Figure 1 Autopsy specimens from 136 consecutive nonrheumatic AF patients without anticoagulation compared with 231 age-matched controls without AF. Data from Yamanouchi *et al.* (13). AF, atrial fibrillation.

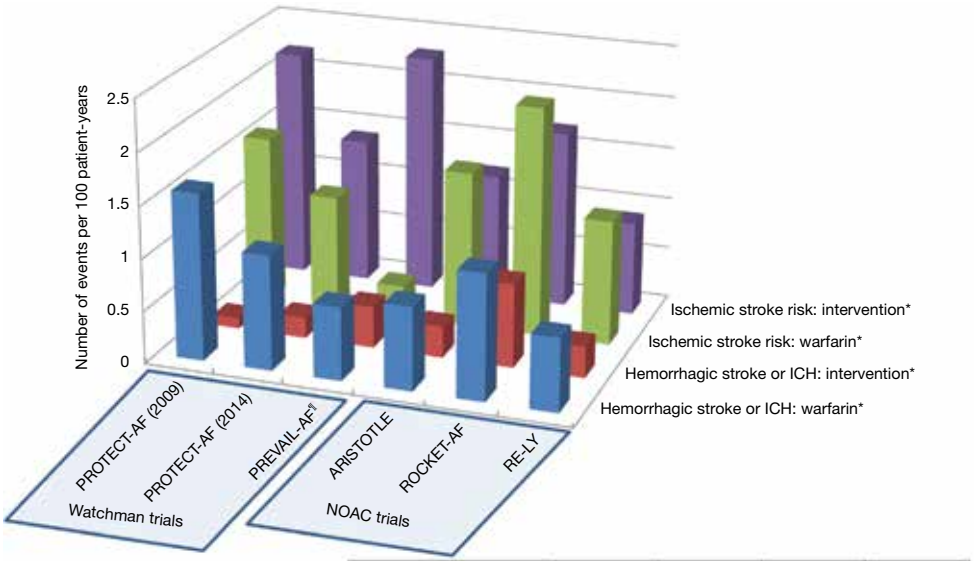
of literature led to the hypothesis that stasis in the LAA leads to thrombus formation in this location and systemic embolization resulting in stroke.

Two challenges in attributing ischemic strokes in AF to LAA thrombi alone are: (I) patients with absence of left atrial thrombus after a recent stroke and (II) lack of temporal association between AF and stroke. Manning *et al.* reported absence of LAA thrombus in 57% after recent stroke (11). The possible explanations include embolization of the entire thrombus mass into the brain, thrombolysis from natural causes or anticoagulation, and etiology of stroke other than AF-related embolism. The reality is likely a combination of these explanations. Etiologies of stroke other than embolism are reported in AF. An analysis from SPAF I–III reported 68% strokes in AF were secondary to cardioembolism. Warfarin reduced cardioembolic stroke, while aspirin reduced non-cardioembolic stroke (12). An autopsy study by Yamanouchi *et al.* is consistent with this observation with 64% cardioembolic strokes in AF patients compared to 3.6% cardioembolic strokes in patients without AF (*Figure 1*) (13). Thus, stroke in AF is a combination of local causes (LAA thrombosis) and systemic factors. Some strokes that can be prevented by medical therapy might not be prevented by left atrial occlusion strategies.

Another confounding question referenced above is the temporal relationship of AF with stroke, or lack thereof. Multiple studies have demonstrated that subclinical AF lasting as little as 6 minutes is a risk factor for stroke (14,15). A substudy from the ASSERT trial reported that only 4/26 (15%) patients had AF in the month prior to the stroke, and only 1/26 was in AF at the time of stroke (16). One explanation is that this study included only patients with >6 minutes of AF and could have missed shorter AF episodes that might predispose to stroke. Another explanation is that atrial rhythm by surface electrocardiogram (ECG) is a poor predictor of left atrial mechanical function as assessed by Doppler echocardiography. Warraich *et al.* reported one fourth of patients with paroxysmal AF had evidence of low LAA ejection velocity even when surface ECG showed sinus rhythm (17). Although temporal association of AF and stroke is unclear, studies are limited by current investigative modalities in terms of detection of brief episodes of AF and poor LAA function despite sinus rhythm on surface ECG.

Surgical LAA exclusion

Recognition of the LAA as a nidus of thrombus formation in non-valvular AF patients led to the practice of appendage ligation and excision in patients undergoing cardiac surgery. Retrospective studies have reported reduction in stroke after complete LAA ligation (18,19). Randomized data regarding efficacy of surgical appendage ligation or excision are lacking. A small randomized pilot study, LAAOS II, reported 1/25 strokes in patients with occlusion compared



	PROTECT-AF (2009)	PROTECT-AF (2014)	PREVAIL-AF¶	ARISTOTLE	ROCKET-AF	RE-LY
Hemorrhagic stroke or ICH: warfarin*	1.6	1.1	0.7	0.8	1.2	0.7
Hemorrhagic stroke or ICH: intervention*	0.1	0.2	0.4	0.3	0.8	0.3
Ischemic stroke risk: warfarin*	1.6	1.1	0.3	1.5	2.2	1.2
Ischemic stroke risk: intervention*	2.2	1.4	2.3	1.2	1.7	0.9

Figure 2 Comparison of ischemic and hemorrhagic stroke risk between Watchman trials and NOAC trials. *, events per 100 patient-years; ¶, updated PREVAIL data from Waksman *et al.* (24), references for PROTECT AF [2009] (4), PROTECT AF [2014] (5), ARISTOTLE (25), ROCKET-AF (26), RE-LY (27); AF, atrial fibrillation; ICH, intracranial hemorrhage.

to 3/25 without occlusion (20). A large RCT (LAAOS III) is currently enrolling 4,700 patients to answer this question, and results are expected in 2020 (21).

The inability to completely exclude or excise the LAA is the Achilles heel of surgical removal of the LAA. In the study by García-Fernández *et al.*, risk of embolic events actually increased in patients with incomplete appendage ligation (18). Another small study reported a 22% risk of embolic events at follow-up in patients with incomplete appendage ligation (22). Incomplete occlusion might increase stroke risk by impending flow of blood resulting in stasis. As many as 36%–100% patients may have incomplete surgical LAA exclusion, and surgical technique and operator experience both have a major impact on the ability to completely exclude the LAA (22,23).

PROTECT AF, PREVAIL AF and study by Wiebe *et al.*

The efficacy of the Watchman device for stroke prevention in AF was assessed by the PROTECT AF and PREVAIL trials. The PROTECT AF trial, published in 2009, included 707 patients randomly assigned in a 2:1 ratio to percutaneous appendage closure with the Watchman device or warfarin (4). Percutaneous appendage closure was non-inferior to warfarin, with a primary efficacy rate (stroke, cardiovascular death, systemic embolism) of 3.0 per 100 patient-years in the intervention arm and 4.9 per 100 patient-years in the control arm. Primary safety events including major bleeding, hemorrhagic stroke, pericardial effusion, and procedure-related ischemic stroke were more common in the intervention arm (7.4 per 100 patient-years *vs.* 4.4 per 100 patient-years). A notable finding in the PROTECT AF study is the high rate of intracerebral hemorrhage in the warfarin arm compared to contemporary trials of anticoagulation with novel oral anticoagulants (NOACs) (*Figure 2*).

Due to concerns raised by the FDA related to acute safety events in the PROTECT AF trial, the PREVAIL trial was designed collaboratively with the FDA by the study sponsor and published in 2014 (3). Enrolling 407 patients in a 2:1 ratio to intervention and control arms, this study failed to demonstrate statistical noninferiority of percutaneous appendage closure. The 18-month rate ratio of primary efficacy endpoint for the intervention to control arm was

Table 1 Comparison of PROTECT AF (5,24), PREVAIL (24) and study by Wiebe *et al.* (6)

	PROTECT AF [2014]	PREVAIL AF	Wiebe *et al.*
Sample size	707	407	102
Age (y, ± SD)	72.5±7.4	74±7.4	71.6±8.8
CHADS2 score (± SD)	2.2±1.2	2.6±1.0	2.7±1.3
Follow-up duration (y, ± SD)	2.3±1.1	1.0±0.5	3.0±1.6
h/o prior stroke (%)	17.70	27.50	17.60
Ischemic stroke/TIA (events per 100 patient-years, %)	1.90	2.30	1.40
ICH or hemorrhagic stroke (events per 100 patient-years, %)	0.30	0.35	1.10
Death (events per 100-patient years, %)	3.20	1.38	3.50

AF, atrial fibrillation; TIA, transient ischemic attack.

1.07, with 95% upper credible interval 0.57 to 1.89, which exceeded the pre-specified noninferiority margin of 1.75. However, the study met the noninferiority criteria for the late-ischemic primary efficacy endpoint (stroke or systemic embolism >7 days after randomization) and the early primary safety endpoint for the intervention arm (6/269 safety events).

Around the same time as the results of PREVAIL were published, long-term follow-up of PROTECT AF were reported (5). After mean 2.3±1.1 years of follow-up, the primary efficacy event rates were 3.0% *vs.* 4.3% per 100 patient-years for the intervention *vs.* control arm, which met the noninferiority criteria. There were numerically more primary safety events in the intervention arm (5.5% *vs.* 3.6% per year; relative risk 1.52; 95% confidence interval 0.95–2.70).

On the basis of the results of the PREVAIL and the long-term follow-up data from PROTECT AF, an FDA panel voted 13:1 in December 2013 that the intervention is safe, effective, and that the benefits of the intervention exceed the risks in the enrolled trial population (24). However, the results available to the panel and published in PREVAIL AF were locked in January 2013. The sponsor updated the PREVAIL AF data in June 2014. There were 13 additional ischemic strokes in the intervention arm compared with one in the control arm. The intervention no longer met the noninferiority criteria for the primary efficacy endpoint, even after including long-term follow-up from the PROTECT AF cohort. Hence, another FDA panel meeting was convened in 2014. The FDA voted 12 to 0 that the intervention is safe, 6 to 7 that it is not effective and 6 to 5 (with one member abstaining) that its benefits outweigh the risk (24). Overall, the panel suggested that the device has a role as second line therapy to anticoagulation for stroke prevention in appropriately selected AF patients. Ultimately, the FDA approved the Watchman device in 2015 for patients with non-valvular AF with elevated risk of stroke based on CHADS2 or CHADS2-VASc scores who are eligible for warfarin but have an appropriate rationale for a nonpharmacological alternative to warfarin (1).

Lack of long-term outcomes is a valid concern with the Watchman device given the increase in ischemic strokes upon follow-up of the PREVAIL cohort. The study by Wiebe *et al.* in 2015 in *JACC Interventions* is a timely study addressing these concerns (6). The authors reported results up to 5 years follow-up from a cohort of 96 patients who underwent percutaneous appendage closure using the Watchman device at a single center. Over mean 3.0±1.6 years of follow-up, stroke/transient ischemic attack (TIA), intracranial hemorrhage (ICH), and death occurred in 1.4%, 1.1%, and 3.5% of the trial population respectively. Among the four patients with ischemic stroke/TIA at follow-up, three events occurred more than 1 year after device implantation. Overall, these data compare favorably to the results of the PROTECT AF and PREVAIL trial (*Table 1*). There continues to be concerns regarding the long-term efficacy of the Watchman device with regards to ischemic stroke prevention, and results of the post-approval studies mandated by the FDA will be valuable in informing patients and providers.

Weighing the risks and benefits of stroke prevention strategies in AF

The success of any therapy must be judged by assessing the

Table 2 Comparison of surgical, endocardial and epicardial LAA exclusion techniques

	Surgical exclusion	Endocardial exclusion	Epicardial occlusion
Devices	Manual ligation, manual excision, AtriClip Pro, Tigerpaw	Watchman, Plaato, Amplatzer cardiac plug, Transcatheter patch, Lambre	LARIAT, Aegis
Availability of large RCTs	LAAOS III expected 2020	Yes, for Watchman	No
Prothrombotic effects	Yes, due to incomplete occlusion	Yes, due to formation of thrombus on device	Less likely if complete exclusion achieved
Electrical LAA isolation	Yes, depending on completeness of exclusion	No	Yes

LAA, left atrial appendage; RCTs, randomized controlled trials.

risks and benefits of the therapy against the alternatives.

Anticoagulation vs. appendage exclusion

Patient compliance and the ability to tolerate long-term medical therapy are major barriers to long-term systemic anticoagulation in patients receiving warfarin or NOACs. Less than 50% of patients with risk factors for stroke and AF are prescribed or fill prescriptions for warfarin after AF presentation (28,29). Even if treatment is initiated, 40% of patients cease to use warfarin at 4-year follow-up (30). Warfarin is inconvenient to patients due to the need for regular international normalized ratio (INR) monitoring, interactions with medications, and diet. Only 60% of patients have an INR in the target range of 2.0 to 3.0, even in closely monitored clinical trial settings (31). NOACs offer more convenience compared to warfarin; however, NOACs also need to be stopped for major surgeries and bleeding episodes. Appendage exclusion will continue to provide benefit in these circumstances while systemic therapy may not.

Surgical vs. endocardial vs. epicardial appendage exclusion

The LAA can be excluded in a variety of methods including surgical methods discussed previously and minimally invasive epicardial and percutaneous endocardial methods. Some of the ischemic stroke risk in endocardial occlusion is from thrombus formation on the device. For this reason, warfarin and clopidogrel are recommended for 3–6 months after endocardial LAA occlusion. Epicardial devices have the benefit of avoiding this issue. There is cessation of LAA electrical activity after epicardial ligation, but it is unclear whether this translates to a reduction in AF burden (32,33). However, epicardial devices require pericardial access, which is a difficult skill to master. Additionally, randomized controlled trials supporting the role of epicardial ligation are lacking compared to endocardial occlusion (*Table 2*).

Future directions in appendage exclusion

Apart from the Watchman device, there are several other epicardial and endocardial LAA exclusion devices under development (34). The LARIAT system offers a hybrid and endocardial and epicardial approach to LAA ligation and was effective in appendage ligation in observational studies (35,36). The Aegis system is a completely intrapericardial ligation approach utilizing a grabber with embedded electrodes to recognize LAA signals and deliver a preformed suture to ligate the appendage. This approach is feasible in humans, and larger randomized trials are awaited (37). Other surgical epicardial ligation approaches under development include the AtriClip Pro and the Tigerpaw system II, which are feasible according to first-in-human studies; further clinical trials are awaited (38,39).

The Plaato device was the first device designed specifically for endocardial appendage exclusion but is no longer under development due to financial considerations (40). Small retrospective studies support the efficacy and safety of the Amplatzer cardiac plug for appendage exclusion (41-44). However, randomized data are not available, and a randomized clinical trial was designed but could not be conducted due to failure to obtain the investigational device exemption from the FDA (45). A percutaneously delivered transcatheter patch utilizing surgical adhesives was effective in atrial appendage exclusion, but further studies are not available (46). An animal study has demonstrated feasibility

of appendage exclusion with the LAmbre device (47).

Conclusions

Similar to several clinical conundrums in medicine, there is no "one-size-fits-all" approach for stroke prevention in AF. Patient characteristics, preferences, cost considerations, and provider expertise must all be taken into account. What is clear is that AF predisposes to strokes that are larger, more disabling, and deadlier than strokes from other causes. Prevention by either anticoagulation or LAA exclusion is essential.

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Footnote

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Five years of keeping a watch on the left atrial appendage—how has the WATCHMAN fared?

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Abstract: Left atrial appendage closure (LAAC) is a promising site-directed therapy for stroke prevention in patients with non-valvular atrial fibrillation (AF) who are ineligible or contraindicated for long-term oral anticoagulation. A variety of LAAC modalities are available, including percutaneous endocardial occluder devices such as WATCHMAN™ (Boston Scientific Corp., Marlborough, MA, USA), and an ever-increasing body of evidence is helping to define the optimal use of each technique. Similarly increased experience with LAAC has revealed challenges such as device-related thrombi and peri-device leaks for which the long-term significance and appropriate management are areas of active investigation. We review the evolution and long-term outcomes with the WATCHMAN™ device with particular emphasis on the nuances of its use and its role in the broader landscape of appendageology.

Keywords: Atrial fibrillation (AF); atrial appendage; stroke; thromboembolism

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Atrial fibrillation (AF) & stroke prevention

AF is the most common cardiac arrhythmia in the United States, affecting approximately 6–7 million individuals nationally, with a projected increase in prevalence to nearly 16 million patients by the year 2050 (1,2). Among the most effective cardiovascular therapies has been systemic anticoagulation with vitamin K antagonists (VKA) such as warfarin, which has been shown to reduce stroke risk in non-valvular AF by 64%, with an absolute risk reduction of 2.7% per year in patients with no history of stroke or TIA (3). Current AF management guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) provide a Class I recommendation for systemic anticoagulation with either warfarin (Level of Evidence, A) or one of a number of non-VKA oral anticoagulants (NOACs), including dabigatran, rivaroxaban, and apixaban (Level of Evidence, B) in those patients with a prior history of stroke or transient ischemic attack (TIA), as well as those with a CHA_2DS_2VASc score of ≥2 (4-7).

Despite the widespread availability of these therapies, there remain significant barriers to providing adequate stroke prophylaxis for many patients with AF (8). In a systematic review of studies examining current treatment practices for stroke prevention in AF, Ogilvie *et al.* found that in over two-thirds of studies of AF patients with prior stroke or TIA, anticoagulation treatment was prescribed in less than 60% of eligible patients (9). This concerning trend stems from a variety of factors such as perceived contraindication to anticoagulation or low stroke risk (10-13),

older age and frailty (14,15), AF classification (15,16), sex (14), narrow therapeutic window (12), significant drug-drug and drug-diet interactions, and patient compliance (12,13). Moreover, even in recent large, randomized control trial settings, the time in the therapeutic range for warfarin has been measured between 55%–66%, and 20%–27% of patients ultimately discontinued their systemic anticoagulation therapy over a follow-up of approximately 2 years (4,5,7).

The "most lethal" appendage: site-directed therapy

These limitations in effective stroke prevention for patients with AF have prompted a search for alternative solutions. The left atrial appendage (LAA) has long been thought to serve as the major nidus for AF-related cardiac thromboemboli and has been implicated in over 90% of cases of non-valvular AF (17). Rooted in this principle, a number of therapies have emerged for mechanical closure of the LAA (LAAC), including surgical ligation and clipping, as well as percutaneous techniques featuring endocardial and epicardial approaches to the LAA (18-21). Consensus statements from both the American College of Cardiology (ACC)/Heart Rhythm Society (HRS)/Society for Cardiovascular Angiography and Interventions (SCAI) (22), as well as the European Heart Rhythm Association (EHRA)/European Association of Percutaneous Cardiovascular Interventions (EAPCI) (23), now provide some guidance regarding consideration of LAAC therapy for stroke prevention in AF, in addition to a set of institutional and operator requirements for a successful LAAC program (24).

Evaluation of the WATCHMAN™ device in clinical trials

The WATCHMAN device (Boston Scientific Corp., Marlborough, MA, USA) represents the first Food and Drug Administration (FDA)-approved percutaneous LAAC device indicated for reducing the risk of thromboembolism from the LAA in patients with non-valvular AF who: (I) are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2VASc scores and are recommended for anticoagulation therapy; (II) are deemed by their physicians to be suitable for warfarin; and (III) have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and efficacy of the device compared to warfarin. This approval was granted by the FDA in March 2015 following a prolonged pre-market approval pathway process featuring two randomized control trials (PROTECT AF and PREVAIL) to study its non-inferiority to warfarin and two prospective registries (CAP and CAP2) to monitor safety and efficacy of the device over time (25-28). In PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation), despite achieving non-inferiority versus warfarin in the combined efficacy endpoint of ischemic or hemorrhagic stroke, systemic thromboembolism, and cardiovascular or unexplained death (3 *vs.* 4.9 events per 100 patient-years, RR 0.62; 95% CI: 0.35–1.25), the WATCHMAN device raised concerns with a higher rate of primary safety events (7.4 *vs.* 4.4 events per 100 patient-years, RR 1.69; 95% CI: 1.01–3.19) mainly related to periprocedural complications such as pericardial effusion (4.8%), major bleeding (3.5%), and procedure-related stroke (1.1%) (20).

Further study of the device in the PREVAIL (Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial failed to demonstrate achievement of a pre-specified, composite efficacy endpoint of stroke, systemic embolism, and cardiovascular/unexplained death (the same composite endpoint used in PROTECT AF; 0.064 in device group *vs.* 0.063 in warfarin group, RR 1.07; 95% CI: 0.57–1.89) (26). The device, however, did meet its second co-primary efficacy endpoint (referred to as the "late ischemic efficacy" endpoint) defined as occurrence of ischemic stroke and systemic embolism beyond 7 days post-randomization and over the follow-up period of 18 months, effectively excluding peri-procedural events given the unique nature of comparison between a device and a drug. The WATCHMAN device similarly met its safety co-primary endpoint in PREVAIL. In a subsequent meeting of the FDA Circulatory Systems Advisory Panel in October 2014, newly available data including eight ischemic strokes in the WATCHMAN group resulted in the reassessment that the device did not meet its second pre-specified co-primary endpoint and failed to demonstrate non-inferiority to warfarin in PREVAIL (22,29). It has been noted, however, that the rate of ischemic strokes in the warfarin control group of PREVAIL was less than half that observed in three recent major trials of NOACs (4,5,7,26), fueling controversy surrounding interpretation of data from yet another WATCHMAN randomized control trial. Ultimately FDA approval was granted in March 2015 for the nuanced

indication noted previously. Incorporation of all available trial and registry data in a patient-level meta-analysis has since supported a statistically significant reduction in hemorrhagic stroke, non-procedure-related bleeding, and cardiovascular death with the WATCHMAN (25). However, the PREVAIL findings and FDA concerns surrounding overall efficacy as compared to warfarin, particularly in the case of ischemic stroke, have emphasized the need for rigorous post-marketing surveillance and long-term follow-up of patients receiving the WATCHMAN device.

Extending the follow-up on WATCHMAN

The longest reported follow-up with WATCHMAN to date has been the 4-year PROTECT AF experience reported by Reddy *et al.* with a mean follow-up duration of 3.8±1.7 years (28). For the composite efficacy endpoint of stroke, systemic embolism, and cardiovascular death, the WATCHMAN group had 39 events among 463 patients (8.4%) *vs.* 34 events in 244 patients (13.9%) in the warfarin group (event rate, 2.3 *vs.* 3.8 per 100 patient-years; RR 0.60; 95% CI: 0.41–1.05), meeting the trial's non-inferiority criteria and demonstrating significant reductions in cardiovascular and all-cause mortality in secondary analyses. The beneficial outcome demonstrated with the WATCHMAN device was attributed largely to reductions in hemorrhagic stroke and cardiovascular death. Ischemic stroke rates in the two groups were not significantly different, though again this result must be interpreted in the context of the subsequent PREVAIL trial, which though it enrolled fewer patients [device group, 463 (PROTECT AF) *vs.* 269 (PREVAIL)], did not demonstrate the non-inferiority of the WATCHMAN as assessed by its two co-primary efficacy endpoints.

With respect to safety, the four-year PROTECT AF data demonstrated a time-dependent distribution of safety events with the WATCHMAN device, consisting of peri-procedural (up to 7 days) serious pericardial effusion in 22/463 (4.8%), procedure-related ischemic stroke in 5 (1.1%), and device embolization in 3 (0.6%). The number of events beyond 7 days post-implantation was considerably less, with major bleeding in 19 (4.1%) compared with 18 (7.4%) in the warfarin group, procedure-related ischemic stroke in 1 (0.2%), and hemorrhagic stroke in 3 (0.6%) compared to 9 (3.7%) in the warfarin group (28). In an intention-to-treat analysis combining all safety events, there was no significant difference between the two groups. In PREVAIL, primary safety events occurred in 6/269 (2.2%) WATCHMAN patients over 18 months follow-up. Due to the unique comparison of a device versus a medication, safety events were not reported for the warfarin group separately, using instead a Bayesian model incorporating data from the prior PROTECT AF study and CAP Registry to compute a performance goal of 2.67% for the WATCHMAN group in PREVAIL. The "early safety" primary endpoint was a composite of all-cause death, ischemic stroke, systemic embolism, or device-/procedure-related events requiring open cardiovascular surgery or major endovascular intervention between randomization and 7 days after the procedure or during the index hospitalization. It was met with the upper bound of the one-sided 95% credible interval computed at 2.652% for the WATCHMAN group.

Recently, Wiebe *et al.* described a relatively large single-center experience of 102 AF patients treated with the WATCHMAN device with up to 5 years follow-up (30). Patients had mean CHA_2DS_2VASc and HAS-BLED scores of 4.3±1.7 and 2.9±1.2, respectively. Procedural success was 96.1% (98/102), exceeding the 91% reported in PROTECT AF and in line with previously published trial and registry data from PREVAIL, CAP (Continued Access Protocol) registry, and the ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) registry (26,27,31).

During a mean follow-up of 3.0±1.6 years, second in duration only to the PROTECT AF four-year follow-up experience (28), two patients (0.7 per 100 patient-years) had ischemic strokes, as compared to 1.4 per 100 patient-years in PROTECT AF and less than the study group's CHA_2DS_2VASc-predicted stroke risk of 4%–6.7% annually. Two patients had TIAs—one at one month and the other beyond 12 months post-implantation. Three patients suffered intracranial bleeding events for a rate of 1.1 per 100 patient-years, which exceeded the rate in PROTECT AF by nearly six-fold (0.2 per 100 patient-years), though it is not reported what percentage of patients continued warfarin long-term, which may explain some portion of the bleeding events. Severe bleeding events occurred in six patients (6.3%) compared to 4.8% in PROTECT AF (28). Freedom from all-cause mortality at 60 months was just less than 82.5%, while this figure was approximately 86% in the PROTECT AF device group at the same point in time.

Device-related thrombi and the anticoagulation conundrum

Importantly, in the study by Wiebe *et al.*, a significant

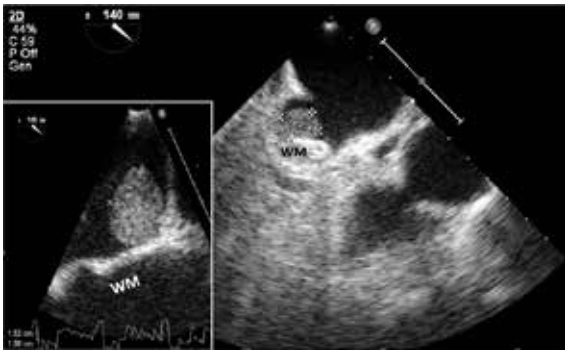

Figure 1 Two-dimensional transesophageal echocardiogram image acquired at 140 degrees rotation showing device-related thrombus (DRT) adherent to the WATCHMAN (WM) device. Inset image was acquired at 145 degrees rotation and magnifies the DRT, showing its dimensions to be 1.9 cm × 1.5 cm.

portion of patients (41/98) were exclusively administered dual antiplatelet therapy (DAPT) post-implantation, while the remaining 57 (58.2%) received the usual VKA for 45 days followed by 6 months of DAPT (30). This was a notable deviation from the protocol utilized in the WATCHMAN trials to treat patients with VKA for the first 45 days post-implantation, followed by DAPT for 6 months. The authors reported that 25 patients were not eligible for anticoagulation. Despite this difference in management, there were device-related thrombi (DRT) in only two cases (4.9%), in addition to one ischemic event, in the DAPT group (*Figure 1*). It is difficult to draw conclusions given the overall low event rate, however in the ASAP Study of 150 warfarin ineligible patients, there were a total of 6 (4%) device-related thrombi and one thought to be implicated in an ischemic stroke (31). This trend of foregoing post-procedural anticoagulation with VKA is more representative of European practice patterns given guideline recommendations to consider LAAC in patients in whom anticoagulation is contraindicated, though it is important to note there are no randomized control trial data studying LAAC in this scenario, as these patients were excluded from the WATCHMAN trials. Nevertheless, it is a key patient population which is in need of a safe and effective alternative for stroke prevention.

In a *post hoc* analysis of the PROTECT AF study population, Main *et al.* found that in 35/485 (7.2%) patients receiving a WATCHMAN device who were suspected by the site investigator and/or the echocardiography core laboratory to have a DRT, 27 were ultimately adjudicated by a panel of three echocardiographers to have had a DRT in one of their post-procedure studies (32). In addition to illustrating the challenge of making the diagnosis, 19 of 33 (56.7%) with an available TEE study had a thrombus detected at the 6-month post-implantation follow-up, while 12/27 (44.4%) with an available TEE study at 12 months post-implantation had a DRT. The primary composite efficacy endpoint of PROTECT AF (stroke, systemic thromboembolism, cardiovascular/unexplained death) was detected in patients with DRT at a rate of 3.4 per 100 patient-years, intermediate in frequency between the device in and warfarin groups in the PROTECT AF study (32).

These findings highlight one of the major challenges and areas for further investigation with the WATCHMAN device vis-à-vis peri-procedural and post-procedural management of LAAC patients. The significance of DRTs and their prevention remain poorly understood. Some considerations include: (I) the possibility that the duration of current anticoagulation/antiplatelet protocols is inadequate in some patients for proper endothelialization over the LAA ostium; (II) the combination of DAPT is insufficient in protecting against thrombus formation; or (III) there are device- and/or patient-related factors which predispose some individuals to thrombus formation (e.g., threaded insert of the device). Furthermore, despite the arbitrary yet commonly employed de-escalation protocol—from aspirin and VKA to DAPT at 45 days and subsequently to aspirin monotherapy after six additional months—a substantial number of patients are not able to be liberated from VKA therapy at 12-month follow-up. This number approaches 7% in the PROTECT AF study population of carefully selected patients treated by experienced operators and is likely to be greater in a "real world" population (28).

Plugging the dike and patient-occluder mismatch

Contributing to the issue is the fact that our understanding of the significance and future ramifications of peri-device leaks remains incomplete, particularly in those cases where the leak exceeds 5 millimeters (*Figure 2*). In a sub-study of the PROTECT AF device group limited by low power and *post hoc* analysis, it was noted that 32% of patients had some residual peri-device flow at 12-month follow-up, but that neither the severity of the leak nor the administration of VKA therapy seemed to correlate with the primary combined efficacy endpoint of that trial (33). Closely related to the issue of leaks are the challenges posed by the anatomical variation of the LAA and the elliptical morphology of the LAA ostium (34,35). With the advent

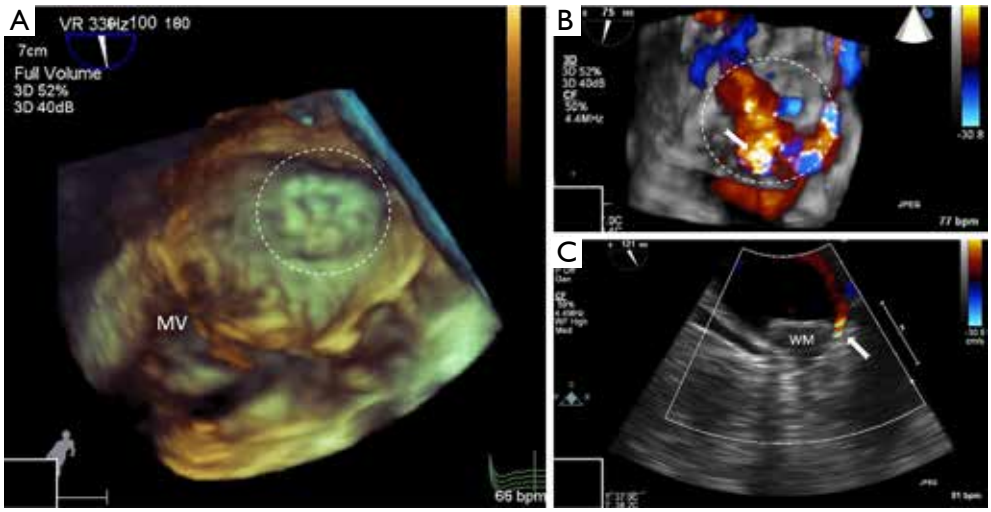

Figure 2 Echocardiographic assessment of residual peri-device leak following WATCHMAN LAAC. (A) Three-dimensional transesophageal echocardiogram (TEE) image acquired at 100 degrees rotation demonstrating a two chamber view with the WATCHMAN device (dotted line) occluding the left atrial appendage (LAA) ostium and its relation to the mitral valvular (MV) apparatus; (B) three-dimensional TEE image acquired at 75 degrees rotation showing an en face view of the WATCHMAN occluding the LAA ostium (dotted line) with Doppler demonstration of a medially located eccentric peri-device leak (arrow); (C) two-dimensional Doppler TEE image acquired at 121 degrees rotation showing the WATCHMAN (WM) seated in the LAA with an eccentrically directed jet (arrow) indicating a peri-device leak.

of new technologies for closure of the LAA, it is hoped that many of these obstacles can be overcome.

Occluder devices featuring a "disc and lobe" configuration such as the AMPLATZER™ Amulet™ (St. Jude Medical, St. Paul, MN, USA), which carries the Conformité Européenne (CE) mark and is widely used in Europe, show promise in offering greater versatility for a variety of LAA morphologies (36,37), though in a small canine study some concern was raised regarding potential interference of the disc with surrounding structures, including the left superior pulmonary vein and the mitral valve apparatus (38). Another CE-marked and also FDA-approved option, the LARIAT® Suture Delivery Device (SentreHEART, Redwood City, CA, USA), features an entirely unique, hybrid (endocardial and epicardial) approach to closing the LAA (21,39). The latter two devices are each currently the subject of a randomized control trial (ClinicalTrials.gov Identifiers: NCT02879448, NCT02513797) (40). Additional LAAC devices, including the WaveCrest (Coherex Medical, Salt Lake City, UT, USA) device, the Occlutech LAA Occluder (Occlutech International AB, Helsingborg, Sweden) (41), and the LAmbre (Lifetech Scientific, Shenzhen, China) device (42), are in various stages of development.

Conclusions and future considerations for LAA-directed therapies

The development and approval of the WATCHMAN device heralds a new era in "appendage-ology" in which it is conceivable that emerging therapies will equip LAAC specialists with an armamentarium capable of providing the right LAAC therapy for the right patient (*Figure 3*). The WATCHMAN has laid the groundwork for this exciting prospect and has confirmed the significance of the LAA in AF-related stroke mechanisms. Despite the need for further study to understand its proper role in the overall approach to stroke prophylaxis, particularly with respect to preventing ischemic stroke, it has also shown a significant reduction in the rate of hemorrhagic stroke, non-procedure-related bleeding, and cardiovascular death. Furthermore, the importance of the LAA in arrhythmia propagation and neurohormonal regulation has been established (43-45), and it would be remiss to avoid their consideration in a comprehensive approach to appendage closure. These aspects of LAAC therapy warrant further investigation, as they may shed additional light on the significance of this most lethal appendage, as well as how its successful closure may confer pleiotropic effects to AF patients.

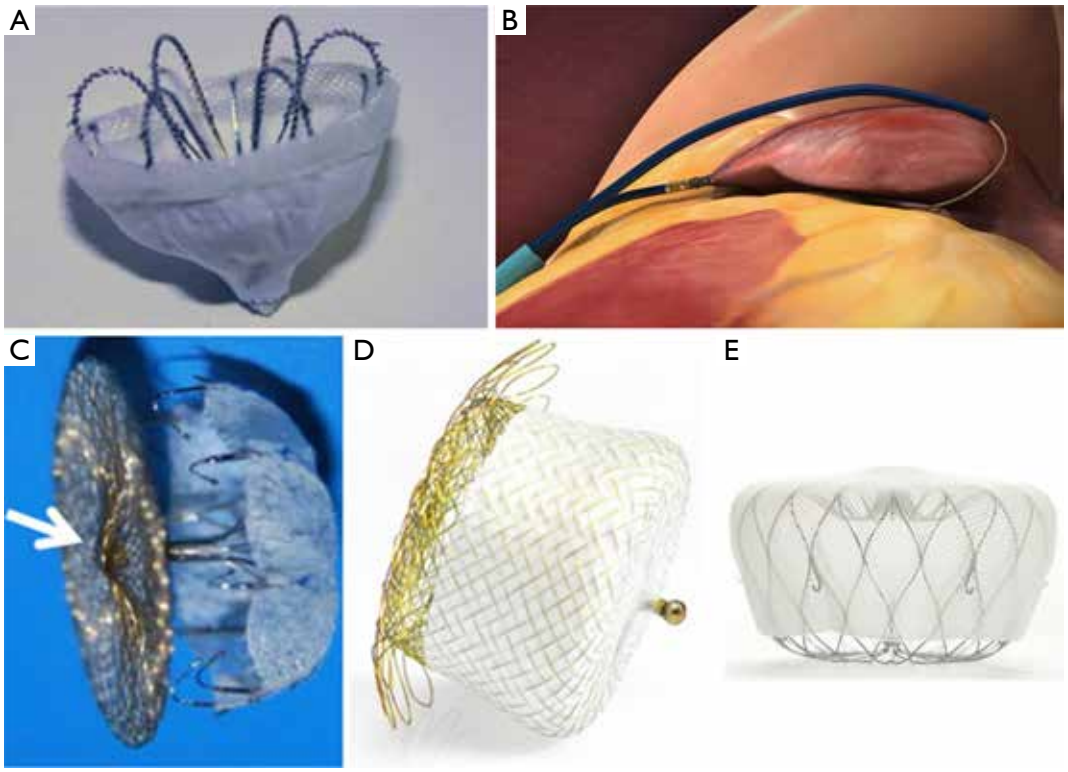

Figure 3 Left atrial appendage closure (LAAC) devices currently in various phases of development, including: (A) WaveCrest (Coherex Medical, Salt Lake City, UT, USA); (B) Aegis Sentinel Ligation System (Aegis Medical Innovations, Inc., Vancouver, BC, Canada); (C) LAmbre (Lifetech Scientific, Shenzhen, China); (D) Occlutech LAA Occluder (Occlutech International AB, Helsingborg, Sweden); and (E) WATCHMAN FLX (Boston Scientific Corp., Marlborough, MA, USA).

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Footnote

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Percutaneous left atrial appendage closure: here to stay

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Stroke prevention has long been perceived as the Achilles heel in the management of atrial fibrillation (AF). In recent years, percutaneous left atrial appendage (LAA) closure, a novel catheter-based therapy designed to occlude the primary nidus responsible for cardioembolic events is emerging as a safe and effective alternative, amidst the multiple limitations encountered with conventional oral anticoagulants (OAC), particularly warfarin (1). Long-term use of warfarin, albeit efficacious (2), is often overshadowed by the need for continuous monitoring and dose adjustments, narrow therapeutic window, food and drug interactions, and most importantly undesirable bleeding hazards. The introduction of direct OAC remains inadequate to address these shortcomings due to the persistent major bleeding complications (3-5).

Presently, the WATCHMAN device (Boston Scientific, Marlborough, MA) is the most commonly utilized LAA occlusion device in contemporary practice, with its efficacy and safety demonstrated by several studies. The device is composed of a self-expanding nitinol frame, and is covered with permeable polyethylene terephthalate membrane and anchoring fixation barbs for stability. It was recently approved by the US Food and Drug Administration for clinical use in non-valvular AF patients who are deemed to have significant stroke risk and with an appropriate rationale to seek an alternative therapy to OAC.

Despite early success with this novel therapy (6), it was not until PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation), the pivotal randomized trial, which drew the attention of medical community to the crucial contribution of percutaneous LAA closure in stroke prevention with the WATCHMAN device, demonstrating non-inferiority to warfarin in the management of non-valvular AF patients. At the initial 1,065 patient-years of follow-up, the cumulative primary efficacy end point of stroke, systemic embolism and cardiovascular death in patients implanted with WATCHMAN was non-inferior compared to the control cohort [3 *vs*. 4.9 events per 100 patient-years; risk ratio (RR) =0.62; confidence interval (CI), 0.35–1.25] (7). With longer-term follow-up of 3.8±1.7 years, the primary efficacy event-rates were 2.3 per 100 patient-years (95% CI, 1.7–3.2) with WATCHMAN and 3.8 per 100 patient-years (95% CI, 2.5–4.9) with warfarin, meeting both the superiority and non-inferiority criteria. There was a 40% risk reduction (RR =0.6; 95% CI, 0.41–1.05) of all cause stroke, systemic embolism, cardiovascular and unexplained death with WATCHMAN. There was also 85% reduction in hemorrhagic stroke (RR =0.15; 95% CI, 0.03–0.49), 63% reduction in disabling stroke (RR =0.37; 95% CI, 0.15–1.00), 60% reduction in cardiovascular death (RR =0.4; 95% CI, 0.23–0.82), and 34% reduction in all-cause mortality (RR =0.66; 95% CI, 0.45–0.98) (8).

In the December 2015 issue of *JACC Cardiovascular Interventions*, Wiebe and colleagues reported their 5-year experience of LAA closure with WATCHMAN at their institution. In this prospective single centre study of 102 consecutive non-valvular AF patients (mean CHADS2, CHA_2DS_2-VASc and HAS-BLED scores of 2.7±1.3, 4.3±1.7

and 2.9±1.2, respectively) who were implanted with the second-generation WATCHMAN, the authors reported a 96.1% procedural success rate. Procedure-related complications, predominantly non-fatal pericardial effusion were identified in 8.8% of the study cohort. However, there was no statistical difference in event-rates between the first and second halves of patients to reflect a learning curve. The annual incidence of cerebral ischemia inclusive of stroke and transient ischemic attack (TIA) was 1.4% per year, which was substantially lower than the predicted stroke risk based on CHA_2S_2-VASc score and was consistent with contemporary studies (8). The rates of major bleeding and death were 2.1% and 3.5% per annum at follow-up to 5 years, respectively. Adequate lobe coverage (<5 mm residual peri-device leak) was achieved in all patients except one. Thrombus formation on the device was detected in 2 of 41 patients who received dual antiplatelet therapy (DAPT) after their procedures. The authors concluded that LAA closure with WATCHMAN to be safe and conferred effective long-term cardioembolic protection in light of the low ischemic event-rates observed (9).

There are a few limitations with this study that should be considered when interpreting their data. Firstly, the results were based on a single-centre observational registry with a considerably smaller population in contrast to contemporary WATCHMAN trials. Data from single centre experience are vulnerable to unsuspected confounders leading to selection bias, and at the same time lacked generalizability of the therapy to clinical practice across the board. Furthermore, post-procedural antithrombotic regimen was not standardized, and may potentially influence the overall outcomes of the device under investigation. On the other hand, the enrolment of consecutive patients reduced selection bias, and the extended period of follow-up is one of the longest available in published literature. Overall, it was a commendable initiative by the authors to elucidate real world experience on the long-term performance of LAA closure with WATCHMAN.

Like all emerging technology, the procedural/device-related limitations need to be explored and balanced with efficacy data, to evaluate the suitability of adopting new technologies. Early experience from PROTECT-AF alerted us to several safety concerns with LAA closure. An estimated 4.8% of the procedures in the trial were complicated by severe peri-procedural pericardial effusion requiring intervention, mostly on the same day of the procedure, thus prolonging the length of hospitalization. Procedure-related stroke as a consequence of air embolism accounted for 1.1% of the cases. Major bleeding (3.5%) and device embolization (0.6%) were also reported. Overall, higher incidence of primary safety events (8.7%) was recorded in the intervention group (7.4 *vs.* 4.4 per 100 patient-years; RR =1.69). Fortunately, with increasing experience, there have been improvements in safety event-rates reported in subsequent studies, 4.2% in the Continued Access Protocol (CAP) registry and 4.5% in the PREVAIL (Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation versus Long-term Warfarin Therapy) study. Serious pericardial effusion warranting surgical drainage (0.2% in CAP, 0.4% in PREVAIL, *vs.* 1.6% PROTECT-AF, P=0.03) and procedure-related stroke (0% CAP, 0.7% PREVAIL, *vs.* 1.1% PROTECT-AF, P=0.02) were both lower in the newer WATCHMAN studies (10,11).

In reality, about 30%–40% of eligible AF patients are not treated with appropriate stroke preventative therapy due to bleeding propensity (12). Currently, both the European Society of Cardiology and the American Heart Association/ American Stroke Association endorsed percutaneous LAA closure with a weak class IIB recommendation for patients deemed high cardioembolic risk who have contraindication to long-term OAC (13,14). Irrespective of the guidelines, patient selection varies geographically and eligibility criteria appear to be diverse. According to the European Heart Rhythm Association survey of 33 European centres, a number of indications have been identified to influence the selection process, including contraindication to OAC (94%), HAS-BLED ≥3 (55%), embolic events despite OAC (55%), end-stage renal failure (30%), triple antithrombotic therapy (24%) and intention to cease OAC after pulmonary vein isolation (15%). One centre even considered LAA closure as a substitute to OAC in the absence of elevated bleeding risk (15).

Another crucial aspect in the evolution of LAA closure is the practice of post-procedural antithrombotic therapy. Currently, the ideal combination remains unknown since there is lack of randomized comparative study. Historically, PROTECT-AF advocated warfarin post-implant, transitioning to DAPT at 45 days after the procedure, provided there is no significant residual peri-device leak. The alternative of antiplatelet therapy without OAC in the immediate post-implant period is increasingly preferred. The ASAP (ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology) registry utilized DAPT for 6 months post-implant without OAC, in an AF population with contraindications to OAC (16). The combined incidence of all-cause stroke

and systemic embolism with WATCHMAN was 2.3% per year, indicating a dramatic 77% reduction in observed annual ischemic stroke rate based on the $CHADS_2$ score of the patient cohort. Interestingly, there was no significant difference in the proportion of device-related thrombus when compared to PROTECT-AF with the OAC protocol post-implant. In the study by Wiebe *et al.*, patients (n=41) receiving DAPT after their procedures had notably low rates of intracranial bleeding and ischemic events (stroke and TIA) of 0.5% and 1.1% per annum, which also helped support the safety of antiplatelet therapy post-LAA closure during device endothelialisation period (10,16).

Additional contemporary real world data from the EWOLUTION registry was recently published. This large multicentre prospective non-randomized study enrolled over 1,000 patients (mean $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores 2.8±1.3, 4.5±1.6 and 2.3±1.2, respectively), and included 62% of patients considered inappropriate for chronic OAC. Almost 60% were treated with DAPT post-procedure. This latest study with WATCHMAN showed an impressive 98.5% procedural success rate, together with the lowest serious procedure-related safety adverse events at 7 days post-implantation at 2.8% (compared to 8.7% with PROTECT-AF, 4.1% with CAP registry, and 4.2% with PREVAIL). Furthermore, in this high-risk population, 30-day ischemic stroke events occurred in only 0.29%. As a whole, these results are of great importance in consolidating the therapeutic role of WATCHMAN for stroke prevention in the real world, especially in the cohort of patients considered ineligible for OAC (17).

The improved procedural success rates in contemporary series highlight the learning curve observed with WATCHMAN implantation, which is anticipated as operators acquire new skillsets and adopt implant strategies that minimize complications (10,17). There are also evidence that the required skillsets can be transferred successfully to new centres and operators with appropriate training (11,17). Hence, concern over under-performance related to the learning curve is unjustified, and should not be the obstacle for adoption of this novel therapy particularly in new sites.

In conclusion, we are starting to witness a global acceptance of LAA closure as a feasible stroke preventative therapy in non-valvular AF patients at risk for cardioembolic events, especially those with contraindications to long-term OAC. Data from randomized controlled trials and real-world registries have helped elucidate the safety and efficacy of this therapy. Future studies with longer-term efficacy data, and comparative trials against direct OAC and between different LAA closure devices are desirable to address current knowledge gaps.

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Footnote

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High risk percutaneous coronary interventions—significance of left ventricular assist device for clinical practice

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Cohen *et al*. have published the article (1), analyzing the use percutaneous left ventricular assist device (PLVAD) to support high risk percutaneous coronary intervention (HRPCI). The authors performed retrospective observational analysis of 339 patients included in the USpella registry, who were supported for HRPCI with a micro-axial rotational pump (Impella 2.5). There were patients that have met eligibility for the Impella arm of the PROTECT II trial (2). In-hospital outcomes of the USpella registry patients were compared with the results of 216 patients treated in the Impella arm of PROTECT II randomized trial. The authors concluded that despite the higher risk of registry patients, clinical outcomes appeared to be favorable and consistent compared with the randomized trial.

It is well known that, in patients affected by extensive and complex coronary lesions with elevated SYNTAX scores such as those with more advanced age, renal dysfunction and congestive heart failure, coronary artery bypass grafting (CABG) was associated with greater clinical benefit, as recommended by the current guidelines (3,4). Because of high operative risk among patients with severe coronary artery disease and multiple comorbidities, CABG intervention could be rejected either by the heart team (5), or by a patient. HRPCI remains a viable revascularization strategy for patients, who are not suitable for surgery or for those refusing it. However, such a subset of patients is considered to be at very high risk for percutaneous coronary intervention (PCI) complications, due to the risk of hemodynamic collapse during balloon inflations or complex procedures, particularly, if coronary dissection with vessel closure or no reflow occurs. Percutaneous mechanical circulatory support to go with HRPCI has been an important step to facilitate care and reduce morbidity and mortality among high-risk patient subsets (6-8). Nowadays, cardiovascular practice has seen rapid growth in cohorts that may benefit from the use of such devices (9). That is why the good results of USpella registry HRPCI patients is very important and the Cohen's *et al*. article is relevant.

It is often thought that patients enrolled in coronary intervention trials are not representative of real-world patients and randomized trial patients are carefully selected with significantly less risk than those treated in a native clinical practice (10). Thus, we expect worse treatment results in real life. The same could be seen in Cohen's *et al.* baseline characteristics analysis. Registry patients were more likely to have chronic kidney disease, prior myocardial infarction, prior CABG, and had more extensive coronary artery disease. However, in-hospital results were inexplicably perfect for registry patients. The mortality in USpella patients was numerically lower than the mortality in the Impella arm of PROTECT II trial and myocardial infarction and repeat revascularization rates were significantly lower in registry patients. There were no incidents of stroke or transient ischemic attacks, emergency CABG, acute aortic regurgitation or valve injury in the registry. Other adverse events including vascular complications, blood transfusions, acute kidney injury, groin hematoma, and transient hypotension during support were similar for the registry and clinical trial patients. Surprisingly better results in a more severe group of USpella registry patients hint at the presence

of patient selection bias.

At present, variables that contribute to elevated risk during PCI have been well defined by 2015 SCAI/ACC/HFSA/STS clinical expert consensus statement (11) and can be categorized into three major groups: (I) patient specific; (II) lesion specific; and (III) clinical presentation specific. The Cohen's *et al*. article shows well the patient specific (age, left ventricular function, symptoms of heart failure, diabetes mellitus, chronic kidney disease, prior myocardial infarction, peripheral vascular disease) and the lesion specific data (multivessel or left main disease, saphenous vein grafts) in both USpella registry and the Impella arm of PROTECT II trial patients. However, the authors did not provide the analysis of patients' clinical presentation. We cannot understand how many patients with acute coronary syndrome or stable angina were in the study groups. The only information that we have from the authors is that patients with ST segment elevation myocardial infarction and cardiogenic shock were excluded (1).

We did not have any data about the proportion of non-ST elevation acute coronary syndrome patients in the registry and clinical trial groups. Nevertheless, we had the evidence of an extremely poor prognosis in non-ST elevation acute coronary syndrome patients with multivessel disease (non-STEMI patients with MV disease) that often undergo HRPCI. For example, based on a single-center real life registry the hospital mortality in the overall cohort of non-STEMI patients with MV disease was 8.7% (in the PCI group: 5.8%, 8% in the CABG group, and 27.8% in the conservative strategy group) (12). In addition, the analysis showed that the majority of non-STEMI patients with MV disease are candidates for emergency or urgent PCI, which can be successfully performed. However, a significant proportion of patients should be considered as candidates for CABG. A significant proportion of patients requiring revascularization by CABG does not get it at the optimal time, which leads to the conversion of a certain number of non-STEMI patients to conservative therapy associated with a very poor prognosis. Non-STEMI patients with MV disease represent a large group of patients with acute coronary syndrome who may be targeted for PLVAD-supported HRPCI (12).

The Cohen's *et al*. article is a very relevant paper that demonstrates encouraging results using PLVAD (Impella 2.5) for patients undergoing high-risk PCI in real-world practice. These in-hospital results were inexplicably perfect for registry patients compared to the Impella arm of PROTECT II randomized trial. Better results in the registry patients may be due to patient selection bias associated with the lack of detailed acute coronary syndrome presentation analysis.

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Footnote

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Percutaneous left ventricular assist device in high risk percutaneous coronary intervention

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"*As to diseases, make a habit of two things-to help, or at least do no harm.*"—Hippocrates.

High-risk candidates for percutaneous coronary intervention (PCI) may include patients with severe multi-vessel coronary artery disease, unprotected left main coronary artery stenosis, or last patent conduit with a stenosis, especially in patients with a left ventricular (LV) ejection fraction of ≤35% (1-4). In addition, the condition and co-morbidities of the patient should be taken into consideration. Traditionally, revascularization in these patients could be better accomplished with coronary artery bypass graft (CABG) surgery; however, sometimes these patients are high-risk surgical candidates, have advanced age and/or have poor distal targets for bypass surgery (5). PCI in these patients is a viable option, however, episodic interruption of blood flow to the target coronary artery in these high-risk patients during contrast dye injections, balloon inflation and stent implantation may result in a decrease in LV performance raising procedural morbidity and/or mortality (3,4,6). Currently, it is thought that hemodynamic support devices like the Impella (Abiomed, Danvers, Massachusetts) percutaneous left ventricular assist device (PLVAD) or intra-aortic balloon pump (IABP) may provide support during high-risk PCI (2,3,7-9).

The largest high-risk PCI study using hemodynamic support available today is the PROTECT II trial that compared Impella 2.5 PLVAD to IABP (3). In this study, 452 symptomatic patients were randomized to Impella (n=226) or IABP (n=226) during high-risk PCI. Patients had a LV ejection fraction of ≤35% with a last patent conduit with a stenosis or unprotected left main coronary artery stenosis, or had a LV ejection fraction of ≤30% with severe three vessel coronary artery disease. The Impella 2.5 is a rotary pump that provides blood flow from the LV into the ascending aorta up to 2.5 L/min. This results in an increase in cardiac output, decrease in myocardial oxygen consumption, and decrease in LV diastolic and pulmonary capillary wedge pressures. The Impella is delivered percutaneously through a 12 French (F) sheath via the femoral artery and is placed in the LV in a retrograde fashion extending across the aortic valve. The Impella became available in the United States of America in 2008 (10,11). The PROTECT II trial demonstrated that in high-risk patients, PCI could be successfully performed using either Impella or IABP. The Impella compared to IABP provided better hemodynamic support with a greater cardiac power output and was associated with a reduction in adverse events driven mostly by a decrease in repeat revascularization at 90 days (3). To better define the effect of Impella in the "real-world", Cohen *et al.*, in a retrospective analysis using data from the USpella registry, compared the results of the Impella arm from the PROTECT II trial to those of the USpella registry patients; these findings were published in the November 2015 issue of the *American Heart Journal* (12).

USpella is an observational on-going multi-center voluntary registry of Impella use in which 47 sites in the United States and 2 sites in Canada are participating.

From this registry, a total of 637 high-risk PCI patients were identified who were supported with the Impella 2.5 during PCI. Of the 637 patients, 339 were identified as having met eligibility criteria for enrollment in the PROTECT II trial referred to as PROTECT II "like" patients. All patients from the USpella registry (n=637) and the sub-group of PROTECT II "like" patients (n=339) from the registry were compared with the patients randomized to the Impella arm from the PRTOETCT II trial (n=216). Baseline characteristics were mostly similar with some noticeable differences between the USpella registry and PROTECT II trial patients. Overall patients in the USpella registry were older, had higher incidence of chronic kidney disease, had less prior CABG or myocardial infarction, and greater LV ejection fraction compared to the PROTECT II trial patients. The PROTECT II "like" patients from the USpella registry were older, had less prior CABG or myocardial infarction, had more prior PCI, had more severe heart failure symptoms, and lower LV ejection fraction compared to the PROTECT II trial patients. All groups had a similar Society of Thoracic Surgery (STS) surgical risk score of approximately 6%. The total number of patients and the PROTECT II "like" patients from the USpella registry had a significantly higher number of diseased coronary arteries and total number of lesions compared to the PROTECT II trial patients; however, the number of treated lesions and number of stents were significantly higher in the PROTECT II trial likely due to the requirement by the trial to perform the most complete revascularization as possible in a single procedure (3,12).

Blood transfusions where not statistically different between the overall USpella registry patients (11%) and the PROTECT II "like" patients (9%) when compared to the PROTECT II trial patients (12.5%). Vascular complications requiring surgery were also not statistically different between the overall USpella registry patients (2.5%) and the PROTECT II "like" patients (2.3%) when compared to the PROTECT II trial patients (1.4%); however, vascular complications not requiring surgery where significantly lower in the overall USpella registry (5.1%), but not the PROTECT II "like" patients (5.6%), when compared to the PROTECT II trial patients (9.3%; P=0.03). Mortality in the USpella registry was numerically lower, but not statistically significant when compared to the PROTECT II trial (overall USpella registry 2.8%; PROTECT II "like" patients 2.7%; PROTECT II trial 4.6%). Myocardial infarction was also significantly lower in the USpella registry (overall USpella registry 1.3%; PROTECT II "like" patients 0.3%; PROTECT II trial 15.3%), as was repeat revascularizations (12). The lower rate of peri-procedural myocardial infarction likely was due to more stringent checking of cardiac biomarkers after PCI in the PROTECT II trial. In addition, one cannot exclude lack of documentation in the registry data, thus capturing less adverse events including repeat revascularization.

Data from the USpella registry demonstrated that "real-world" patients who underwent high-risk PCI using Impella support mostly had similar baseline characteristics and derived similar results to those patients enrolled in the Impella arm of the PROTECT II randomized trial (12). Interpretation of these results are important as utilization of PLVAD for prophylactic use in high-risk PCI has increased significantly over the last decade (13). Per the 2011 PCI Guidelines by the American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions, the elective insertion of an appropriate hemodynamic support device as an adjunct to PCI may be reasonable in carefully selected high-risk patients, however, this recommendation was based on expert opinion (4). Recommendations and increased popularity of PLVAD must be closely counterbalanced with their procedural morbidity, particularly bleeding and vascular complications due to larger vascular access needed for device insertion and due to the fact that two arterial access sites must be used, one for the Impella and one for PCI. Thus, the important question that arises is when is it necessary to use a PLVAD. There are certainly cases that Impella may be useful in high-risk PCI similar to those identified in the PROTECT II trial. It should be mentioned, however, that in similar high-risk patients PLVAD was not used also resulting in good outcomes. There is a lack of data in high-risk PCI comparing Impella with no Impella, and the decision currently solely falls on the interventional cardiologist clinic experience and judgment when to use a PLVAD.

The potential risk associated with larger vascular access for the Impella device and the need for a second arterial access site needs to be carefully deliberated when considering its use. A high rate of blood transfusions (11%) was noted in the USpella Registry (12). There was a learning curve effect, however, as transfusion rates decreased over the years from 12% in 2009 to 6% in 2011 as operators became more adept and proficient with vascular

access and the utilization of percutaneous closure techniques for large vascular access sites; a similar trend was seen in the PROTECT II trial (3,12). In the original PROTECT I trial, the incidence of bleeding was greater compared to PROTECT II with a hematoma incidence of 40%, however, this study included a small number of patients (2). In addition, several other studies have demonstrated bleeding complications associated with Impella use during PCI in high-risk patients ranging from 6% to 40% (2,14-17). Further, the incidence of bleeding is high with prolonged use of a hemodynamic support device (18). It should be emphasized that bleeding associated from PCI when evaluated in over 300,000 patients from the CathPCI National Cardiovascular Data Registry (NCDR) from January 2004 to March 2006 was only 2.4% (19).

Vascular complications were high with Impella use in the USpella registry and PROTECT II trial (12). In addition, other studies have also reported increase vascular complications as high as 15% likely associated from larger sheath size placement in the femoral artery in order to accommodate the 12F Impella device and need for a second arterial access site (14,17,20). In an observational study of over 100,000 patients undergoing PCI via femoral artery access using a 6F, 7F or 8F guiding catheter, vascular complication rates significantly increased with larger guiding catheter size. Post-procedural hemoglobin was more likely to fall by >3 g/dL in the 7F and 8F guiding catheter groups with a significantly higher rate of blood transfusions as compared to the 6F catheter group. Vascular access site complications were higher in the 8F group regardless of whether a vascular closure device was used (21). As a comparison, when analyzing over 3,000,000 patients from the CathPCI NCDR from January 2007 to September 2012, vascular complications were only 0.45% when femoral artery access was obtained for PCI (22).

Bleeding and vascular complications associated with PCI are much lower than reported in studies when using Impella, however, comparison may be misleading due to lack of knowledge of underlying patient co-morbidities, vascular access site information, type of pharmacotherapy used, and extent of coronary artery disease requiring PCI, but should be carefully noted.

The USpella registry and PROTECT II trial demonstrate favorable results with Impella use during high-risk PCI (3,12). The Impella can provide adequate hemodynamic support possibly preventing morbidity and mortally during high-risk PCI. The pioneering work by Dr. O'Neill and team on LV assist devices, particularly the Impella, have added considerable knowledge to the field. The Impella has provided interventional cardiologist with a tool to provide hemodynamic support during high-risk PCI to inoperable patients in which may have been treated medically in the past. However, it is important to not dismiss that given the larger sheath size and use of two arterial access sites the risk of sustaining higher rates of vascular and/or bleeding may occur. In addition, prolonged use of Impella may further increase complications. For obvious reasons, a control group was not used in these studies. It should be noted, however, that certain "gold standard" procedures in the past (e.g., IABP, leave-in pulmonary artery catheter, others) were eventually shown to have no benefit (23,24). Although unlikely, it would be of great clinical importance if a small pilot study were conducted to answer this important question; perhaps, Dr. O'Neill with his extensive experience and clinical wisdom can conduct such a study. It should also be noted that the Impella has enabled interventional cardiologist to perform complicated procedures and thus, has enhanced their experience; these interventional cardiologist are now often able to perform the same procedures without the Impella due to this experience. At present, it is prudent that careful selection of patients who would net a clinical benefit from undergoing prophylactic Impella insertion be determined on a per patient basis guided by clinical experience and judgment, and on cardiac catheterization laboratory experience. This dilemma will likely be encountered more frequently as patients with complex coronary artery disease are turned down for CABG due to their significant co-morbidities and more of these patients are treated with high-risk PCI; however, in our efforts to help, we should be careful and "*at least do no harm*" (25).

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Footnote

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Shedding light on the gray zone

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Over two decades have passed since Pijls *et al.* proposed that invasively-determined myocardial fractional flow reserve (FFR) could serve as an index of the functional severity of coronary artery stenosis (1). FFR is derived from the ratio of mean pressure at the distal epicardial coronary conduit of an atheromatous coronary lesion to that of the aortic root in pharmacologically induced hyperemia, and represents the very fraction of maximal myocardial blood flow (MBF) that can be maintained despite coronary artery stenosis. The theoretical normal value of FFR is 1.00 regardless of the patient, the specific vessel studied or concurrent hemodynamic changes. However, when the microcirculation remains intact, the FFR value falls with the progression of a flow-limiting coronary lesion and as an increasing amount of myocardium becomes supplied by a flow-limiting coronary artery. Sequential non-invasive exercise tests, myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) and stress echocardiography have confirmed that an FFR value of ≤0.75 represents stress-inducible myocardial ischemia (2). The DEFER trial (3) demonstrated that the revascularization (REV) of coronary stenosis with FFR >0.75 did not improve clinical outcomes compared with those of patients deferred to receive optimal medical treatment (OMT). Otherwise, the subsequent FAME II (Fractional Flow Reserve Guided PCI versus Medical Therapy in Stable Coronary Disease II) clinical trial (4) showed that REV of coronary stenosis with FFR ≤0.80 improved clinical outcomes compared with OMT alone. Thus, FFR values between 0.75 and 0.80 are referred to as the FFR gray zone, namely, an area of uncertainty regarding the actual degree of ischemia in patients with stable coronary artery disease (CAD). This gray zone of uncertainty affects decisions about which patients are selected for REV and those that will receive OMT.

The authors focused on patients in the gray zone, and confirmed the prognostic legitimacy of REV in such patients. They classified 1,459 patients with single-segment disease and FFR values within three strata as ischemic, gray zone and non-ischemic (0.70–0.75, 0.76–0.80 and 0.81–0.85, respectively) in a retrospective single-center study. The clinical endpoints of major adverse cardiac events (MACE) defined as the composite of overall death, myocardial infarction (MI) and target vessel REV were assessed in 1,010 of the patients who received OMT alone and 449 who were treated by REV + OMT and were followed up for 25 (range, 6–48) and 26 (range, 13–47) months, respectively. Although differences in MACE rates between patients treated with OMT alone and with REV + OMT were not statistically significant in the gray zone, trends towards higher rates of death or MI and overall death were observed in the group treated with OMT alone in comparison with REV + OMT (9.4% *vs.* 4.8%, P=0.06 and 7.5% *vs.* 3.2%, P=0.059, respectively). An increase in the MACE rate was statistically significant across the three FFR strata in the OMT group, especially when the lesion was proximally

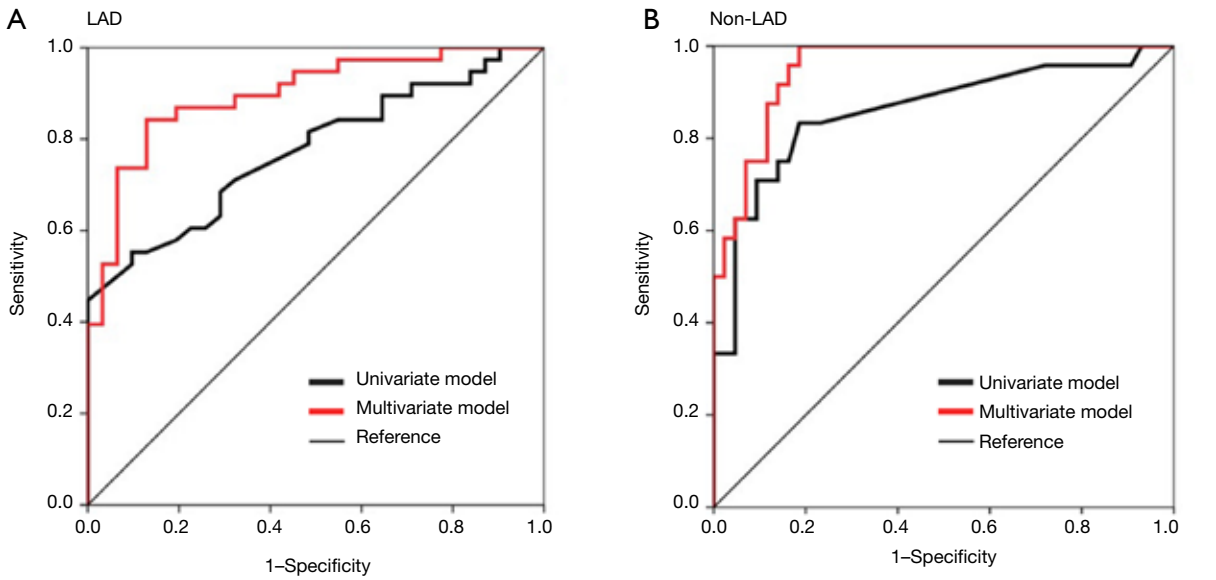
Table 1 Multivariate analyses of independent factors predicting FFR <0.80 among quantitative parameters of myocardial perfusion abnormalities and non-invasive parameters

Parameter	Coefficient	SE	P	OR	95% CI	
					Lower	Upper
LAD						
Stress TPD—rest TPD (%)	0.909	0.295	0.002	2.481	1.391	4.427
TID ratio	1.343	0.441	0.002	3.832†	1.615	9.093
LVEF at rest (%)	–0.117	0.041	0.004	0.889	0.821	0.964
β-blockers	–2.392	1.024	0.020	0.091	0.012	0.681
Constant	–6.750	3.873	0.081			
Non-LAD						
Stress TPD—rest TPD (%)	1.275	0.439	0.004	3.579	1.515	8.453
LVM (g)	–0.036	0.014	0.009	0.965	0.940	0.991
LVEF at rest (%)	–0.105	0.046	0.021	0.900	0.823	0.984
RCA lesions (%DS ≥50%)	4.188	1.843	0.023	65.859	1.778	2,439.761
TID ratio	–0.967	0.468	0.039	0.380†	0.152	0.952
Age (years)	–0.112	0.067	0.092	0.894	0.784	1.018
Constant	25.123	9.295	0.007			

†, change in transient ischemic dilation ratio of 0.1 corresponds to described OR. CI, confidence interval; DS, diameter stenosis; FFR, fractional flow reserve; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; OR, odds ratio; RCA, right coronary artery; SE, standard error; TID, transient ischemic dilation; TPD, total perfusion defect. Reproduced with permission from the publisher (9).

located. Otherwise, the MACE rate remained similar in the REV + OMT group regardless of the actual FFR value. These findings could serve from a prognostic viewpoint as a rationale for selecting REV to treat patients in the gray zone especially those with proximal lesions.

This evidence has also raised the issue of how to non-invasively diagnose patients who have stable CAD and flow-limiting coronary lesions corresponding to FFR ≤0.80. Coronary computed tomographic angiography (CCTA) derived FFR (FFR_{CT}) is a novel and promising non-invasive approach that can precisely localize flow-limiting coronary artery stenosis as it applies computational fluid dynamics to calculate the FFR of each of three vessels from image acquisition by the standard rest CCTA study without a need for vasodilator-stress conditions. Although its application to severely calcified coronary arteries and patients with chronic kidney disease is somewhat limited, FFR_{CT} might serve as a promising gatekeeper for invasive FFR assessment in routine clinical practice, because clinical data have shown strong correlation with invasive FFR and a reduction in false-positive findings in standard interpretation of CCTA images (5). Another potent modality that could address this issue is MPI-SPECT, because a nuclear sub-study of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (6) demonstrated that MPI-SPECT findings could predict improved outcomes after REV. However, to predict FFR solely by standard interpretation of MPI-SPECT images seems somewhat limited, because MPI-SPECT findings represent changes in relative MBF between hyperemia and the resting state that can be affected by microcirculatory and myocardial properties in addition to epicardial coronary perfusion. Furthermore, interpretation is dependent on the presence and accurate identification of a region of normal perfusion. This is a particular impediment in diffuse or multi-vessel disease that could include, "balanced ischemia" and a scant obviously normal reference region (7). Actually, FFR and invasive coronary flow reserve (CFR) values have



	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
Univariate model	0.774 (0.665–0.883)	71	68	73	66
Multivariate model	0.897 (0.824–0.971)	84	87	89	82

	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
Univariate model	0.861 (0.761–0.962)	54	95	87	79
Multivariate model	0.953 (0.909–0.996)	75	93	86	87

Figure 1 Comparison of diagnostic accuracy of multivariate and univariate models using stress TPD—rest TPD to predict regions of interest with coronary lesions corresponding to FFR <0.80. Receiver operating characteristic curves were developed based on univariate and multivariate logistic regression analyses using stress TPD—rest TPD to predict whether LAD (A) and non-LAD (B) regions have lesions with FFR <0.80. Diagnostic accuracy at predicted value of 0.50 in LAD regions was better and AUC was larger (P=0.013) in multivariate, than in univariate models. Despite improved diagnostic accuracy, AUC in non-LAD region did not significantly differ between univariate and univariate models (P=0.054). Net reclassification analysis revealed that multivariate model significantly reclassified 15% of FFR ≥0.80 and 13% of FFR <0.80 predicted by the univariate model. AUC, area under the curve; CI, confidence interval; FFR, fractional flow reserve; LAD, left anterior descending artery; NPV, negative predictive value; PPV, positive predictive value; TPD, total perfusion defect. Reproduced with permission from the publisher (9).

occasionally been mismatched, especially in patients with diffuse diseases of epicardial conduit vessels or diseases of the coronary microvasculature (8). We recently showed that a flow-limiting FFR of <0.80 could be predicted from findings of quantitative MPI with quantitative perfusion SPECT (QPS) and other non-invasive parameters identified by multivariate analyses (*Table 1*) (9) by assessing 136 diseased vessels in prospectively-identified 84 patients with stable CAD who were assessed by MPI-SPECT and invasive FFR. The formulas based on these analyses demonstrated to predict major vessels of interest with FFR <0.80 with defined probabilities (sensitivity, specificity and accuracy for LAD and non-LAD: 84%, 87% and 86%, and 75%, 93% and 87%, respectively) (*Figure 1*) (9). Although somewhat limited by a sample size and a single-center design, an appropriately-designed validation cohort study might provide a novel adjunctive tool that could diagnose functionally significant CAD from MPI findings.

Other approaches to assess parameters that might be more appropriate to the physiological characterization of CAD than FFR are in progress. Absolute MBF quantitation, measurable in the order of mL/g/minute, which allows the non-invasive calculation of myocardial flow reserve (MFR) or CFR using stress cardiac positron emission tomography (PET) demonstrated superior risk stratification and incremental prognostic value (10,11). However, a benefit of CFR quantitation in terms of selecting patients for REV has not yet been demonstrated in randomized clinical trials.

Absolute MBF quantitation using stress cardiac magnetic resonance (CMR) (12) or dynamic SPECT imaging (13) is based on a theory similar to that of cardiac PET. However, more evidence is required before this concept could be applied to routine clinical practice.

The issue then, is whether or not all patients with stable CAD should be assessed by invasive FFR. We believe that a non-invasive diagnostic modality or a combination of such approaches with highly accurate prognostic value for stable CAD that can precisely clarify the contribution of epicardial coronary stenosis to abnormal findings, might eventually resolve this issue.

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Footnote

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The fractional flow reserve gray zone has never been so narrow

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Fractional flow reserve (FFR) is the gold standard in the invasive hemodynamic assessment of epicardial coronary artery stenoses. FFR is defined as the ratio of maximal flow achievable in the stenotic coronary artery to the maximal flow achievable in the same coronary artery if it was normal. In other words, FFR informs the clinician to what extent blood flow is reduced and can be improved after revascularization: e.g., a FFR of 0.60 means that coronary blood flow is 60% of what should be in the absence of the epicardial stenosis, and it could improve by 40% after percutaneous coronary intervention. FFR is highly reproducible, has an unequaled spatial resolution and it is easy to measure during diagnostic coronary angiography. A FFR ≤0.75 has 100% positive predictive value, whereas FFR >0.80 has more than 95% negative predictive value for reversible myocardial ischemia at non-invasive functional testing (1). The DEFER trial, conducted in the era of bare metal stents, has demonstrated that it is safe to defer to medical therapy coronary stenoses with FFR above 0.75 in stable patients with single vessel disease (2). In the era of drug eluting stents, the threshold of 0.80 was adopted in the FAME 1 and 2 trials to guide clinical decision-making, because in a minority of patients an FFR value between 0.75 and 0.80 was found to be associated with typical exercise-induced angina and reversible flow maldistributions (3). Performing revascularization of coronary stenosis with FFR ≤0.80 has been consistently associated with improved clinical outcome in randomized trials as well as in routine clinical practice (4,5). Nevertheless, none of these studies have specifically investigated the clinical impact of coronary stenoses with FFR within the so-called gray zone of values comprised between 0.75 and 0.80. Johnson *et al.* demonstrated a risk continuum between FFR and clinical outcome (6), i.e., the lower the FFR values the higher the risk of cardiovascular events if these patients are treated with conservative therapy. Conversely, the benefits potentially deriving from revascularization progressively increase with decreasing FFR values. Interestingly, the balance between risks and benefits of revascularization tilts over to optimal medical therapy just in correspondence of the FFR gray zone. In fact, with FFR values above 0.80 no additional clinical benefits are to be expected from revascularization as compared with medical therapy, but rather an inappropriate increased iatrogenic risk of events related to the procedure or to the associated antiplatelet therapy. This risk continuum has been recently confirmed also in the narrow range of FFR values comprised between 0.70 and 0.85 (7). In fact, a progressive decrease in major adverse cardiovascular event (MACE)-free survival has been observed in patients with single vessel single stenosis but with FFR values going from 0.85 to 0.70 (*Figure 1*). This gradient of MACE rate was particularly evident with lesions located in proximal coronary segments, underscoring the importance to warrant revascularization to these stenoses even with FFR values within the gray zone of 0.75–0.80.

Dr. Tanaka *et al.* recently highlighted the challenges and opportunities of non-invasive diagnostic imaging in detecting coronary stenoses with abnormal FFR values (i.e., ≤0.80), raising the question if invasive FFR assessment is indeed necessary in all patients with stable coronary

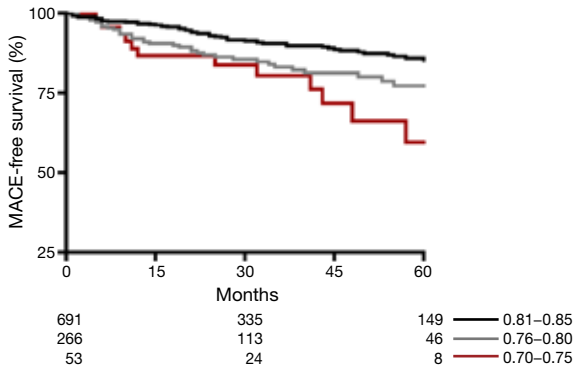

Figure 1 MACE-free survival (%) in patients of the medical therapy group stratified by FFR strata (log-rank, 15; P<0.001) [adapted from (7)]. FFR, fractional flow reserve; MACE, major adverse cardiovascular event.

artery disease (8). In patients with single vessel disease and clear-cut positive non-invasive functional evaluation, clinicians might refrain from performing additional tests and undertake the appropriate decision-making based on the coronary angiography. Yet, FFR in this setting might still confirm the relative contribution of the epicardial disease to the ischemic burden and suggest the expected improvement achievable in the coronary flow after revascularization. In patients with multivessel disease, the role of invasive FFR is paramount due to the limited spatial resolution of traditional non-invasive functional assessment. In these patients, the interventional cardiologists are aware of the presence of an ischemic substrate though are left with dilemmas as to which coronary segment is indeed responsible and deserves revascularization. Nevertheless, novel techniques like the FFR-derived from coronary computed tomography angiography (FFR-CT), the CT perfusion (CTP), the Transluminal Attenuation Gradient by 320-detector row computed tomography (TAG320) or the combined myocardial perfusion scintigraphy with CT (MPS-CT) are raising increasing interest for their ability to provide non-invasively both anatomic and hemodynamic information of coronary artery. Initial studies have, in fact, confirmed improved specificity, and superior diagnostic accuracy as compared with the traditional techniques to predict abnormal invasive FFR values (9). In addition, these techniques might significantly impact the management strategies by reducing the rate of patients with non-obstructive coronary artery disease referred to invasive angiography (10). Remaining potential challenges associated with some of these techniques like the dose of radiations and volume of contrast medium might still hamper their widespread application.

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Footnote

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Very long-term follow-up for left main coronary artery stenting: a missing piece of the jigsaw puzzle

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Significant left main coronary artery (LMCA) stenosis, which is defined as a 50% diameter stenosis that corresponds to a 75% area stenosis of the LMCA, is found in approximately 5%–10% of all coronary angiograms performed for symptomatic coronary artery disease (1,2). Data obtained before the modern age of pharmacotherapy of coronary artery disease suggested that significant LMCA stenosis has a very grim prognosis when treated medically, with a mortality rate of 50% within 3 years of diagnosis (3,4). Coronary artery bypass surgery (CABG) offered superior and durable survival advantage over medical therapy, which was supported by very long term follow-up data up to 10 years' post-bypass (5,6). After these seminal works, CABG was accepted as the gold standard—and perhaps the singular—treatment for significant LMCA stenosis. This assumption was never questioned until the recent technical developments had allowed safe and durable revascularization with percutaneous coronary intervention (PCI).

As the LMCA supplies the majority of blood flow to the left ventricle, an acute closure of the vessel during or after the procedure nearly uniformly leads to catastrophic events. High elasticity of the LMCA vastly increases the rate of elastic recoil following balloon dilatation (7). These two features of LMCA intervention makes the vessel a highly unattractive target for sole balloon angioplasty, which was noted by Grüntzig himself in his original description of percutaneous transcatheter balloon angioplasty (8). With the advent of stents, however, the rates of abrupt vessel closure dropped dramatically, paving the way for PCI for unprotected LMCA stenosis.

Short and long-term follow-up data for unprotected LMCA stenting

Bare-metal stents (BMS) offered high periprocedural success rate that offered an option for revascularization in patients deemed high risk for surgical revascularization or when the LMCA occlusion was acute as a result of myocardial infarction (MI). Short and mid-term follow up data for BMS, however, had indicated target lesion revascularization (TLR) rates as high as 20%, and higher mortality rates compared to CABG.

Following the introduction of drug-eluting stents (DES), the interest for percutaneous LMCA intervention was renewed as the need for repeat revascularization was significantly lower in patients treated with a DES. The prespecified subgroup analysis of the SYNTAX trial that compared paclitaxel eluting stents with CABG showed that neither major adverse cardiovascular or cerebrovascular events (MACCE), nor mortality was significantly different in patients treated with DES, as compared to patients treated with CABG (9). The five year results of the PRECOMBAT trial, which was a dedicated study that only included patients with an unprotected LMCA stenosis (10) showed a mortality rate of 5.7% with sirolimus eluting stents. The MAIN-COMPARE registry, which was the largest registry that had directly compared unprotected LMCA stenting with CABG, demonstrated that event-free survival was 88.5% for BMS and 87.3% for DES groups (11). A common theme that was constantly observed in all registries and randomized controlled trials (RCTs) was a

higher TLR rate in PCI group, which necessitated repeat intervention or CABG, but this high TLR rate did not translate into an increase in mortality (9-12). Although TLR rate was higher for both BMS and DES, the rate of stent thrombosis was low at short and long term, with the majority of studies had reported a definite stent thrombosis rate of <2%. In the MAIN-COMPARE registry, 11 of 784 patients who underwent DES implantation had experienced definite stent thrombosis at 5 years (1.4%), and only 4 them had very late stent thrombosis although older-generation DES were used at the time of registry. A recent study utilizing newer-generation DES platforms (everolimus and zotarolimus coated stents) for unprotected LMCA disease reported 1-year mortality rates similar to older-generation DES, but with a possible reduction in MI (13). More data on the safety and comparative efficiency for newer-generation DES will be available after the completion of the EXCEL (Evaluation of Xience Prime or Xience V Versus CABG for Effectiveness of Left Main Revascularization) study.

Very long-term data for the feasibility of unprotected left main stenting: the LE MANS trial

One piece of critical data missing for unprotected LMCA interventions is the very long term (10 years or more) follow-up results, which is available for CABG (14). As CABG was considered as the benchmark therapy for revascularization of unprotected LMCA stenosis, until recently, very long term data on unprotected LMCA interventions were limited and biased as only patients that did not accept CABG or patients who deemed too risky for surgical intervention were included to registries and retrospective studies. In the ASAN-MAIN registry (15), 10-year results for BMS indicated that even implantation of BMS is safe for unprotected LMCA stenosis as cardiac mortality at 10 years (6.9%) was similar to CABG (11.0%, P=0.1). As expected, both repeat revascularization (43.1% *vs.* 6.7%, P<0.001) and TLR (24.9% *vs.* 4.9%, P<0.001) was higher in BMS group compared to CABG. While the results of ASAN-MAIN registry had hinted that stents (even BMS) are a safe alternative to CABG for unprotected LMCA lesions, as aforementioned before, retrospective data is inherently biased and data from RCTs should be available before establishing the safety of percutaneous interventions for unprotected LMCA.

In this regard, the LE-MANS RCT (16) was the first study that had reported 10 years results for unprotected LMCA intervention, as compared to CABG. The initial study group included 52 patients allocated to PCI (35 patients with DS and 17 patients with BMS) and 53 patients allocated to CABG groups. At 10 years, the investigators have reported that the survival rate was close to 70% in PCI group, and MACCE-free survival was numerically better for PCI (OR: 1.57, P=0.1). In contrast to previous studies and registries that had reported more repeat revascularization and a higher TLR for percutaneous interventions, the LE-MANS trial found that the rate of repeat revascularization was comparable between PCI and CABG groups (P=0.46), mainly due to an increase in repeat revascularizations in CABG group two years after the operation. Finally, the authors had reported a higher ejection fraction in PCI group as compared to CABG group (54.9%±8.3% *vs.* 49.8%±10.3%; P=0.07), although this latter finding did not reach statistical significance.

Perhaps the most important finding of the LE MANS study was the demonstration of a similar survival rate in PCI and CABG groups both in the short, long and very long terms (16), thereby suggesting that the excellent short-term results obtained with PCI is durable and safe, even 10 years after the index revascularization. As the number of patients included in LE MANS study was relatively low (n=52 for PCI and n=53 for CABG groups), these preliminary findings should be regarded as hypothesis-generating rather than definite in the absence of data from larger RCTs, such as SYNTAX or PRECOMBAT (9,10). The analysis of SYNTAX score for LE MANS cohort revealed that all patients included in the study had syntax scores <32 (low and middle SYNTAX groups). A similar finding was also reported in the 5-year data of the SYNTAX study, suggesting that patients with less complex lesions or lesions limited to LMCA have a survival rate similar to CABG after LMCA interventions (9). Therefore, these "excellent" very-long term results of the LE MANS study should be interpreted in this context, and are not necessarily applicable to patients with more complex lesions (i.e., bifurcation lesions) or those with extensive coronary artery disease.

A more controversial finding from the LE MANS study was the similarity of TLR and repeat revascularization in PCI and CABG groups, which was not supported by previous registry and RCT data (9,10,16,17). Special subsets of patients, such as patients with LMCA aorto-osteal or shaft lesions, or patients treated with provisional one-stent technique for distal bifurcations lesions, were known to have comparable (11,17-19) TLR rates with CABG. The

angiographic properties of the patients included in the LE MANS study were similar to other studies reported in the literature, and patients with a distal LMCA stenosis received bifurcation stents as needed (13,16). Therefore, neither patient characteristics nor the interventional techniques could explain this exciting yet extraordinary findings. As aforementioned before, the number of patients included in the LE MANS study was limited, so the results should be interpreted with caution and more data from larger studies should be waited before suggesting a similar revascularization rate in PCI and CABG groups in the long term.

Conclusions

While there are abundant data on short and long term survival following unprotected LMCA intervention, data on very long-term survival after unprotected LMCA stenting was notably missing. In this regard, the LE MANS trial was the first RCT that provided evidence for the efficiency and safety of stents in the very-long term. As the number of patients included in the study was quite low (only 52 patients were randomized to the PCI group), statistical power of the study was severely limited. The very-long term safety and efficiency of stents will be better defined in the future as more data emerges from the large RCTs and studies. Other surprising findings of the LE MANS study, such as the similar repeat revascularization rate in PCI and CABG groups, definitely needs further data as the majority of large studies and RCTs conducted so far had suggested an increase in TLR and repeated revascularization in PCI patients followed-up for short and long term.

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Completeness of revascularization in multivessel coronary artery disease

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Multivessel coronary artery disease (CAD) is frequently encountered in clinical practice among patients with both stable and unstable presentations (1). The question of whether such patients should undergo complete (CR) versus incomplete (IR) revascularization continues to be debated (1-3). This issue was originally recognized and described among patients undergoing coronary artery bypass graft (CABG) surgery, where it was observed that CR conferred both a survival and symptomatic benefit in comparison to IR (3), with CR consequently achieving the stature of a surgical mantra and accepted as a truism (4).

Despite a wealth of studies exploring whether the goal the revascularization should be CR, numerous questions exist at the present time (*Figure 1*). These dilemmas arise not only from clinical studies with conflicting results, but also because our understanding of how we define CAD has evolved over time with a shift towards pursuing functional CR, in which ischemic-causing lesions undergo coronary revascularization [CABG, percutaneous coronary intervention (PCI) or hybrid] and non-ischemic lesions are treated with optimal medical therapy (5-7).

In a single-center, prospective, observational, cohort study of consecutive patients with multivessel CAD undergoing PCI with drug-eluting stents (DES) from January 2003 through December 2013, Chang *et al.* compared outcomes in those with CR *vs.* IR (8). Using propensity-score matching, there was no significant difference in the primary outcome of all-cause mortality (8.6% *vs.* 9.0%; HR 1.03; 95% CI, 0.80–1.32, P=0.83), as well as in the secondary outcomes of stroke and repeat revascularization; whereas the risk of acute myocardial infarction (MI) on follow up was higher in those with IR *vs.* CR (HR 1.86; 95% CI, 1.08–3.19, P=0.02) (8).

We offer the following observations. First, the study by Chang *et al.* used an anatomical definition of CR, in which CR was defined as the absence of diameter stenosis ≥50% in major epicardial coronary arteries or their side branches with diameter ≥2.5 millimeters after successful stent implantation during index hospitalization irrespective of the function or viability of relevant myocardium (8). It should be emphasized that there is no guideline or expert-consensus document addressing how CR should be defined with various existing definitions as summarized in *Table 1* (1,2,9). While the anatomical-based definition has been the most widely used classification in completeness studies, reported in nearly 90% of manuscripts included in a large meta-analysis (10), in contemporary clinical practice, a functional and/or physiological approach is encouraged. According to this definition revascularization of ischemic territories, as demonstrated by either non-invasive stress testing or fractional-flow reserve, is pursued while medical management is recommended for non-flow limiting stenosis (5-7). Therefore, while the findings of the study by Chang *et al.* are informative and expand on the results seen in other observational studies of CR *vs.* IR we believe a prospective randomized clinical trial of CR *vs.* IR would have been preferable to retrospective propensity-matching.

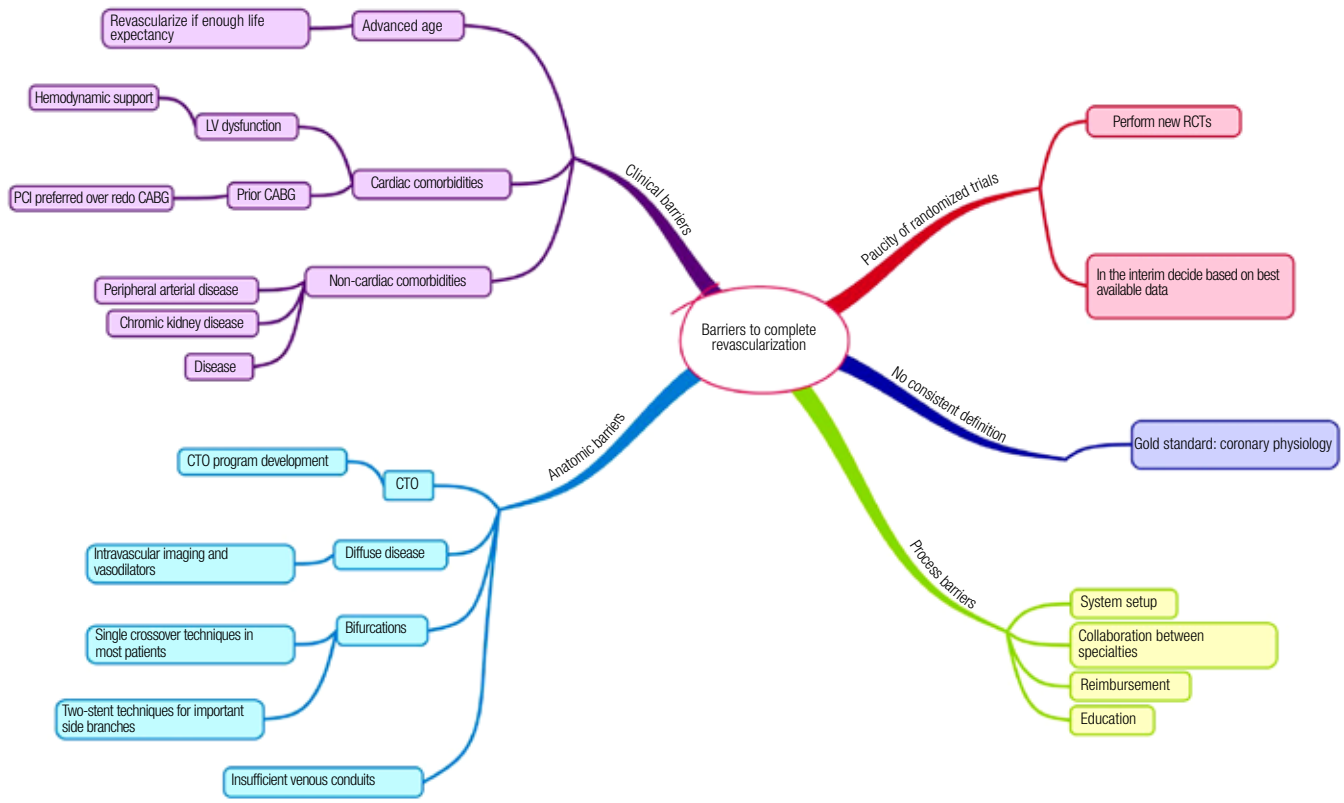

Figure 1 Barriers to achieving complete revascularization.

Table 1 Definitions of complete revascularization

Variable	Definitions
Anatomical or traditional	All diseased arterial systems with vessel size ≥1.5 (2.0–2.25 mm for PCI) with at least one significant stenosis >50% receive a graft (or stent)
Functional	All ischemic myocardial territories are grafted (or stented); areas of old infarction with no viable myocardium are not required to be reperfused
Numerical	Number of distal anastomosis ≥ number of diseased coronary segments/systems
Score-based	Scoring of stenosis in different vessels. Different weight given to different vessels according to number of myocardial segments supplied. A residual score of 0 is usually considered equivalent to CR
Physiology-based	All coronary lesions with fractional-flow reserve ≤0.75–0.80 receive a graft or stent

PCI, percutaneous coronary intervention; CR, complete revascularization.

Furthermore, an ischemia-guided definition of CR that takes into account the functional status of the stenosis and the myocardium subtended by the vessel in question would have better reflected contemporary practice.

Recent data using myocardial perfusion imaging (MPI) has further elucidated on the importance of using a functional/physiological approach to define CR (11). In a small, retrospective analysis, Li *et al.* examined patients with evidence of stress-induced myocardial ischemia on SPECT MPI who had significant stenosis of the left main coronary artery and/or stenosis of at least one major coronary artery that had undergone PCI within 3 months after MPI with the purpose of evaluating the impact of IR by angiographic *vs.* functional (MPI) criteria (11). Similar to the findings by

Chang *et al.*, using the anatomical/angiographic definition, Li and colleagues demonstrated that a mean follow-up of 47±21 months there was no statistical difference in the cumulative incidence of all-cause death (primary endpoint) (12% *vs.* 24%, P=0.08); with no difference observed in major adverse cardiac events (MACE) (composite of all-cause death, non-fatal MI, repeat revascularization) (20% *vs.* 30%, P=0.28). However, when using the MPI criteria, patients with functional CR had a significantly lower cumulative incidence of both all-cause death (12% *vs.* 27%, P=0.048) and MACE (17% *vs.* 36%, P=0.025). The findings of this small, yet provocative study provide further insights into the value of using a functional/physiological-based definition.

Further supporting the use of functionally-guided CR, the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) sub-study assessed whether the presence of residual angiographic disease using the residual SYNTAX score (RSS) and SYNTAX revascularization index (SRI) had prognostic significance after achieving functionally CR with FFR guidance and demonstrated that residual angiographic lesions that are not functionally significant do not predict a worse outcome (12).

Second, it has long-been recognized in studies examining CR *vs.* IR that observational studies have yielded conflicting results and large multicenter randomized clinical trials, while preferable from a methodological standpoint, are lacking (10). Ijsselmuiden *et al.* randomized 219 patients with multivessel disease to CR or culprit-only revascularization and found no benefit of CR during a follow-up of 4.6±1.2 years (13). There are 3 published RCTs showing benefit of CR in patients with ST-segment elevation acute myocardial infarction (STEMI) (14-16) and a large ongoing RCT (*COMPLETE*) trial (NCT01740479) expected to have results in 2018. Two large meta-analyses have been performed and both have favored CR over IR (10,17). Our group performed the largest meta-analysis (assessing both CABG and PCI) of CR in 35 studies including 89,883 patients, and demonstrated that relative to IR, CR was associated with a 30% reduction in long-term mortality, 22% reduction in MI, and a 26% reduction in repeat coronary revascularization; with the mortality benefit being consistent across studies irrespective of revascularization modality (CABG: RR 0.70; 95% CI, 0.61–0.80, P<0.001; and PCI: RR 0.72; 95% CI, 0.62–0.81, P<0.001) and the definition of CR (anatomic definition: RR 0.73; 95% CI, 0.67–0.79, P<0.001; and non-anatomic definition: RR 0.57; 95% CI, 0.36–0.89, P=0.014) (10). Similarly, Aggarwal *et al.* performed a large meta-analysis (nine studies, including 37,116 patients) focused exclusively on PCI during the stent era and demonstrated that compared to IR, patients undergoing CR had a 18% reduction in mortality, 33% reduction in non-fatal MI and 30% reduction subsequent CABG, with no difference in the incidence of repeat PCI (17).

Similarly, and in contrast to the findings by Chang *et al.*, a recent large study of 23,342 patients assessing the long-term outcome of IR after PCI in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) (18), in which IR was defined as any non-treated significant (at least 60%) stenosis in a coronary artery supplying over 10% of the myocardium, demonstrated that IR was associated with an adjusted hazard ratio (HR) of 2.12 (95% CI, 1.98–2.28, P<0.000) for the composite end-point of death, MI, or repeat revascularization at 1-year.

In summary, the study by Chang *et al.* adds to the existing literature of observational studies with conflicting results between IR and CR. Despite the existing differences observed among various observational studies, large meta-analyses studies have suggested a significant benefit of CR over IR. Many of the previously existing barriers to achieving CR, such as the presence of chronic total occlusion (CTO) have been surpassed in contemporary registries using the hybrid approach now reporting procedural success in over 90% of cases (19). Until we have more definitive data from *COMPLETE*, the best available evidence in 2016 suggests that CR using a physiology-based definition should be pursued whenever feasible in symptomatic patients with multivessel disease.

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Footnote

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To complete, or not to complete, that is the question of revascularization in percutaneous coronary intervention with drug-eluting stents for multivessel disease

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In patients with multivessel (MV) coronary artery disease (CAD) (MV-CAD) except for acute myocardial infarction (acute MI, AMI) [including acute ST-segment elevation MI (STEMI)], the clinical impact of completeness of revascularization (RV) in percutaneous coronary intervention (PCI) with drug-eluting stents (DES) (DES-PCI) on major adverse cardiac (and cerebrovascular) events [MAC(C)E] remains unclear. Recently, Chang *et al.* (1) compared the outcomes in patients with MV-CAD achieving complete versus incomplete RV (C-RV *vs.* IC-RV) at the time of PCI. This analysis included consecutive 3,901 patients with MV-CAD undergoing DES-PCI, and the primary and secondary outcomes were all-cause death; and the rates of MI, stroke, and repeat RV (R-RV), respectively. Propensity-score matching was used, and 1,402 pairs of similar baseline characteristics in each group of C-RV and IC-RV were identified. As compared with C-RV at a median follow-up of 4.9 (interquartile range, 2.4 to 7.5) years, IC-RV was associated with similar risks of all-cause death [hazard ratio (HR), 1.03; 95% confidence interval (CI), 0.80 to 1.32; P=0.83], stroke (HR, 1.26; 95% CI, 0.76 to 2.09; P=0.37), and R-RV (HR, 1.15; 95% CI, 0.93 to 1.41; P=0.19); but a higher risk of MI (HR, 1.86; 95% CI, 1.08 to 3.19; P=0.024). As compared with C-RV in patients with MV-CAD (except for STEMI) treated with DES-PCI, the authors (1) concluded that IC-RV was associated with a similar risk of all-cause death but a higher risk of MI during follow-up.

A number of meta-analyses (2-4) have been performed to focus C-RV versus IC-RV in PCI or coronary artery bypass grafting (CABG) in patients with MVD (except for AMI). In unrestricted PCI, the first meta-analysis by Garcia *et al.* (2) of 35 studies including 89,883 patients with 4.6±4 years follow-up showed that C-RV was associated with lower all-cause death [risk ratio (RR), 0.73; 95% CI, 0.65 to 0.82; P<0.001], MI (RR, 0.80; 95% CI, 0.71 to 0.91; P=0.001), and R-RV (RR, 0.72; 95% CI, 0.63 to 0.81; P<0.001) relative to IC-R. In unlimited CABG, however, C-RV was associated with lower all-cause death (RR 0.70; 95% CI, 0.62 to 0.80; P<0.001); but with neither MI (RR, 0.69, 95% CI, 0.44 to 1.10; P=0.12) nor R-RV (RR, 0.92; 95% CI, 0.67 to 1.28; P=0.64) (2). In PCI with stents (including not only DES but also bare-metal stents), a recent meta-analysis by Zimarino *et al.* (3) of 28 studies including 83,695 patients with 4.7±4.3 years follow-up confirmed that C-RV conferred clinical benefits in all-cause death (RR, 0.73; 95% CI, 0.64 to 0.82), MI (RR, 0.69; 95% CI, 0.59 to 0.82), and R-RV (RR, 0.74; 95% CI, 0.63 to 0.86) as compared with IC-R. In CABG with arterial graft(s) in

Table 1 Design of major studies of complete versus incomplete revascularization (C-RV versus IC-RV) in percutaneous coronary intervention (PCI) with drug-eluting stents (DES) for multivessel coronary artery disease (MV-CAD)

Study (reference)	Inclusion	Exclusion	Adjustment	Patient number	Follow-up
Chang 2016 (1)	Unselected, real-world population	Acute STEMI within 24 hours	PSM	2,804	Median, 4.9 (IQR, 2.4–7.5) years
Toma 2016 (5)	Elective and successful PCI for CTO	–	MCPHR	1,662 (MV-CAD, 80.1%; DES, 95.4%)	Median, 2.6 (IQR, 1.1–3.1) years (2,002 original-cohort patients)
Sohn 2014 (6)	Chronic LV systolic dysfunction	Acute MI	WCPHR with IPTW	263	Median, 40 (IQR, 20–66) months
Wu 2013 (7)	PCI with DES or BMS	Acute MI within 24 hours	PSM	13,022 (BMS only, 5.6%)	Median, 3.9 (IQR, 3.4–4.6) years
Gao 2013 (8)	PCI with DES or BMS	Acute MI within 24 hours	MCPHR	7,065 (BMS only, 12.3%)	Mean, 16 months
Chung 2012 (9)	Successful PCI	Acute STEMI	PSM + MCPHR	550	Median, 3.9 (IQR, 3.1–4.8) years
SYNTAX (Head) 2012 (10)	De novo LMD and/or TVD	Acute MI	MCPHR	896 (LMD only or LMD + SVD, 11.9%)	3 years
Song 2012 (11)	(PCI with DES for MV-CAD)	STEMI	PSM + MCPHR	510	Median, 35 (IQR, 29–42) months
Kim 2011 (12)	(PCI with DES for MV-CAD)	Acute MI within 24 hours	WCPHR with IPTW	1,400	5 years
ARTS-II (Sarno) 2010 (13)	Stable angina, unstable angina, or silent ischemia	Transmural MI in the preceding week	None	588	5 years
AUTAX (Gyöngyösi) 2009 (14)	Stable angina, unstable angina or non–STEMI	STEMI within 48 hours	MCPHR	441	2 years
Hannan 2009 (15)	(PCI for MV-CAD)	Acute MI within 24 hours	MCPHR	11,294 (BMS only, 12.0%) 9,936 (at least one DES)	18 months
Tamburino 2008 (16)	(PCI with DES for MV-CAD)	–	PSM + MCPHR	273 (acute MI within 24 hours, 12.6% of 508 original-cohort patients)	Median, 26.2 (IQR, 22.2–36.3) months
Valenti 2008 (17)	PCI with DES for at least one CTO	–	MCPHR	486 (MV-CAD, 85.6%; acute STEMI, 10.7%)	Median, 2.0 (IQR, 1.1–2.8) years

ARTS-II, part-II Arterial Revascularisation Therapies; AUTAX, Austrian Multivessel TAXUS-Stent; BMS, bare-metal stent; CPHR, Cox proportional hazards regression; CTO, chronic total occlusion; IPTW, inverse-probability-of-treatment weighting; IQR, interquartile range; LMD, left main disease; LV, left ventricular; MI, myocardial infarction; MCPHR, multivariable CPHR; PSM, propensity-score matching; STEMI, ST-segment elevation MI; SVD, single-vessel disease; SYNTAX, Synergy between PCI with TAXUS and Cardiac Surgery; TVD, triple-vessel disease; WMCPHR, Weighted CPHR.

≥80% of cases, however, C-RV was associated with reduced all-cause death (RR, 0.76; 95% CI, 0.63 to 0.90); but with neither MI (RR, 0.89; 95% CI, 0.67 to 1.18) nor R-RV (RR, 0.94; 95% CI, 0.65 to 1.36) (3). Another recent meta-analysis (4) of exclusive adjusted-risk estimates from 14 studies enrolling 30,389 patients demonstrated a statistically significant reduction in follow-up mortality with C-RV relative to IC-RV CABG (HR, 0.63; 95% CI, 0.53 to 0.75; P<0.00001).

For MV-CAD (except for AMI), despite evidence from the meta-analyses (2-4) regarding impacts of C-RV versus IC-RV in PCI (including DES-PCI) and CABG, findings concerning effects of RV completeness in exclusive DES-PCI are limited. Our systematic search using keywords including "complete" or "completeness"; "incomplete" or "culprit"; "revascularization"; and "drug-eluting" identified 14 studies (1,5-17) summarized in *Tables 1,2*. The design of all studies was a non-randomized observational study, and all but one (13) studies reported adjusted HRs for outcomes of interest in "C-RV *vs*. IC-RV" or "IC-RV *vs*. C-RV". Nine (1,5-7,9,11,13-15), 5 (6,8,9,16,17), 3 (1,6,11), 2 (1,6), 5 (1,6,11,13,16), and 11 studies (1,6,8-16) provided HRs

Table 2 Results of major studies of complete versus incomplete revascularization (C-RV versus IC-RV) in percutaneous coronary intervention with drug-eluting stents for multivessel coronary artery disease

Study (reference)	Adjusted hazard ratio [95% confidence interval]							
	Comparison	All-cause death	Cardiac death	MI	Stroke	R-RV	MAC(C)E	
Chang 2016 (1)	IC-RV *vs.* C-RV	1.03 (0.80–1.32)	–	1.86 (1.08–3.19)*	1.26 (0.76–2.09)	1.15 (0.93–1.41)	All-cause death, MI, or stroke	1.12 (0.90–1.39)
Toma 2016 (5)	C-RV *vs.* IC-RV	0.59 (0.42–0.85)*	–	–	–	–	–	
Sohn 2014 (6)	C-RV *vs.* IC-RV	0.48 (0.29–0.80)*	0.40 (0.18–0.88)*	0.49 (0.17–1.41)	0.76 (0.29–1.99) (CVA)	0.88 (0.47–1.66)	All-cause death, MI, CVA, or R-RV	0.65 (0.44–0.95)*
Wu 2013 (7)	IC-RV *vs.* C-RV	1.16 (1.06–1.27)*	–	–	–	–	–	
Gao 2013 (8)	IC-RV *vs.* C-RV	–	2.56 (1.03–6.41)*	–	–	–	Cardiac death, non-fatal MI, or R-RV (TV-RV)	1.08 (0.83–1.39)
Chung 2012 (9)	C-RV *vs.* IC-RV	0.66 (0.34–1.28)	0.50 (0.18–1.40)	–	–	–	All-cause death or MI	0.51 (0.28–0.95)*
							Cardiac death or MI	0.39 (0.16–0.96)*
							All-cause death, MI, or R-RV	0.84 (0.60–1.19)
							Any adverse cardiac events	0.93 (0.64–1.35)
SYNTAX (Head) 2012 (10)	IC-RV *vs.* C-RV	–	–	–	–	–	All-cause death, MI, CVA, or R-RV	1.55 (1.15–2.08)*
Song 2012 (11)	C-RV *vs.* IC-RV	0.74 (0.35–1.54)	–	0.67 (0.22–1.94)	–	0.52 (0.31–0.86)*	All-cause death, MI, or R-RV	0.62 (0.41–0.94)*
Kim 2011 (12)	C-RV *vs.* IC-RV	–	–	–	–	–	All-cause death, MI, or stroke	0.84 (0.59–1.20)
							All-cause death, MI, stroke, or R-RV	0.94 (0.75–1.18)
ARTS-II (Sarno) 2010 (13)	IC-RV *vs.* C-RV	1.62 (0.81–3.24)†	–	–	–	1.48 (1.03–2.11)*†	All-cause death, MI, or R-RV	1.11 (0.71–1.73)†
							All-cause death, MI, CVA, or R-RV	1.32 (0.96–1.80)†
AUTAX (Gyöngyösi) 2009 (14)	IC-RV *vs.* C-RV	3.71 (1.30–10.34)*	–	–	–	–	All-cause death or non-fatal acute MI	3.84 (1.60–9.11)*
							All-cause death, non-fatal acute MI, CVA, or R-RV (TL-RV)	1.18 (0.61–2.19)
Hannan 2009 (15)	IC-RV *vs.* C-RV	1.23 (1.04–1.45)*	–	–	–	–	All-cause death or MI	1.27 (1.09–1.47)*
		1.21 (0.99–1.46)					All-cause death or MI	1.30 (1.09–1.53)*
Tamburino 2008 (16)	C-RV *vs.* IC-RV	–	0.17 (0.05–0.62)*	–	–	0.41 (0.25–0.66)*	Cardiac death or non-fatal MI	0.22 (0.07–0.66)*
							Cardiac death, non-fatal MI, or R-RV	0.31 (0.20–0.48)*
Valenti 2008 (17)	C-RV *vs.* IC-RV	–	0.44 (0.22–0.87)*	–	–	–	–	

*, Significantly (P<0.05) favorable for C-RV; †, Unadjusted hazard ratio. ARTS-II, part-II Arterial Revascularisation Therapies; AUTAX, Austrian Multivessel TAXUS-Stent; CVA, cerebrovascular accident; MAC(C)E, major adverse cardiac (and cerebrovascular) events; R-RV, repeat revascularization; MI, myocardial infarction; SYNTAX, Synergy between PCI with TAXUS and Cardiac Surgery; TL-RV, target-lesion revascularization; TV-RV, target-vessel revascularization.

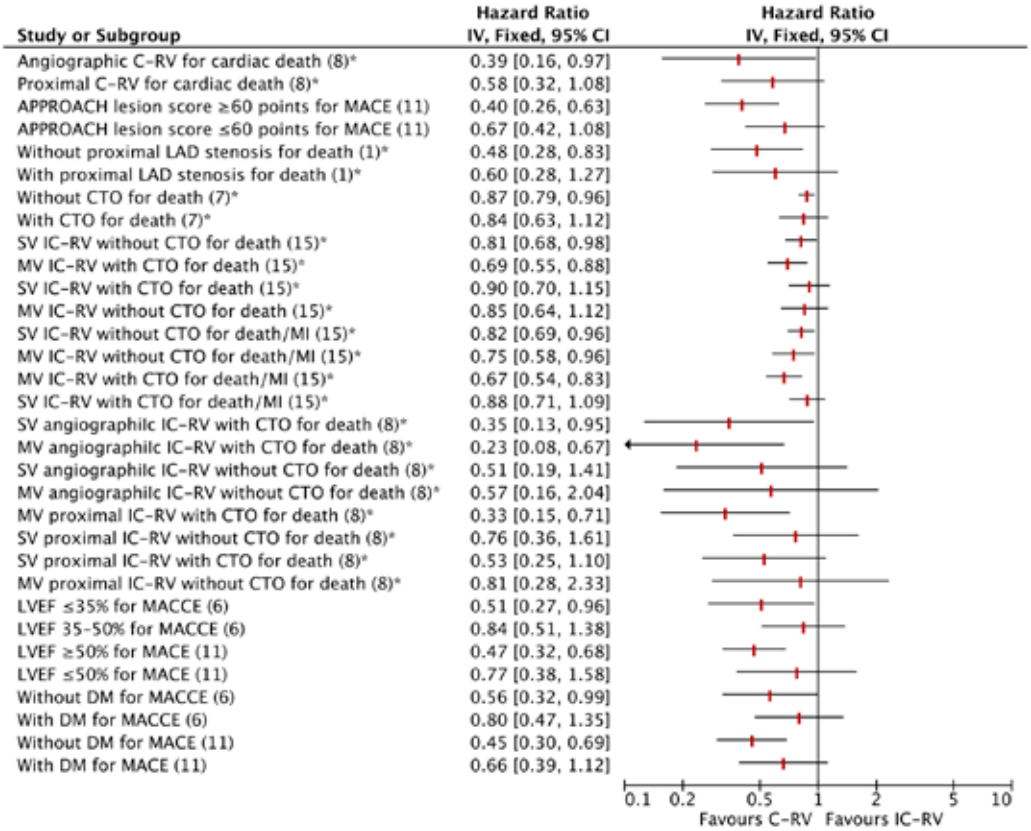

Figure 1 Important subgroup analyses in studies of complete versus incomplete revascularization in percutaneous coronary intervention with drug-eluting stents for multivessel coronary artery disease (except for acute myocardial infarction).

for all-cause death, cardiac death, MI, stroke, R-RV, and MAC(C)E, respectively. In 5 (5-7,14,15) of the 9 studies, C-RV was associated with reduced all-cause death. In all but one (9) of the 5 studies, C-RV was associated with reduced cardiac death. In one (1) of the 3 studies, C-RV was associated with reduced MI. Only two studies (1,6) reported no association of C-RV with stroke. In 3 (11,13,16) of the 5 studies, C-RV was associated with reduced R-RV. In 8 (6,9-11,13-16) of the 11 studies, C-RV was associated with reduced MAC(C)E.

There were a number of important issues, however, in the aforementioned studies (1,5-17) of C-RV versus IC-RV in DES-PCI for MV-CAD (except for AMI) (*Figure 1*). First, "angiographic" (successful angioplasty of all diseased lesions in the major epicardial coronary vessels and their first degree side branches) and "proximal" C-RV definitions (successful angioplasty of all diseased proximal arteries) according to a study by Kim *et al.* (18) are more accurate and clinically relevant. In a study by Gao *et al.* (8), although angiographic IC-RV (not meeting the definition of angiographic C-RV) was associated with a higher rate of cardiac death (P=0.04), proximal IC-RV (not meeting the definition of proximal C-RV) was not (P=0.08).

Second, although the angiographic Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score (19) is used to assess the complexity of CAD, the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) lesion score (20) is calculated to assess the amount of myocardium at risk. In a study by Song *et al.* (11), the incidence of MACE was significantly lower in the C-RV group than in the IC-RV group for patients with an APPROACH lesion score ≥60 points (HR for C-RV *vs.* IC-RV, 0.41; 95% CI, 0.26 to 0.63); but not for those with that <60 points (HR, 0.67; 95% CI, 0.42 to 1.08).

Third, the impact of the completeness of PCI may be based on presence of proximal left anterior descending artery (LAD) stenosis. In the study by Chang *et al.* (1), the group without proximal LAD stenosis suggests better survival

with C-RV (HR for IC-RV versus C-RV, 2.08; 95% CI, 1.20 to 3.59) than that with proximal LAD stenosis (HR, 1.66; 95% CI, 0.79 to 3.51) (1). Also in a study by Wu *et al.* (7), IC-RV was associated with significantly greater risk of death than C-RV in the group without proximal LAD stenosis (P=0.003); but not in that with proximal LAD stenosis (P=0.30).

Fourth, persistent chronic total occlusion (CTO) lesions are associated with significantly worse survival than persistent non-occlusive coronary lesions. Within the group of IC-RV in a study by Toma *et al.* (5), mortality differed significantly depending on whether the IC-RV involved CTO (HR for IC-RV with succeed versus failed CTO, 0.67; 95% CI, 0.50 to 0.92; P=0.012). Whereas, in the study by Wu *et al.* (7), IC-RV was associated with significantly greater risk of death than C-RV in the group without CTO (P=0.004); but not in that with CTO (P=0.24).

Fifth, IC-RV may sometimes be justified in patients with CTO (in danger of having worse longer-term outcomes) when there is no viable myocardium to be preserved. In a study by Hannan *et al.* (15), IC-RV was associated with significantly higher mortality in patients with single-vessel (SV) IC-RV without CTO (P=0.03) and those with MV IC-RV with CTO (P=0.002); but in neither those with SV IC-RV with CTO (P=0.39) nor those with MV IC-RV without CTO (P=0.26). IC-RV was also associated with significantly higher mortality/MI rates in patients with SV IC-RV without CTO (P=0.02), those with MV IC-RV without CTO (P=0.03), and those with MV IC-RV with CTO (P<0.001); but not in those with SV IC-RV with CTO (P=0.24). These results suggest that although the benefit of C-RV is highest for patients with MV IC-RV and CTO, those with SV IC-RV and no CTO have significantly higher mortality and mortality/MI than C-RV patients do, and those with MV IC-RV and no CTO have significantly higher mortality/MI than C-RV ones do (18). Meanwhile, in the study by Gao *et al.* (8), angiographic IC-RV patients had significantly higher rates of cardiac death for SV IC-RV with CTO (P=0.04) and MV IC-RV with CTO (P=0.007); but for neither SV IC-RV without CTO (P=0.20) nor MV IC-RV without CTO (P=0.38). Whereas, proximal IC-RV was associated with significantly higher rates of cardiac death only for MV IC-RV with CTO (P=0.005); but not for SV IC-RV without CTO (P=0.47), SV IC-RV with CTO (P=0.09), and MV IC-RV without CTO (P=0.70) (8).

Sixth, improvement of left ventricular (LV) ejection fraction (LVEF) by reduction of ischemic burden after C-RV could possibly contribute to the decline of mortality in long-term follow up. In a study by Sohn *et al.* (6), although the rate of MACCE for patients with LVEF <35% was significantly lower in the C-RV group (HR, 0.51; 95% CI, 0.27 to 0.96), that for those with LVEF ≥35% (and <50% of inclusion criteria) was not (HR, 0.84; 95% CI, 0.51 to 1.38). Meanwhile, in the study by Song *et al.* (11), the incidence of MACE was significantly lower in the C-RV group than in the IC-RV group for patients with LVEF ≥50% (HR for C-RV versus IC-RV, 0.47; 95% CI, 0.32 to 0.68); but not for those with LVEF <50% (HR, 0.77; 95% CI, 0.38 to 1.58). Silent ischemia might mask the need for RV in ischemia-driven PCI, which is a possible explanation for the attenuation of the C-RV effect in patients with LV dysfunction.

Last, diabetes mellitus (DM) is an independent predictor of target-vessel RV after DES-PCI (21), which may attenuate the benefit of C-RV. In the study by Sohn *et al.* (6), although the rate of MACCE for patients without DM was significantly lower in the C-RV group (HR for C-RV *vs.* IC-RV, 0.56; 95% CI, 0.32 to 0.99), that for those with DM was not (HR, 0.80; 95% CI, 0.47 to 1.35). Also in the study by Song *et al.* (11), the incidence of MACE was significantly lower in the C-RV group than in the IC-RV group for patients without DM (HR for C-RV *vs.* IC-RV, 0.46; 95% CI, 0.30 to 0.69); but not for those with DM (HR, 0.66; 95% CI, 0.39 to 1.12).

To investigate aforementioned important issues, further studies of C-RV versus IC-RV in DES-PCI for MV-CAD (except for AMI) should be required. Furthermore, to determine whether C-RV is associated with reduced all-cause death, cardiac death, MI, stroke, R-RV, or MAC(C)E, a meta-analysis of currently available studies would be performed.

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Footnote

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Where do we go from here? Reappraising the data on anticoagulation in pulmonary arterial hypertension

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Provenance: This is an invited Perspective commissioned by the Section Editor Yue Liu (Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China).

Abstract: The use of anticoagulation as part of the treatment regimen in pulmonary arterial hypertension (PAH) remains a topic of debate. A recently published analysis of anticoagulation use in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) study offers conflicting conclusions regarding the benefit of this therapeutic strategy. There remains no robust randomized trial in PAH weighing the risks versus benefits of including anticoagulation in treatment regimens, leaving clinicians to surmise value in individual patients. Reexamination of available data may help to provide guidance on this controversial topic in the absence of future dedicated investigations.

Keywords: Warfarin; pulmonary hypertension; randomized registry trial; prostacyclins; vitamin K antagonists (VKA)

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The utility of anticoagulation in pulmonary arterial hypertension (PAH) has long been a source of debate between experts in the field (1,2). There is strong pathophysiologic rationale for this type of therapy, as numerous studies have identified *in situ* thrombosis and a pro-coagulant milieu in PAH (3-9). Unfortunately, a paucity of randomized controlled studies has left practicing clinicians relying on a handful of observational investigations to guide practice patterns (1,2,10,11). Prior to publication of the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) registry anticoagulation report, there were 9 cohort studies [2 prospective (12,13) and 7 retrospective (6,14-19)] specifically addressing the question of anticoagulation in PAH. Overall, the data favored anticoagulation, with a 31% reduction in mortality described in a meta-analysis and systematic review—although with concern for publication bias (10,20). In line with this finding, international guidelines continue to recommend use of anticoagulation in idiopathic pulmonary artery hypertension (iPAH) but recognize the scarcity of supportive trials (9,21,22). Guidance for anticoagulation in connective tissue disease-associated PAH (CTD-PAH) remains even more elusive (14). Only 2 (13,14) of 9 studies included in the meta-analysis by Caldeira and colleagues (10) explicitly address CTD-PAH and they demonstrate incongruous findings.

The 2015 *Circulation* publication describing analysis of anticoagulation in the REVEAL registry increases the clinical uncertainty surrounding this question (23). This United States based-retrospective registry assessed the effect of warfarin treatment on survival in patients with iPAH and systemic sclerosis-associated PAH (SSc-PAH). iPAH and SSc-PAH patients who started warfarin after enrollment into the registry were matched with patients never on warfarin based on enrollment center, etiology and diagnosis status. In the iPAH cohort, there was no significant survival benefit observed in the unadjusted or REVEAL risk score (24) -adjusted analyses. The SSc-PAH warfarin cohort had increased mortality with an unadjusted hazard ratio of 2.03 (P=0.03), decreased to an insignificant 1.6 when adjusted for the risk score. An adjusted time-varying cox proportional model was performed on the

unmatched sample to account for frequent warfarin starts and stops. The iPAH warfarin cohort still had no significant survival benefit, but interestingly the hazard ratio dropped below 1. The SSc-PAH group maintained a similar trend toward increased mortality in warfarin users.

The stir generated by this publication is amplified in the setting of a similar registry study, the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry, published almost two years earlier with discordant results (14). COMPERA also examined anticoagulation in PAH, with analysis of both iPAH and SSc-PAH cohorts, in a mostly German population. Similar to REVEAL, COMPERA found no mortality benefit with a trend toward decreased survival in the SSc-PAH group treated with anticoagulation. On the other hand, both matched and unmatched survival analyses demonstrated a statistically significant mortality benefit in iPAH anticoagulation users. In the matched analysis, the survival difference was 4%, 11% and 12% at 1, 2, and 3 years follow-up, respectively (P=0.017).

The results of the COMPERA analysis overall align with the previously published studies (10)—so what is different about these seemingly similar registries that may account for the novel findings in regards to iPAH and anticoagulation in REVEAL? Focusing on iPAH, both studies enrolled a similar number of patients and the matched-pair analyses were comparable in size (REVEAL: 144 pairs, COMPERA: 183 pairs). The mean age of patients in the iPAH cohorts is quite different: those in the COMPERA registry are approximately 20 years older than the comparison REVEAL group (72 *vs.* ~50 years of age). COMPERA had 56% female participants, compared to 80% in REVEAL. The COMPERA iPAH patients also appear sicker, with a lower baseline 6-minute walk distance (6MWD) and worse World Health Organization (WHO) functional class: 96% of patients with class III/IV *vs.* only ~55% in the REVEAL iPAH cohort. Comorbidities were comparable between iPAH patients on warfarin compared to those not on warfarin in the REVEAL study, but have not been reported from COMPERA, limiting direct evaluation (14,25). One possible explanation is that the older, more morbid and male iPAH participants in the COMPERA study represent a changing demographic admixed with the more stereotypical iPAH patients described in prior studies and the REVEAL registry population (26). There is great potential that this differing demographic has unidentified comorbidities, such as arrhythmias, that could explain the mortality benefit with anticoagulation seen in COMPERA and not REVEAL (27,28). Arguing against this hypothesis, however, is the fact that the REVEAL registry population is actually more similar to the previously published studies that did find survival benefit with anticoagulation (10).

There are also noteworthy differences in the PAH-targeted therapies employed in the two registries, reflecting variance in clinical practice patterns between US and European experts (29). In the REVEAL iPAH cohort, 58% of patients on warfarin and 32% not on warfarin received a prostacyclin analogue (intravenous, subcutaneous, inhaled or oral). This contrasts with the medications reported in COMPERA, where far fewer patients were reported to be on prostacyclin analogues. Prostacyclin therapy not only provides vasodilation in PAH, but has also been shown to alter hemostatic and platelet pathways, possible decreasing the *in situ* thrombosis and hypercoagulability observed in patients with PAH (3,7,30-32). Of note, bleeding risks are increased in patients with iPAH, CTD-PAH and chronic thromboembolic pulmonary hypertension when vitamin K antagonists (VKA) were used in conjunction with prostacyclin (33). Considering these data, increased use of prostacyclin in the REVEAL registry potentially provides enough anticoagulation or anti-platelet activity to mitigate any possible observed benefit of VKA therapy. Moreover, although the occurrence of fatal bleeding complications was similar in COMPERA and REVEAL, neither study was designed to capture all bleeding events. Increased bleeding risk in REVEAL (as a result of increased concurrent prostacyclin and VKA use) could theoretically increase morbidity and mortality, decreasing observed benefit of anticoagulation use in iPAH.

Even more interesting is the disparity between warfarin use patterns in the two registries; a point which more than any raises concern of comparability. The more recently published REVEAL registry reported a mean time on warfarin of 11.8 months, with 3, 9 and 16.5 months for the 25th, 50th and 75th percentiles, respectively. The mean INR was reported at 1.9 in the iPAH participants. While COMPERA does not provide mean INR measurements, limiting our ability to assess quality of anticoagulation, the duration of use is notably longer. Fifty-six percent of patients used warfarin for the entire 36-month follow-up period, with 85% anti-coagulated for >50% of the time (>18 months). These results raise the possibility that in iPAH there is a critical duration of anticoagulation that provides benefit—the majority of patients in REVEAL may not have reached this crucial threshold and therefore have no improvement in survival. Although REVEAL

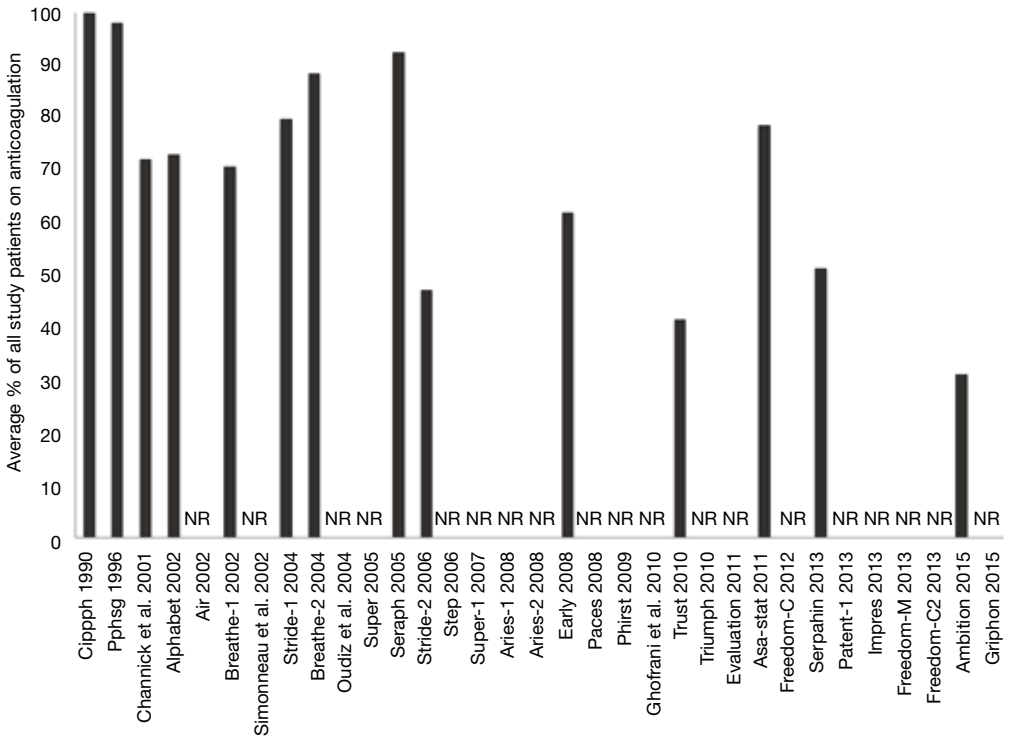

Figure 1 Reported anticoagulation use in PAH therapy randomized controlled trials. Clinical trials are denoted by trial acronym and year, unless no acronym available, in which case first author and year. Channick *et al.* (35); Simonneau *et al.* (36); Oudiz *et al.* (37); Ghofrani *et al.* (38). NR, not reported.

included a time-interval time-varying covariate model, this statistical strategy only addressed ever versus recent use, not cumulative duration.

The concern of immortal time bias (ITB) was raised in both the COMPERA and REVEAL manuscripts and a contemporary review in *Circulation* (2,14,23). Fundamentally, the concept of ITB implies that patients included in the warfarin group must survive long enough to start therapy, potentially biasing towards increased survival in the warfarin cohort; that is to say, that patients included in the no warfarin cohort may die from another cause prior to having a chance to start warfarin therapy (2,34). Study design in the REVEAL registry decreases the probability of ITB compared to COMPERA and may explain the lack of mortality benefit, but the degree to which this bias alters the results is uncertain.

So where do we go from here? There are still only 10 studies specifically addressing anticoagulation in PAH and the data therein remains of questionable utility. The two most influential publications attempting to answer this question have conflicting results and debatably should not be compared in light of differing demographics. Moreover, a minor and decreasing proportion of randomized trials (*Figure 1*) and registries (*Table 1*) report the use of warfarin or other types of anticoagulation. COMPERA and REVEAL are the only 2 modern registries reporting anticoagulation use to provide direct analysis of morbidity and mortality related to this controversial therapeutic strategy. Almost more striking is the decline in reporting from randomized trials (*Figure 1*). In the first two decades of major PAH investigation, 50% reported the use of anticoagulation and the pooled percent of patients taking anticoagulants ranged from 47%–100%. Since 2010, only approximately 30% of studies disclose anticoagulation, and use ranges from 31%–79%. Whether this reduction in reporting reflects decreased anticoagulation use in practice or simply waning interest remains to be seen.

More robust data in the form of a well planned, international randomized controlled study would provide great insight into this topic (2). Alternatively, this area of clinical uncertainty would be well suited for a randomized registry study (64), an attractive, economic avenue that

Table 1 PAH registries and reported anticoagulation use

Registry	Enrollment dates	No. of patients	Types of PH [%]	Age at enrollment (mean ± SD)	% of female	Anticoagulation use
U.S. NIH (39,40)	Prospective 1981–1985	187	iPAH	36±15	63	NR
U.S. PH Connection (41)	Retrospective 1982–2004; prospective 2004–2006	578	iPAH [48], CTD-PAH3 [0], CHD-PAH [11]	48±14	77	28% VKA, 13% ASA
Scottish-SMR (42)	Retrospective 1986–2001	374	iPAH [47], CTD-PAH [30], CHD-PAH [23]	52±12	70	NR
Mayo (43)	Prospective 1995–2004	484	iPAH/fPAH [56], CTD-PAH [24]	52±15	75	NR
Spanish (44)	Retrospective 1998–2006; prospective 2007–2008	866 (CTEPH 162)	iPAH [30], CTD-PAH [15], CHD-PAH [16]	45±17	71	NR
Chinese (45)	Prospective 1999–2004	72	iPAH [94]	36±12	72	50% VKA
UK & Ireland (46,47)	Prospective 2001–2009	482	iPAH [93]	50±7	70	NR
French (48-50)	Prospective 2002–2003	674	iPAH [39], CTD-PAH [15], CHD-PAH [11]	50±15	65	91% VKA (n=190) (49)
U.S. REVEAL (23,51-61)	Prospective 2006–2009	2,967	iPAH [46], CTD-PAH [25], CHD-PAH [10]	53±14	80	53% VKA, 16% ASA, 2% clopidogrel
COMPERA (14,25)	Prospective 2007–present	1,283	iPAH [62]	Median 68 (IQR 55–75)	64	58% (93% VKA, 6% heparin, 1% novel anticoagulant)
New Chinese (62,63)	Prospective 2008–2011	956	iPAH [35], CTD-PAH [19], CHD-PAH [43]	36±13	70	33%

PAH, pulmonary artery hypertension; SD, standard deviation; IQR, interquartile range; iPAH, idiopathic pulmonary artery hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; CTD, connective tissue disease; CHD, congenital heart disease; fPAH, familial PAH; NR, not reported; VKA, vitamin K antagonist; ASA, aspirin.

has not been successfully employed in PAH as of yet (65). While not without consequences (9,33), anticoagulation retains a place in treatment algorithms, prompting urgent reconciliation of this therapeutic dilemma in PAH.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Registry to evaluate early and long-term disease management in PAH (REVEAL)

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Pulmonary artery hypertension (PAH) is a condition with significant clinical symptoms, poor quality of life and early mortality. Heath-Edwards classification which was based primarily on pulmonary vascular histology changes include a spectrum of lesions like vasoconstriction, intimal hyperplasia, medial hypertrophy, plexiform arteriopathy, perivascular inflammation, and thrombotic lesions within the pulmonary vasculature (1-3).

Abnormalities of antithrombotic factors and fibrinolytic system contributing to a prothrombotic state have been discussed in the etiopathogenesis of patients with idiopathic pulmonary arterial hypertension (IPAH) (4). Thrombotic pulmonary vascular lesions results in pulmonary vascular remodelling, luminal narrowing and increased vascular resistance leading to the progression of the disease process (5).

Although there are a wide range of pulmonary arterial vasodilators which have contributed to an improved prognosis in PAH (6), 1-year mortality rates remain considerable at 7%–17% (7) and is particularly worse in scleroderma-associated PAH (8).

The use of warfarin is based on the concept that *in situ* thrombosis plays a potential role in disease progression. An analysis from the Registry to Evaluate Early and Long-Term Disease Management in PAH (REVEAL), the largest PAH registry ever developed and published in this circulation issue further reinforces the questionable role of warfarin in PAH management (9). Although this registry has used newer statistical methods to analyze the data and adjustments for the confounding factors, many unknown confounding factors might still influence the outcome of the impact of specific drug therapy on the PAH disease progression. Since there are no randomized trials so far on the role of anticoagulation in PAH and unlikely to come, registry-based analyses remain the best available source of information.

In a landmark pathologic study of the lung vessels by Wagenvoort (10) involving 156 clinically diagnosed cases of primary pulmonary hypertension, 20% had evidence of thromboembolic pulmonary hypertension and 4% had mixed vasoconstrictive and thrombotic lesion suggesting that these subsets may have better outcome when treated with warfarin than others with nonthrombotic lesions.

A study of 120 PAH patients by Fuster *et al.* (2) revealed that 18% had autopsy findings most consistent with chronic thromboembolic pulmonary hypertension and the use of systemic anticoagulation therapy was one of the strongest positive prognostic factors. One- and 3-year survival respectively was 80% and 50% for those receiving warfarin and 60% and 25% for those not receiving warfarin. The low rate of survival was likely due to the non-availability of specific pulmonary vasodilators.

A subsequent study by Rich *et al.* (11) concluded that warfarin when added to calcium channel blocker (CCB) improved survival in patients who were either CCB responders or non-responders. Non-responders who were treated with warfarin in addition to CCBs benefitted better than those who were not. Warfarin users also had a better survival than the nonusers at 1, 3 and 5 years (91%, 62%, 47% *vs.* 52%, 31%, 31%, respectively).

A retrospective cohort study of PAH patients by Kang

et al. (12) showed survival rates at 1, 3, 5, and 10 years were 100.0%, 100.0%, 88.9%, and 74.1%, respectively, in the warfarin group, and 85.7%, 69.7%, 48.9%, and 16.3%, respectively, in the non-warfarin group and a 2-fold higher mean survival (12.0 years in the warfarin group *vs.* 6.1 years in the non-warfarin group).

As a result of these studies, warfarin became a well accepted drug in the armamentarium of PAH therapy and widely used in all group 1 PAH patients as recommended in the guidelines.

The use of warfarin is fraught with risks like difficulty in maintaining therapeutic international normalized ratio, labile anticoagulation profile in patients with advanced right ventricular dysfunction, drug interactions and bleeding complications including fatal cerebral hemorrhage and serious gastrointestinal bleeding especially in scleroderma associated PAH with gastrointestinal telangiectasia (13).

In a meta-analysis by Johnson *et al.* (14), 5 out of 7 observational studies suggested survival benefit associated with warfarin in the treatment of IPAH, whereas two observational studies were not in favor of this association. These are epidemiological studies with inherent methodological issues, including selection bias and unmeasured confounding factors leading to dubious conclusions regarding the effect of anticoagulation therapy on survival in patients with IPAH.

The Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), enrolled patients from seven European countries with a major contribution from German centers (15). Anticoagulation usage was 45% and 65% in connective tissue disease associated PAH and IPAH respectively.

Warfarin anticoagulation was associated with better outcomes in IPAH cohort in contrast to worse outcome in connective tissue associated PAH. In scleroderma-associated PAH, warfarin therapy had an increased hazard for death in COMPERA study, in concordance with REVEAL analysis who had similar adverse outcomes (unadjusted hazard ratio, 2.03, P=0.03; REVEAL risk score–adjusted hazard ratio, 1.60, P=0.15) compared with those who were not on warfarin. The role of warfarin in the management of scleroderma-associated PAH is doubtful or maybe it is harmful. In contrast to the concordant results regarding the impact of warfarin treatment in scleroderma-associated PAH in REVEAL and COMPERA registry, outcome of warfarin in IPAH cohort did not show any benefit in the REVEAL registry. Both the registries differ greatly in their patient characteristics and management patterns which would possibly explain the varying outcomes in the IPAH cohort.

The difference in the outcome of these two registries may also be very well explainable by variation in many features like mean age of patients (68 *vs.* 51 years in COMPERA and REVEAL respectively), range of the international normalized ratio (1.5 to 2.5 in REVEAL and 2.0 to 3.0 in COMPERA) and the type of enrolled patients (Primarily prevalent patients in REVEAL whereas COMPERA had only incident patients) and usage of parenteral prostanoids.

In the REVEAL registry a higher percentage of patients (46%) were on intravenous or subcutaneous prostanoids along with warfarin as compared to only 2% in the COMPERA registry. Antiplatelet effects of these parenteral prostanoids results in lesser thrombotic events in the IPAH cohort which might have reduced any added beneficial effect of warfarin in the REVEAL registry even after statistical methods to adjust for the influence of other PAH medications in the outcome. Two-year survival in the COMPERA and REVEAL cohorts not treated with warfarin was 81% versus 89% and 3-year survival was 66% versus 81% respectively. A more aggressive combination PAH therapy in the warfarin treated COMPERA cohort improves the 2-year survival to 89% *vs.* 81% in the cohort not treated with warfarin.

Another reason for the difference between the two registries in the IPAH cohort may be due to immortal time bias in the COMPERA registry. In the COMPERA, those patients who never initiated warfarin because of death due to nonthrombotic causes were compared with those who were initiated warfarin in the study which could have skewed the analysis in favor of warfarin cohort.

The survival curve of patients initiating warfarin in the REVEAL registry matches to that of those not initiating warfarin. A major group of patients (75%) stopped warfarin during the study period as it was poorly tolerated according to the authors, however such high discontinuation rate make the results skeptical. The authors used a time-varying covariate to examine the longitudinal effect of warfarin use due to high discontinuation rates, which would yield comparable results to that of other analytic methodology.

The conflicting results and methodological issues regarding the efficacy of warfarin in IPAH in previous observational studies, meta-analysis as well as in the COMPERA and REVEAL registries needs to be further ascertained by randomized control trials. However, it seems impossible for conducting such trials in PAH due to the complex logistics and lack of industry funding for a less

common disease as this. But it is evident that warfarin is no more useful in connective tissue disease associated PAH. Since the final word is yet to be told regarding the survival benefit of warfarin in IPAH, it may be concluded that there is insufficient evidence to recommend warfarin in these patients except for a small subgroup of patients at greater risk of thromboemboli, long term immobility, chronic indwelling central catheters and low cardiac output state.

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Footnote

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Anti-coagulation in pulmonary arterial hypertension: the real blood and guts

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We read with interest the "Perspective" by Cirulis *et al.* and the accompanying editorial by Pakshirajan, both of which discuss our recent publication analyzing the effect of anticoagulation with warfarin in patients with pulmonary arterial hypertension (PAH) enrolled in the REVEAL registry (1).

The REVEAL registry is a US-based multicenter cohort and the largest database to date of patients with group I PAH. Analysis of the REVEAL database "revealed" information contrary to multiple historical reports suggesting that anticoagulation is beneficial to patients with PAH. Despite enrolling 3,500 patients and tracking them for 5 years, REVEAL suffers from the inherent limitations of any registry. Yet, it and the European-based PH registry COMPERA have both queried our current recommendations about anticoagulation in PAH patients (2). Although the observations from REVEAL and COMPERA are congruent in some forms of PAH [no benefit in connective tissue disease (CTD)-PAH], they are conflicting in others [idiopathic PAH (IPAH)]; thus, they do not provide incontrovertible direction for the clinician.

Based on these observations, what should we do today? For patients with CTD-associated PAH, the answer is clear: there are no data suggesting a positive effect of warfarin. Moreover, recent information (especially with scleroderma patients) suggests a detrimental outcome. However, the issue remains controversial for patients with IPAH: should we anti-coagulate these individuals?

The conflicting data generated over the past 40 years can only be truly rectified by a randomized clinical trial evaluating the effect of anti-coagulation in PAH patients. Whether this will ever occur is problematic (we think it is highly unlikely). But if it did occur, what would be the ideal design?

First, and foremost, it would include IPAH patients. Patients with drug-induced PAH and hereditary PAH could also be considered, as their characteristics and outcomes mirror IPAH. The trial would be randomized, placebo-controlled, double-blinded, and would require multiple centers. Because we lack robust surrogate markers for long-term outcomes in PAH, the primary endpoint would have to be the most difficult to use in a PAH trial: survival.

Prostacyclins have anticoagulant properties due to the effect on platelet aggregation. In addition, they are generally reserved for the sicker, more advanced patients. Therefore, stratification based on exposure to prostanoids would be advisable.

One interesting difference between COMPERA and REVEAL was the exposure time to warfarin. US patients did not seem to tolerate warfarin as well as European patients: in REVEAL, at 3 years only a third of patients were still taking the drug, while in COMPERA, the patients had a much better retention time and rate. Thus, one might speculate that part of the lack of effect in REVEAL may have been due to the insufficient time on warfarin. As such, the trial would make every effort to choose a drug that is

well-tolerated.

Given these considerations, would the newer, direct anticoagulants (DOACs) be more appropriate drugs to study in PAH? DOACs have proven efficacy and safety in a host of cardiovascular disorders, as both prevention and treatment (3). Their mechanisms of action include direct thrombin inhibition and factor Xa inhibition. The main advantages over traditional anticoagulants, such as warfarin, include a lower overall mortality, mainly due to fewer episodes of fatal intracranial bleeding (4) and lack of need for blood monitoring. However, they are not a panacea, since they are contraindicated in patients with significant renal impairment and in obese patients. If the PAH community ever embraces, by necessity, this very long, survival trial, it seems to us that DOACs may best fit the profile of the appropriate agent. In fact, a trial evaluating the efficacy and safety of apixaban in scleroderma-associated PAH is currently underway in Australia (5); its primary endpoint is time to clinical worsening in this high risk population.

In conclusion, use of anticoagulation has become more controversial in patients with PAH. We, as clinicians, have the duty to inform our patients of the conflicting evidence, and as researchers, to advance knowledge in this area by resolving the issue with evidence-based medicine.

Although PAH is a rare disease, the recently concluded long-term, event-driven randomized trials, SERAPHIN (6), AMBITION (7), and GRIPHON (8), enrolled over 500 patients each, suggesting that long-term, large clinical trials in PAH are in fact feasible.

In sum, we are making an appeal to the international PH community to design and perform a large multi-national trial that would finally clarify the role of anticoagulation in patients with PAH.

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Footnote

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Effects of acute hyperglycaemia on cardiovascular homeostasis: does a spoonful of sugar make the flow-mediated dilatation go down?

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Introduction

Patients with diabetes mellitus are at substantially increased risk for adverse outcomes in association with occurrence of acute coronary syndromes (1) and in the presence of atrial fibrillation (2). Although the occurrence of acute myocardial dysfunction in the presence of hyperglycaemia has been shown to be associated with poor short-term outcomes, the issue of the contribution of instantaneous (or recent) elevation of blood sugar level (BSL) to this risk remains incompletely evaluated. Currently there is only fragmentary understanding of the potential nexus between elevation of BSL and thrombotic diathesis.

A number of studies in the literature have evaluated the cardiovascular effects of transient increases in BSL, whether in normal subjects or in patients with underlying cardiometabolic disease states in virtually all cases focusing on effects on vascular reactivity, and in particular vascular endothelial function. We now examine the significance of these findings, their implications regarding nitric oxide (NO) signalling in other tissue such as platelets, and the potential mechanisms underlying these physiological changes. Finally, we review the arguments for rapid reversal of hyperglycaemia during cardiovascular crises as a form of ancillary therapeutic measure.

Impact of hyperglycaemia on the generation and signalling of NO

Acute elevation of BSL is associated with increases in oxidative stress [for review see (3)], and hence has the potential to result in disordered vascular, myocardial and platelet physiology. In practice, effects of hyperglycaemia on vascular function might theoretically involve impairment of generation of NO, for example via increased tissue concentrations of the NO synthase inhibitor asymmetric dimethylarginine (ADMA) (4) and/or via increased tissue arginase activity (5), either of which might also be associated with "uncoupling" of NO synthase. On the other hand, increased oxidative stress in association with hyperglycaemia might well contribute to "scavenging" of NO by superoxide anion (O_2^-) and/or partial inactivation of soluble guanylate cyclase (sGC), resulting in attenuation of tissue responses (6) to NO (see *Figure 1* for schematic representation).

Assessment of vascular function using flow-mediated dilatation (FMD)

FMD represents one of several techniques in common clinical use which can quantitate vascular endothelial function (7), in this case via measuring post-ischemic

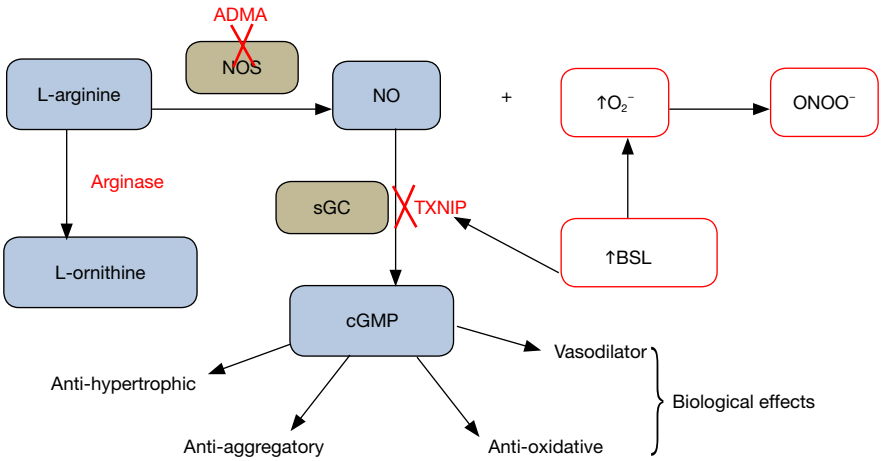

Figure 1 Schematic for impact of hyperglycaemia on nitric oxide (NO)/soluble guanylate cyclase (sGC) pathways. Under normal physiological conditions, NO is generated mainly from L-arginine under the influence of nitric oxide synthase (NOS), which is negatively regulated by asymmetric dimethylarginine (ADMA). Via activation of sGC/cyclic GMP pathway, NO exerts various physiological effects such as anti-aggregation, anti-oxidation and vasodilation. However, during acute hyperglycaemia (BSL ↑), the excessively generated superoxide "scavenges" NO, contributing to attenuation of tissue responsiveness of NO and formation of peroxynitrite ($ONOO^-$). Furthermore, increased expression of the pro-inflammatory protein thioredoxin-interacting protein (TXNIP) increases oxidative stress, potentially contributing to dysfunction of sGC. Major sites of resultant impairment of NO effect are: (I) "scavenging" of NO; (II) sGC oxidative dysfunction. BSL, blood sugar level; GMP, guanosine monophosphate.

reactive hyperaemia (largely NO-independent). Investigation of FMD physiology suggests that the hyperaemic response of the circulation to a period of relative ischemia is mediated largely by formation and release of NO (8). On the other hand, few investigations have addressed the extent to which FMD responses reflect changes in NO generation versus integrity of NO signalling: indeed it has been found that there is only a moderate correlation in individual patients between magnitude of FMD and extent of response to NO donors (9), as a probe of integrity of NO signalling pathways. Recent studies have also raised some doubts about the reproducibility of FMD data for individual subjects (10), somewhat limiting the clinical utility of this measure.

The significance of findings from Loader *et al.* [2015]

A recent study (11) examined the impact of acute glucose loading on FMD, utilizing a design involving meta-analysis of the published literature, focusing on 39 articles. The vast majority of these studies had utilized changes in FMD (as a "macrovascular" test of endothelial function) in healthy subjects treated with a single oral glucose load (usually of 75 grams). A minority of studies had evaluated similar changes in type 2 diabetic subjects. Few studies had evaluated "vascular smooth muscle function" simultaneously. However, as this evaluation was achieved via infusion of either sodium nitroprusside or glyceryl trinitrate (GTN) (both NO donors), the process was actually an evaluation of integrity of vascular NO signalling, rather than vascular smooth muscle function. In summary, the available data suggested a decrease in FMD of approximately 1.5% in both normal subjects and type 2 diabetics in the presence of acute hyperglycaemia. On the other hand, there was no consistent change in responses to NO donors during acute hyperglycaemia.

Superficially, this analysis argues that the adverse effects of acute hyperglycaemia on vascular function are mediated largely or entirely by decreased formation of NO. Therefore it is appropriate that we examine the known effects of acute hyperglycaemia on factors such as kinetics of ADMA and of arginases, which might represent mechanisms for decreasing NO release.

Potential mechanisms affecting NO signalling during hyperglycaemia

There is some evidence that activation of tissue arginases

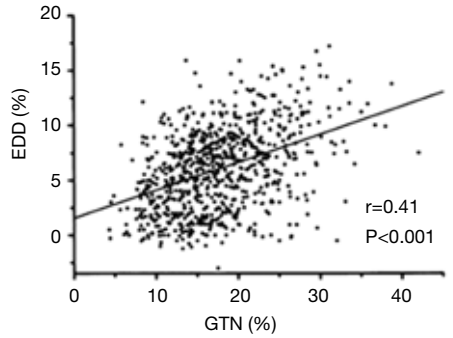

Figure 2 Relationship between FMD and vascular response to GTN. EDD, endothelium dependent dilation; FMD, flow-mediated dilatation; GTN, glyceryl trinitrate. [Reprinted with permission (9)].

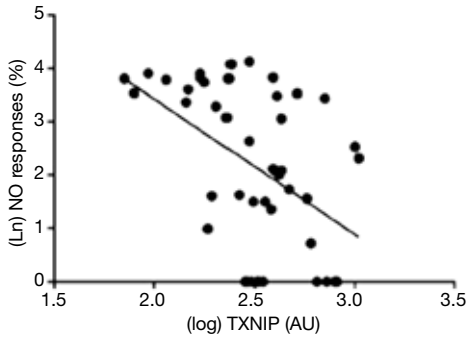

Figure 3 The anti-aggregatory response to NO is negatively correlated with the platelet content of TXNIP, r=–0.5, P<0.0001. NO, nitric oxide; TXNIP, thioredoxin-interacting protein. [Reprinted with permission (17)].

may be insulin-dependent. For example, Kashyap *et al.* (12) showed a direct correlation between extent of hyperglycaemia in diabetics and plasma arginase activity, with insulin infusion decreasing arginase activity. Ishizaka *et al.* (5) also showed that hyperglycaemia in rabbits was associated with enhanced arginase activity. A number of studies have also linked hyperglycaemia with increased ADMA production. For example, Mah *et al.* (13) showed that ADMA concentrations increase with post-prandial hyperglycaemia. Therefore the finding that FMD decreases with increasing BSL is easily explained by data of this type, although it is somewhat surprising that glucose loading in diabetics, which would be expected to more markedly increase oxidative stress, does not lead to greater changes in FMD.

The total failure of this meta-analysis to document variability in vascular responses to NO according to BSL is, however, surprising. For example, Adams *et al.* (9) previously documented (*Figure 2*) that FMD responses are directly correlated with extent of vascular response to NO donors, a finding which suggests partial commonality of controlling factors. In order to understand this more fully, it is appropriate to consider the literature related to NO responses in platelets, where influence of variable NO generation tends to be less important than integrity of signalling mechanisms.

Given the known mechanistic overlap (*Figure 1*) and the previously demonstrated nexus between FMD and NO response (9), it is possible that the failure of some studies to document changes in vascular responses to NO donors in response to hyperglycaemia results from the common practice of utilizing drug doses which induce near-maximal responses.

Studies in platelets: impact of hyperglycaemia

The major stimulus for evaluation of the impact of changes in BSL on platelet responsiveness to NO and its determinants has been a series of clinical findings which indirectly implicate hyperglycaemia as a focus of impaired NO signalling. Hyperglycaemia represents a basis for increased mortality risk in acute myocardial infarction (14) and the results of the DIGAMI-I trial suggest that rapid reversal of hyperglycaemia by intravenously infused insulin might also reverse this risk (15).

Is there a need to reverse hyperglycaemia during cardiovascular crisis?

In 2007, Worthley *et al.* (16) reported that in diabetic patients with acute coronary syndromes there was an inverse relationship between instantaneous BSL and extent of inhibition of platelet aggregation by the NO donor sodium nitroprusside. This reflected primarily incremental "scavenging" of NO by O_2^- release. With insulin infusion leading to rapid reversal of hyperglycaemia, there was also a fall in O_2^- generation, together with marked improvement in NO response.

More recently, we have noted that the pro-inflammatory protein thioredoxin-interacting protein (TXNIP) appears to control platelet NO signalling under chronic conditions irrespective of hyperglycaemia: there was a reciprocal relationship between NO response and platelet TXNIP

content at steady state (17) (*Figure 3*), while treatment with ramipril simultaneously suppressed TXNIP expression and potentiated platelet NO signalling (17,18). It would be expected that TXNIP expression would also change in response to variability in BSL: after all, there is a glucose response element on the gene coding for TXNIP expression (19). However, platelet TXNIP content did not fall significantly over 12 hours of insulin infusion in hyperglycaemic patients (20), despite restoration of NO responses, suggesting that the associated falls in O_2^- release were TXNIP-independent. This evidence of relatively slow changes in TXNIP expression may be relatively specific for platelets by virtue of limited DNA content. Previous studies suggest that TXNIP expression may be more rapidly adjusted in vasculature (21). It seems more likely that insulin-induced suppression of protein kinase C-dependent activation of NAD(P)H oxidase (22) may have been critical to decreases in O_2^- formation affecting NO "scavenging" in platelets.

Conclusions

It therefore appears that acute hyperglycaemia markedly impairs vascular endothelial function, primarily via diminished NO formation, and also impairs NO signalling, mainly in platelets. These findings constitute a compelling argument for limiting hyperglycaemia (for example via insulin infusion) at the time of all cardiovascular crises. The failure of the CREATE-ECLA trial (23) to improve outcomes in acute myocardial infarction should remind us that the latter was not really a study of reversal of hyperglycaemia, but rather evaluation of a strategy of increasing myocardial glucose utilization.

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Footnote

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Hyperglycemic endothelial dysfunction: does it happen and does it matter?

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In the September issue of *Arteriosclerosis, Thrombosis and Vascular Biology*, Loader *et al.* (1) present the results of a meta-analysis on the effect of acute hyperglycemia on vascular function. The authors did an extensive search of literature and report on findings in 39 studies that measured endothelial function and/or vascular smooth muscle function during euglycemia and during acute induction of hyperglycemia. The studies varied considerably in terms of subject type, age, method of induction of hyperglycemia, and method of measurement of endothelial function. The authors in the analysis specifically focus on differences between studies that measured macrovascular versus microvascular endothelial function.

The results showed that there may be publication bias present, but that as a whole endothelial function is impaired by acute induction of hyperglycemia and vascular smooth muscle function is not. They specifically found that acute hyperglycemia impaired macrovascular, but not microvascular, endothelial function. The authors emphasize this point several times but also note that fewer studies of microvascular endothelial function (9 *vs.* 30 studies) were performed which may have limited their ability to detect an effect. This is an important limitation because, as they acknowledge, impairments of microvascular endothelial function may lead to impairment of macrovascular function by altering shear stress in the conduit arteries. Clinically, there is no clear evidence regarding whether impairment of macrovascular or microvascular endothelial function is more significant or whether one precedes the development of the other. It is clear, however, that abnormal endothelial function precedes the development of structural vascular changes, such as increases in carotid artery intima medial thickness (2,3). This is also supported by the authors' finding of no effect of hyperglycemia on vascular smooth muscle function.

The fact that endothelial dysfunction is the earliest discernable, pathophysiological precursor to atherosclerotic cardiovascular disease is what makes understanding the effects of hyperglycemia on endothelial function so important. As Loader and colleagues (1) point out, the frequency of pathological hyperglycemia is increasing with increasing obesity and type 2 diabetes and there is also a progressive increase in sugar-sweetened beverage consumption, all of which are going to increase the frequency of hyperglycemia within the population and within a given individual. Thus, if acute hyperglycemia does cause acute endothelial damage, as demonstrated by their results, we are facing the potential of marked increases in future cardiovascular disease. Interestingly, there is evidence both *in vivo* (4) and *in vitro* (5) that increased glucose variability causes more severe endothelial damage than prolonged hyperglycemia. This is a scary possibility as high glucose variability would be expected in individuals who frequently consume sugar-sweetened beverages.

Two key caveats must be considered regarding these findings. Loader *et al.* (1) review the methods of endothelial function measurement but do not describe the precise outcome measures in the studies. Measurement of endothelial function usually involves a ratio or percent change of some post- to pre-intervention measure. The measure may be

brachial artery diameter, forearm blood flow, or forearm vascular resistance and the intervention will usually either be acetylcholine infusion or vascular occlusion. The former directly stimulates endothelial nitric oxide release and the latter creates a shear stress which increases endothelial nitric oxide release. The problem is that if there is a change in the pre-intervention baseline measures it is difficult to truly interpret what changes in the ratio really mean. In many of the studies reviewed, the hyperglycemic intervention would cause not only an increase in glucose but likely a significant increase in insulin as well and insulin is a well-known vasodilator (6) that acts through endothelial stimulation (7). Beyond this hyperglycemia without changes in plasma insulin has been shown to markedly increase baseline forearm blood flow in healthy adults (8) and youth with type 1 diabetes (9). If there is a ceiling effect as to how much vasodilation can be maximally achieved the increase in pre-intervention blood flow would mathematically necessitate a decline in the post- to pre-intervention ratio while maximal vasodilation and endothelial function is unimpaired. Against this potential explanation, however, is a study by Greyling *et al*. (10) which found that increasing blood flow through increasing temperature prevented a hyperglycemic-induced fall in conduit artery flow mediated vasodilation. They hypothesized that this was due to increased shear stress due to increased flow.

The second caveat is that hyperinsulinemia accompanying hyperglycemia may confound the results in many of the reviewed studies. Of the reviewed studies, only in the report by Dye *et al*. (9) of adolescents with type 1 diabetes is it likely that insulin levels are not increased during hyperglycemia and there is likely to be a wide degree of variability to the degree of increase. Endothelial function is impaired during low dose and high dose euglycemic clamp (11). Thus, for most of the studies cited by Loader *et al*. (1) the effect of hyperglycemia cannot be easily separated from the effects of hyperinsulinemia. Beyond this there are likely other hormones involved as demonstrated by the potential protective effects of glucagon like peptide 1 in the study by Ceriello *et al*. (12). From a clinical standpoint separating the effects of hyperglycemia from those of hyperinsulinemia may not matter since the two will usually accompany one another in most clinic situations except in type 1 diabetes or type 2 diabetes with extreme β-cell failure.

In summary, the meta-analysis by Loader *et al*. (1) indicates that induction of hyperglycemia has an acute impact on endothelial function although the exact reasons for the effect are not clear. It is likely that if frequently repeated this hyperglycemia-induced endothelial damage will have significant adverse clinical consequences. Further research will be needed to determine what vascular measurement changes (pre- or post-intervention) are responsible for this decline, on the effects of hyperglycemia on microvascular function, and on the independent roles of glucose, insulin and other hormones. In addition, if we are to prevent future cardiovascular disease we will need to develop interventions to block the effect of hyperglycemia. Early studies with ascorbic acid have shown potential effectiveness (11,13-15).

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Footnote

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Acute hyperglycemia impairs flow-mediated dilatation through an increase in vascular oxidative stress: winter is coming for excess sugar consumption

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In two editorials recently published in the *Journal of Thoracic Disease*, Robert P. Hoffman and John David Horowitz *et al*. separately reviewed the interaction between acute hyperglycemia and vascular function (1,2) with a focus on the results of our meta-analysis published in *Arteriosclerosis, Thrombosis and Vascular Biology* (3). We thank the authors for their interest in our research and for their contribution to further understanding the effects of acute hyperglycemia on cardiovascular health.

Hoffman importantly highlighted that although our meta-analysis defined the methods used to assess vascular function, the primary outcome of each study wasn't clearly described. Indeed, it can be confirmed that for all studies included in the meta-analysis, the percentage increase from baseline measurement in response to a specific test of vascular reactivity was the primary outcome for both microvascular data (e.g., acetylcholine and sodium nitroprusside iontophoresis) and macrovascular data (e.g., flow- and nitrate-mediated dilation); and was used to determine standardized mean difference between vascular function in the acute hyperglycemic and normoglycemic states. In agreement with Hoffman, if there is a ceiling effect to the maximal vasodilatory capability of a blood vessel, then variations in baseline measurements due to the potential vasodilating effects of increased blood glucose or blood insulin concentrations during acute hyperglycemia would limit interpretation of the results when expressing vascular data solely as the percentage increase from baseline (1). Given that only a few studies in the meta-analysis provided absolute values for baseline measurements of microcirculatory blood perfusion or brachial artery diameter, comparisons to detect differences in baseline data between the acute hyperglycemic and normoglycemic states were not possible. Such research deficiencies emphasize the need for future studies to clearly report absolute values of vascular function.

Further to this, Hoffman continued to address the potential confounding effects of the hyperinsulinemia that accompanies acute hyperglycemia. Indeed, insulin is a recognised vasodilator that contributes to vascular smooth muscle relaxation in an endothelium-dependent manner by stimulating the synthesis of nitric oxide via the PI3K/Akt pathway and the subsequent activation of endothelial nitric oxide synthase (eNOS) by phosphorylation at serine 1177 (4). Given that shear stress induces vasodilation through the same endothelium-dependent mechanism (5), it may be hypothesized that the impairment of the PI3K/Akt pathway that may be responsible for the acute hyperglycemia-mediated decrease in flow-mediated dilation may also cause a reduction in the vasodilatory action of insulin. Furthermore, it must be acknowledged that whilst

blood glucose concentration increases rapidly following sugar consumption, increases in blood insulin concentration and its vasodilatory action are significantly delayed (6,7). Therefore, it is likely that the deleterious vascular effects of acute hyperglycemia may occur and be measured prior to any significant vasodilatory influence of insulin; moreover, suggesting the redundancy of insulin's implication in potentially mediating heterogeneity between acute hyperglycemic and normoglycemic baseline measurements in vascular assessments performed soon after sugar consumption.

Considering that our meta-analysis highlighted the role of decreased nitric oxide bioavailability in acute hyperglycemia-mediated endothelial dysfunction, Horowitz *et al.* presented mechanisms that may contribute to impaired nitric oxide release (2). Nitric oxide synthesis is catalyzed by eNOS, which oxidizes L-arginine at its N-terminal oxygenase domain. However, L-arginine can also be converted to asymmetric N^G, N^G-dimethylarginine (ADMA) by protein arginine N methyltransferase (PRMT) (8) and arginase (9). The authors argue that elevated production of reactive oxygen species (ROS) during acute hyperglycemia may increase PRMT and arginase activity resulting in decreased bioavailability of L-arginine and increased ADMA. In addition to limiting substrate availability required for nitric oxide synthesis, ADMA directly competes with arginine for eNOS binding sites, thereby decreasing nitric oxide bioavailability. An increase in ROS (oxidative stress) during acute hyperglycemia may also impair eNOS activity by oxidizing its essential co-factor, tetrahydrobiopterin (BH_4) to dihydrobiopterin (BH_2) (10). Such elevations in BH_2 concentration decrease the binding of BH_4 to the active site of eNOS, compounding the superoxide generation (11) that reduces nitric oxide bioavailability and subsequently impairs endothelial function.

Given that it is now clearly established that acute hyperglycemia induces transient oxidative stress that is responsible for endothelial dysfunction (12), there is a great interest in approaches that increase antioxidant defenses that can prevent endothelial dysfunction. Physical activity is one such method that is known to stimulate antioxidant mechanisms, which may enhance eNOS coupling and eNOS activation by phosphorylation at serine 1177 (13). Nevertheless, further experimental and clinical studies are needed to explore the ability of exercise training to prevent oxidative stress and the eNOS uncoupling phenomenon occurring during acute hyperglycemia.

In conclusion, our meta-analysis provided evidence that acute hyperglycemia induces endothelial dysfunction. Due to limited availability of microcirculatory studies, this effect was contained to the macrocirculation. However, further research is needed to clearly establish that acute hyperglycemia-mediated endothelial dysfunction might also occur in the microcirculation. Given that added sugar consumption has increased dramatically in recent decades, especially in children, highlights the importance of conducting such research that will inform public health policy on the role of excess sugar consumption in the pathogenesis of cardiovascular disease.

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Wave mice: a new tool in the quest to characterize aortic valvular disease etiologies

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Introduction

Although many patients with non-rheumatic aortic regurgitation (AR) are asymptomatic and do not require surgical intervention, chronic AR can lead to left ventricular (LV) hypertrophy and, eventually, heart failure (1). The progression from mild to chronic AR is poorly understood and relatively few animal models of chronic AR have been described. In a recent study published in *Arteriosclerosis, Thrombosis*, and *Vascular Biology*, Hajj *et al*. report the characterization of a "Wave" mouse model whose predominant valvular function abnormality is AR, despite the valves exhibiting many of the features traditionally associated with aortic stenosis (AS) (2). Unlike previously described models of AS (3,4), the valvular dysfunction exhibited by Wave mice is independent of the fibrocalcific changes found in the aortic valves of these mice. Thus, the results of this study challenge some of the current paradigms of aortic valve disease and are likely to impact pathophysiological conclusions related to both AR and AS.

Challenging the AR *vs.* AS paradigm

Wave mice possess a single nucleotide mutation in the gene encoding the epidermal growth factor receptor (EGFR), resulting in over 90% global reduction of EGFR tyrosine kinase activity (5). This mutation affects the valvulogenesis of the semilunar valves, yielding valvular dysfunction, LV hypertrophy, and eventual heart failure (5,6). However, previous studies of Wave mice have produced conflicting reports regarding whether AS or AR was the predominant valvular pathology (5,6). The aortic valves of Wave mice exhibit numerous AS hallmarks—such as thickened leaflets, proteoglycan enrichment, lipid deposition, osteoblastic differentiation of the valvular interstitial cells (VICs), calcification, and increased aortic valve pressure gradient—which would appear to make AS a logical diagnosis. But the elegant work by Hajj *et al*. provides multiple lines of evidence indicating that AR is the principal valvular disorder in Wave mice.

At 6 months of age, Wave mice possessed aortic valves that showed signs of thickening, lipid deposition, and calcification that were consistent with prior mouse models of AS (4,7). Valvular pressure gradient and LV volume and mass were also significantly elevated. However, in 52 of 55 mice, measurement of aortic cusp separation revealed no difference between Wave and control mice, indicating the absence of AS. Meanwhile, moderate to severe AR was detected in 81% of Wave mice at this age. The authors went on to further prove that the valvular dysfunction was not due to calcific events by treating the mice with pioglitazone, a compound previously found to attenuate valve calcification (4). While pioglitazone treatment successfully reduced both calcification and osteogenic differentiation in Wave mouse aortic valves, it did not have any effect on the prevalence or severity of AR in these valves. Thus, despite displaying several hallmarks of AS, the aortic valves of Wave mice appear to serve almost exclusively as a model for myxomatous AR. This dissociation of fibrocalcific changes from valve function is an important finding that is likely to

impact future investigations of both AR and AS.

A critical role for the extracellular matrix (ECM)

In addition to challenging the current paradigms of evaluating valvular disease, the findings by Hajj *et al*. suggest that changes in the valve ECM potentially play a major role in driving valvular pathogenesis—an observation that could influence not only our understanding of aortic valve pathologies, but also our treatment of them. By as early as 1.5 months of age, the aortic valves of Wave mice exhibit increased collagen and proteoglycan deposition relative to controls. Proteoglycan enrichment is a hallmark of both myxomatous valvular disease and AS, and is hypothesized to be an initiating event in the progression of both pathologies (8). Although only correlative in nature, the findings by Hajj *et al*. support this hypothesis, as alterations in ECM composition preceded all other histopathological changes. Moreover, the authors specifically identified increased levels of intact versican (but not biglycan) in Wave mice. An earlier study found that mice developed myxomatous valvular disease due to a decrease in versican cleavage (9). It remains unclear why versican, and not other proteoglycans, contributed to the pathology observed in both papers—a mechanism which warrants further study. Overall, it is becoming increasingly apparent that the valve ECM is a delicately balanced structure that can exert a powerful influence on the development of valvular pathologies (10). The ability of the ECM to potentially drive subsequent events in the development of both AR and AS also raises the possibility of targeting molecules involved in ECM remodeling to stop disease progression.

Elucidating the sequence of pathological events in aortic valvular diseases

The investigation by Hajj *et al*. also serves to further highlight our gaps in knowledge with respect to understanding the sequence of pathobiological events that lead to either AR or AS, as well as the challenges in obtaining causative evidence linking these events. One intriguing observation is that the Wave mice exhibit ECM disruption and valve dysfunction prior to upregulation of fibrotic markers and fibrosis. While these results imply that myofibroblast activity is not necessary to induce ECM disarray and that fibrosis is not necessary for development of AR and LV dysfunction, the causative factor for initiation of fibrotic activity cannot be determined from this study. Transdifferentiation of VICs can be driven by ECM composition (10) as well as the mechanical environment (11), so both ECM changes and hemodynamic alterations are possible contenders for guiding the fibrotic and osteogenic events described in Wave mice. The finding that AR and AS can share so many histopathological similarities also raises the question of which cellular- and ECM-level characteristics are responsible for progression towards each of these pathologies. The Wave mouse model, in combination with existing models of AS (3), provides an important tool in addressing such questions. Tissue-engineered models of valvular disease are also poised to serve a critical role in such investigations (12); although they lack the full complexity of native valves, they enable a controlled manipulation of causative connections that is often not possible with *in vivo* models.

In the analysis of data obtained from mouse models, it is also important to consider their limited potential in recapitulating human valve anatomy and physiology. For example, mouse aortic leaflets do not possess the same trilayered ECM structure characteristic of human aortic valves (13). Myxomatous valve disease as described in this particular model of AR is not considered common in the aortic valves of humans in the absence of congenital abnormalities or rheumatic heart disease (14). Moreover, the extent of calcification and lipid deposition reported for both Wave mice and mouse models of AS is substantially lower than what is found in humans. For instance, the amount of calcification in mouse AS models (4,7) (and Wave mice) has been <10% of the total leaflet area, while mild to moderate AS in humans can be accompanied by 40%-80% mineralization (15).

Conclusions

In summary, the development of a much-needed mouse model of AR is a significant scientific contribution on its own, but the work by Hajj *et al*. has implications that reach beyond this accomplishment. Their report not only has consequences for the pathophysiological evaluation of valve tissues, but also highlights the current gaps in our knowledge of the mechanistic pathways of both AR and AS, and what features may be common *vs*. divergent across these two pathologies. The continued development of novel animal models, combined with tissue engineering-based approaches, is likely to be needed to fully elucidate these

etiologies and causative relationships.

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Footnote

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Aortic regurgitation and heart valve disease in mice

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Heart valve disease, in both congenital and acquired forms, is an important and growing public health problem. Epidemiologic studies in the United States have revealed an overall prevalence of 2.5%, and the incidence increases with age. Heart valve disease has a growing clinical impact and significant economic burden (1,2). In patients with aortic stenosis (AS) or aortic regurgitation (AR), morbidity and mortality is increased because of heart failure from chronic left ventricle (LV) disfunction (3,4). An analysis of the mechanism by which chronic LV volume overload leads to heart failure due to AR or AS is important and a useful mice model is timely.

Epidermal growth factor receptor (EGFR) is one of the most physiologically important receptor tyrosine kinases. It plays important biological roles in developmental biology and tissue homeostasis (5,6). EGFR signaling regulates the embryonic formation of semilunar heart valves. Mice homozygous for a single-nucleotide substitution mutation in *EGFR* showed a global 90% reduction in EGFR-tyrosine kinase activity. $Egfr^{Wa2/Wa2}$, or waved-2 (Wave), mice have histological and functional abnormalities in the aortic valve (7,8).

In this issue, Hajj and colleagues provide comprehensive functional, histological, and molecular characterization of spontaneous valvular-volume-overload cardiomyopathy in a mouse model (9). The authors first examined the aortic function and structure and found a significant transvalvular gradient in Wave mice with AR, even when AS was not present. Other researchers have reported fibrosis, calcification, and elevated transvalvular gradients in aortic valves of Wave mice and interpreted the results as indicative of calcific AS (8). For Hajj and colleagues, aortic cusp separation (ACS) was normal in Wave mice at all ages. However, in 3 of 55 Wave mice, ACS was <0.66 mm; the mice had hemodynamically important AS and also severe AR. On color Doppler echocardiography, the prevalence of moderate or severe AR was 70%, 81%, and 73% in Wave mice at 1.5, 6, and 12 months of age, respectively. Aortic valve regurgitant fraction was significantly increased in all Wave mice. However, interestingly, mitral regurgitation was trivial or absent in all mice. Despite the presence of normal ACS, Wave mice showed substantial systolic pressure gradients across the aortic valve. The increased transvalvular gradient was associated with increased aortic pulse pressure, which is consistent with AR but not AS. Increased transvalvular gradient and ACS were not correlated. Mice without AS showed a remarkable quadratic relationship between LV stroke volume and transvalvular systolic gradient, which implies that the gradient is produced by AR. The findings are exciting for two reasons. First, they provide novel information of significantly increased aortic-valve regurgitant fraction and trivial or absent mitral regurgitation in all mice. Second, they confirm that the transvalvular systolic gradient was produced by the AR.

Then Hajj and colleagues examined histological changes in the aortic valve. Valve collagen levels, valve calcification and lipid deposition were undetectable in Wave mice at 1.5 months of age but were significantly increased at 6 and 12 months. Levels of proteoglycans in the aortic valve were significantly elevated in Wave mice at 1.5, 6, and 12 months of age. All these data provide an interesting observation that aortic valve dysfunction occurs in the presence of excess proteoglycans level, including versican, in valve cusps, but precedes fibrosis, calcification, apoptosis, and lipid deposition in the valve.

The authors investigated the mechanism of valve dysfunction in Wave mice. They identified myxomatous structural incompetence and consequent diastolic prolapse of valve cusps as major mechanisms of AR, features that are common in humans with isolated AR (10). A novel finding was that deficient proteoglycan breakdown occurs postnatally in Wave mice. Despite significant increases in polymeric intact versican level, level of cleaved versican was reduced in Wave mice at 6 months of age.

In investigating ventricular morphology and function, Hajj and colleagues found significant LV chamber enlargement, consistent with volume overload, in Wave mice with AR. LV stroke volume and LV mass, indexed to body mass, was elevated. LV ejection fraction was normal in mice at 1.5 and 6 months of age but was significantly decreased by 12 months, which indicated the onset of LV dysfunction. In mice with AR, the features of LV mass, LV end diastolic volume, and LV ejection fraction were similar in males and females at 6 months of age. The authors further examined myocardial fetal gene expression and collagen isoforms, which occurs early and persists essentially unchanged for months (11). Myocardial expression of β-myosin heavy chain, myocyte-enriched calcineurin-interacting protein-1.4, collagen-1, and collagen-3 was significantly increased in Wave mice at 6 months of age. Mice at 12 months old showed fibrosis in the myocardium. Then, authors examined structural changes in individual cardiomyocytes in this mouse model. Cardiomyocyte transverse tubules (TTs) critically regulate excitation–contraction coupling by facilitating Ca^{2+} release from the sarcoplasmic reticulum. TT disruption leads to disease progression from hypertrophy to heart failure (12). At 1.5 and 3 months of age, when Wave mice demonstrated LV hypertrophy and normal LV systolic function, TT organization was normal. At 12 months of age, when both LV hypertrophy and systolic dysfunction were present, TT organization was significantly disrupted. All these data suggest that 6 to 12 months might represent the age of onset of LV dysfunction.

Hajj and colleagues have provided many exciting findings to reinforce the importance of the comprehensive characterization of aortic valve function *in vivo* when assessing the therapeutic efficacy of interventions to protect or improve valve function even in heart valve disease.

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Footnote

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Statin therapy for heart failure: to prescribe or not?

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Since the publication of the first large randomised trial (1), the overwhelming body of evidence has demonstrated significant benefits of statins in patients with atherosclerotic cardiovascular disease (ASCVD). Despite strong recommendations of statins in ASCVD (2,3), controversy exists in patients with heart failure (HF). Although numerous observational studies have demonstrated favorable prognosis in HF patients treated with statins, two landmark randomized trials with rosuvastatin, GISSI-HF and CORONA studies (4,5), have not confirmed any marked reduction of all-cause mortality and non-fatal myocardial infarction (MI) and stroke in HF patients. Therefore, current guidelines do not explicitly recommend the use of statins in HF patients (1,2). However, a meta-analysis by Preiss and co-workers has further fuelled this debate (6).

Preiss *et al*. have examined the effects of statins on the risk of HF hospitalization and HF death by analyzing all primary and secondary randomized controlled trials with statins between 1994 and 2014. In 17 trials conducted over 4.3 years with 132,538 participants without HF at baseline, statins reduced low-density lipoprotein cholesterol (LDL-C) by 0.97 mmol/L, resulting in a 26% reduction of non-fatal MI. For the first time, the authors observed that statins modestly reduced the risks of non-fatal HF hospitalization and a composite HF outcome (HF death or non-fatal HF hospitalization) with no demonstrable difference in risk reduction between those who suffered an MI or not. Interestingly, despite a clear reduction in LDL-C and non-fatal MI in all participants, these effects of statin therapy were not related to the risk of first non-fatal hospitalization or the composite HF outcomes (6).

Statin therapy has been well-documented to reduce the risk of ASCVD in primary- and secondary prevention populations. The cardioprotective effects of statins are primarily derived from their cholesterol-lowering effects (1,2). However, non-lipid-modulation effects of statins, termed as pleiotropic effects, have been implicated in their cardioprotection, including anti-inflammation and anti-oxidation, endothelium protection, immunomodulation, and so on (7). Of note, no relationship was observed by Preiss *et al*. between reduction of non-fatal MI or LDL-C by statins, and risk of non-fatal HF hospitalization or the composite HF outcome (6). It indicates that the potential benefits of statins on HF could be associated with their pleiotropic effects rather than cholesterol-lowering effects. Interestingly, in GISSI-HF and CORONA trials, reduction of hs-CRP by rosuvastatin have not contributed to lower major events in HF patients (4,5). However, rosuvastatin has been proven to reduced hs-CRP levels resulting in significant lower incidence of major cardiovascular events (8). Therefore, it implicates that anti-inflammation is not one of candidate pleiotropic effects of statin protection against HF. The underlying mechanism of statins on HF remains to be identified.

Unlike the subjects with symptomatic HF (New York Heart Association class II, III, or IV) in GISSI-HF and CORONA trials (4,5), this meta-analysis included the participants without HF at baseline (6). It could be a principal explanation for their discrepancies about HF outcomes by statins. According to the classification system of HF stages (9), the participants with symptomatic HF in GISSI-HF and CORONA trials should be at Stage C or Stage D of HF. In contrast, the majority of the patients in this meta-analysis are at the first 2 stages (A and B) of

HF. There are two plausible reasons to further explain the difference of HF outcomes between the subjects in these two trials and those in the meta-analysis. Firstly, HF is considered as a progressive pathological condition (9). During the development and progression of HF, cholesterol, served as an essential component for human body, will be consumed for biosynthesis of various hormones and maintenance of cell membranes. Thus, HF patients have lower total cholesterol and LDL-C as compared with non-HF patients. In contrast to patients without HF, a low total cholesterol portends a poor prognosis in patients with HF (1). It is therefore not surprising that more reduction of LDL-C will not result in lower incidence of HF events in patients with established HF (6). Secondly, the cause of death in patients with coronary artery disease without HF is different from those with HF. Non-HF patients die primarily from acute MI and ventricular fibrillation, whereas HF patients are more likely to die from progressive HF and stroke (10). Therefore, no reduction of HF events were observed in all participants despite a marked reduction in non-fatal MI. Similarly, no relationship was indicated between reduction of MI or LDL-C by statins, and risk of HF events (6).

Despite controversy about the role of statins in patients with symptomatic HF, it is recommendable that statin therapy should be used in HF related to ischemic heart disease because coronary heart disease is acknowledged as the first cause of HF and incident HF always carries a dismal clinical prognosis (9). More importantly, the study by Preiss and co-workers reminds us that prevention of new-onset HF and HF hospitalization can be achieved by statins particularly in patients with coronary heart disease.

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The use of statins in patients with heart failure: more questions than answers

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Abstract: The use of statins to treat patients with heart failure (HF) is controversial due to conflicting results from large, prospective, randomized, placebo-controlled trials and other smaller studies. A recent comprehensive, well-conducted meta-analysis from Preiss and colleagues sought to determine whether statin therapy had an effect on major HF outcomes such as hospitalization and death. Although the study demonstrated a significant effect of statin therapy on HF hospitalizations, several limitations involving the participant data and nature of statin used in the analyzed trials raise questions about the inferences that can be drawn from the study results.

Keywords: Hydroxymethylglutaryl-CoA reductase inhibitors; heart failure (HF); meta-analysis

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Management of heart failure (HF) remains a significant challenge facing clinicians today despite recent advances in medical and device therapies. Although treatments such as angiotensin-converting enzyme inhibitors, beta-adrenergic antagonists, and implantable cardioverter-defibrillators have significantly improved outcomes for patients suffering from HF, mortality remains high at around 50% after 5 years from initial diagnosis (1). The prevalence and cost of treating HF are also high (2), prompting investigators to search for additional therapies. 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) serve as a cornerstone in the treatment of hypercholesterolemia. Statins are indicated for the primary and secondary prevention of atherosclerotic cardiovascular events (3), and demonstrably decrease the risk of myocardial infarction (MI) in both settings through lowering low-density lipoprotein cholesterol (LDL-c) (4). Since many cases of HF are consequent to MI (2), statins could potentially prevent the development of HF by decreasing the incidence of MI or through other mechanisms (5). The use of statins in patients with existing HF, however, is disputed.

The controversy surrounding the use of statin therapy for HF patients stems mainly from the results of two large, randomized, prospective, placebo-controlled trials: the CORONA trial (6) and the GISSI-HF trial (7). Both trials examined the effect of rosuvastatin on mortality and morbidity in HF patients. Although treatment was well tolerated, both trials failed to show a significant effect of the statin therapy on the predetermined endpoints, which contrasted with the positive results observed in many smaller randomized and non-randomized trials (8). As a result, the most recent ACC/AHA guideline on treatment of blood cholesterol makes no recommendation on the use of statin therapy in patients with New York Heart Association class II-IV HF (3).

A recent large, well-conducted meta-analysis by Preiss and colleagues (9) sought to determine whether statin therapy had an effect on major HF events through examining comprehensive published and unpublished data from randomized trials. Participant data was drawn from primary, secondary, and mixed prevention trials with a mean follow-up of 4.3 years. Thirteen of the 17 trials selected

for overall analysis reported baseline HF amongst study participants, allowing the authors to perform separate analyses for patients with and without symptomatic HF prior to statin therapy. Main findings from the overall analysis of up to 132,568 pooled participants include a significant reduction in non-fatal MI [risk ratio (RR) 0.74 statin therapy *vs.* control, 95% confidence interval (CI): 0.70-0.78], and a significant but modest reduction in first non-fatal heart failure hospitalizations (HFH) (RR 0.90 statin therapy *vs.* control, 95% CI: 0.84-0.97). The composite outcome of HF death and HFH was also significantly reduced in the statin treated groups (RR 0.92, 95% CI: 0.85-0.99), but was driven exclusively by a reduction in HFH. No significant effect on HF death was observed (RR 0.97, 95% CI: 0.80-1.17) (9).

The finding that statin therapy reduced risk of non-fatal MI is not new, since statins have previously been shown to decrease the risk of such events (4). On the other hand, the observation that statins significantly decreased the incidence of HFH is intriguing. Retrospective analysis of the previously mentioned CORONA trial (6) revealed a similar effect. In their 2014 analysis of CORONA trial data, Rogers and colleagues found that rosuvastatin therapy significantly reduced the number of repeat HF hospitalizations by about 15% compared to placebo (10). Additionally, a 2014 meta-analysis by Wang and coworkers of trials conducted in HF patients found that statin therapy reduced HF rehospitalizations by approximately 16% (11). Preiss and coworker's study adds strength to that signal. Furthermore, their investigation may have underestimated the benefit of statin therapy since it looked at only first non-fatal HFH rather than repeat HF hospitalizations (9).

Another noteworthy finding from the Preiss paper concerns the mechanisms by which statin therapy reduced the risk of HFH. The authors performed meta-regression analyses to determine whether the reduction of HFH was driven by either a reduced risk of non-fatal MI or a decrease in LDL-c. Interestingly, neither of those factors correlated with the risk of HFH. These results raise the possibility that statins might have exerted beneficial effects on HFH through their pleiotropic (i.e., non-LDL-c lowering) properties. Statins are known to improve endothelial function, ameliorate inflammation in the setting of HF, attenuate myocardial remodeling, and reduce cardiac arrhythmias (5,8). Whether these effects are potent enough to improve mortality outcomes in patients with HF is unclear.

Although the results from Preiss and colleagues' meta-analysis suggest that statin therapy does have a beneficial effect on HFH, there are several key limitations that prevent the study from addressing the question of which patients benefit from this effect. The data that were used for the analyses came from primary, secondary, and mixed prevention trials. Thus, the study offers little insight into whether statin therapy is more effective in a primary or secondary prevention setting. A second flaw is that a large number of patients used for the main analyses had unknown baseline HF status. Of the 17 trials used for the main analysis, 13 noted HF status of participants at baseline, providing a pool of around 92,600 participants (90,001 without HF at baseline) to scrutinize. When the authors analyzed data from only the participants without baseline HF symptoms, the results were inconclusive. In this cohort, no statistically significant effect of statin therapy on HFH (RR 0.94, 95% CI: 0.85-1.05), HF death (RR 0.97, 95% CI: 0.69-1.38), or composite outcome (RR 0.94, 95% CI: 0.83-1.06) was detected, due to the decreased number of HF events in the participant pool and resulting loss of power. These analyses complicate the conclusions that can be drawn from the study, since ~42,500 participants—whose data were used in the overall analysis that found a significant effect of statin therapy on HFH in 132,568 participants—had unknown HF status at baseline. Due to this lack of information, it is difficult to determine whether the significant effect of statins on HFH was due to the therapy reducing the onset of new cases of HF, or if statins prevented the worsening of pre-existing cases of HF. Evidence for the utility of statins in the former scenario is readily available, with several studies demonstrating that statin therapy decreases the incidence of HF at follow up in secondary prevention populations (12-14). On the other hand, though numerous small studies have demonstrated a beneficial effect of statin therapy in the setting of HF through improved surrogate endpoints, the negative results of the CORONA and GISSI-HF trials—which, in contrast to the smaller studies, were powered to determine the effects of statins on major outcomes—outweigh the positive results observed in the smaller trials (15). Therefore, if the beneficial effect of statin therapy on HFH described in the Preiss meta-analysis had been driven by a reduction in HFH in patients with HF, it would have represented an important novel finding. Unfortunately, due to the large number of participants with unknown baseline HF status, it is not possible to draw a conclusion on that matter.

A third limitation of the meta-analysis concerns the particular statins used in each of the contributing trials.

Recent evidence suggests that there is not a class effect for statin use in the setting of HF due to chemical differences between statin molecules. Statins can be classified based on solubility as either hydrophilic or lipophilic. Lipophilic statins may be more readily taken up by cardiac muscles, thus leading to greater beneficial effects in the setting of HF (8). Evidence from a meta-analysis of randomized controlled trials of statins in HF showed a significant benefit of atorvastatin—a lipophilic statin—on all-cause mortality, left ventricular ejection fraction, and hospitalization due to HF, whereas similar effects were not observed in patients randomized to the hydrophilic rosuvastatin (16). A 2014 meta-analysis of prospective, randomized controlled trials by Liu and co-workers found a significant effect of lipophilic statins on major outcomes in patients with HF (17). More recently, an adjusted indirect-comparison meta-analysis of randomized trials by Bonsu and colleagues demonstrated a significant beneficial effect of lipophilic statins on left ventricular ejection fraction and plasma concentrations of multiple biomarkers including brain natriuretic peptide, high-sensitivity C-reactive protein, and interleukin 6 (18). In the Preiss meta-analysis, 8 of the 21 trials included used hydrophilic statins. The diversity of statins utilized in the trials may have introduced an undesirable confounding variable into the analyses. Further analysis on the impact of lipophilic statins in this study may have helped clarify whether lipophilic statins have greater efficacy in reducing HF-related outcomes and dispel the notion of a class effect for statins.

While the work of Preiss *et al.* demonstrated a significant beneficial effect of statin therapy on HFH, it also raised numerous questions regarding the types of patients that would benefit from the treatment. The study did not focus on the use of statins in patients with existing HF. Indeed, several of the trials that supplied data for the meta-analysis did not even report baseline HF status. Thus, the reduction in HFH resulting from statin therapy as demonstrated by the study does not constitute a sufficient rebuttal to the results from the CORONA and GISSI-HF trials. Furthermore, when the authors focused on patients without existing HF at baseline, the effect of statin therapy on HF outcomes was inconclusive. It seems that the meta-analysis, which intended to answer whether statins had an effect on major HF outcomes, instead only raised more questions.

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Footnote

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Major adverse cardiovascular and cerebral events in hypothyroid patients undergoing percutaneous coronary intervention

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Zhang *et al*. (1) carried out a large prospective naturalistic study on patients who underwent percutaneous coronary intervention (PCI) evaluating the role of thyroid hypofunction on major clinical outcomes from in-hospital stay up to 10 years of follow up with a median observation of 3 years. The enrolled population was representative of adult patients (mean age of the whole cohort 64.6 years) with several traditional risk factors (previous cardiovascular events or coronary artery disease, hypertension, diabetes mellitus, obesity, dyslipidemia and smoking status), which accounted for high risk of cardiovascular events. The diagnosis of hypothyroidism, only defined by the presence of serum TSH level above 5 mIU/L at PCI time-point, was associated with underlying clinical features at baseline [age, female gender, history of myocardial infarction (MI), diabetes mellitus, heart failure (HF), hypertension, hyperlipidemia, arteriopathy as well as ACE/ARB and amiodarone administration] and a worse clinical composite outcome during follow up [cardiac death, MI, HF events, repeat vascularization (TRV) and stroke]. The risk of composite endpoint in hypothyroid patients remained significantly higher even after adjusting for several potential confounding factors, and accounted for about 30% of the increased risk. In detail, the greatest correlation between hypothyroidism and single endpoints was observed for MI, HF, TRV and stroke. By stratifying hypothyroid patients on the basis of serum TSH value (≥5<10 mIU/L and ≥10 mIU/L), the authors demonstrated that even a mild increase of serum TSH (≥5<10 mIU/L) was significantly associated to the composite endpoint and the occurrence of MI, although to a lesser extent as compared to patients with TSH ≥10 mIU/L, while the statistical significance was not reached for the other single endpoints. On the other hand, patients with a marked increase of serum TSH (≥10 mIU/L, defined as affected by overt hypothyroidism independently from analyzing the level of serum free thyroxin) presented a greater risk of either the composite endpoint or all the single endpoints as compared to euthyroid patients. It is noteworthy that patients receiving adequate L-thyroxin replacement therapy (TRT) showed a significant reduction of composite or single endpoints while, those with inadequate TSH target value (≥5 mIU/L) maintained a risk profile similar to hypothyroid patients not receiving any TRT. Finally, in a nested group of patients randomly selected with a ratio of 1/3 from the two cohorts (euthyroid and hypothyroid patients at baseline) and evaluated in single blind by coronary angiogram at follow-up, the authors documented a significant worsening of target vessel diseases in hypothyroid as compared to euthyroid patients.

Although the study had some limitations mainly represented by the study design (observational), the definition of hypothyroidism (only based on a single TSH measurement without taking into account the level of serum free thyroxin) and the lack of age specific serum TSH reference ranges, the results are robust and consistent with previous experiences confirming the important role of thyroid function on the cardiovascular system especially in adult population younger than 65–70 years (2,3). In this regard, the link between thyroid function and cardiovascular risk factors is widely recognized and some meta-analyses

documented an increased risk for CV events and mortality only in young adult population (<65 years). At molecular level, thyroid hormones (TH) play a determinant role in the circulatory system, from heart structure and function to vessels and blood flow regulation (2-5). Moreover, as stated by Zhang *et al.* (1) and previously documented by our group both in experimental and human models (6,7), mild thyroid failure is associated to endothelial dysfunction (reduced NO induced vasodilatation) and a certain degree of systemic inflammation (6,7). These findings along with the effects of thyroid failure on intermediate metabolism (8) could at least in part explain the increased CV risk of hypothyroid individuals also in the presence of mild dysfunction as observed in subclinical hypothyroidism (SCH) (9-11). In this regard, the study by Zhang *et al.* showed a link between hypothyroidism and HF events both at baseline and during follow up, but only in individuals with serum TSH >10 mU/L, suggesting that heart function may be affected mainly by the extent of thyroid dysfunction, in agreement with the results of the largest pooled meta-analysis (12). Moreover, a recent meta-analysis, which analyzed data on 47,573 adults, documented a trend for risk of stroke only in subject younger than 65 years, which increases with increasing TSH value (13). Similarly, another meta-analysis documented an increased risk of cognitive alterations only in individuals younger than 75 years, more evident in those with higher serum TSH values (14). On the other hand, a recent systematic review and meta-analysis showed that either subclinical or overt hypothyroidism are independent predictors of hospitalization and mortality in HF patients, but only in those older than 65 years (15). Interestingly, data from our laboratory either in humans or animal models, showed that, apart from the extent of serum TSH increase, both endothelial and mitochondrial dysfunction were affected by the duration of the exposure of tissues and organs to the mild TH deficit of SCH (16,17). In this setting, a recent Editorial to the European Thyroid Association guidance for treating subclinical thyroid dysfunctions suggested to consider thyroid dysfunction as a cardiovascular risk factor that acts in continuum, depending from the patient's age, the extent of thyroid dysfunction and the duration of the disease, similarly to other conventional cardiovascular risk factors such as hyperlipidemia, systemic hypertension, diabetes mellitus etc. (18).

SCH is a common feature in clinical practice, its prevalence is higher in women and increases with increasing age (5). In order to obtain an accurate diagnosis of SCH in the elderly, we have to consider the observed shift of serum TSH level toward upper values during age (19). In this setting, data from scientific literature obtained in disease free, oldest old population (>80–85 years) suggested that well ageing is characterized by a certain degree of down regulation of the hypothalamus-pituitary-thyroid peripheral axis, and this finding might lead to the idea that a mild decline of thyroid activity at the tissue level has favourable effect (2,20). However, sharing this interpretation with older people at all should be done with caution since a mild elevation of serum TSH may occur by either the aging process itself or an actual thyroid disease. Indeed, we should also consider that the prevalence of circulating anti-thyroid autoantibody levels increases with ageing (21), suggesting actual subclinical thyroid impairment as the cause of TSH raise in the elderly. Therefore, a correct diagnosis of SCH is challenging in the oldest old population (i.e., elevated serum TSH according to age related reference ranges and documented thyroid disease) but crucial in avoiding significant misclassification of patients with abnormal TSH value, who may or may not have an actual thyroid failure and may receive unnecessary or even harmful therapy (2,3,22,23). Keeping in mind these considerations, the fundamental clinical question regarding older persons with slightly elevated serum TSH value is how they have to be dealt with and, in the case of confirmed thyroid failure, whether they need hormone replacement therapy (2,19,23). The study by Zhang *et al.* demonstrated in an indirect way that an adequate L-thyroxin replacement may reverse the CV risk of SCH, however this is not easily to obtain in clinical practice since in a certain number of cases (mainly older women) the treatment could be detrimental if an excess of therapy is administered and a strict monitoring of serum TSH value is warranted (1,24).

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Footnote

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Evidence and controversies regarding the screening for subclinical hypothyroidism in patients with cardiovascular disease

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Subclinical hypothyroidism is defined as thyroid-stimulating hormone (TSH) level above the upper limit of the reference ranges with normal free thyroxine (T4) concentrations (1). Current data suggest that the prevalence of subclinical hypothyroidism can reach up to 10% in the elderly (2) and around 30% of subject can progress to overt hypothyroidism (low levels of T4) depending on the initial serum TSH concentrations and the presence of anti-thyroid peroxidase (anti-TPO) antibodies (3). Thyroid hormones have different effects on the cardiovascular system (4). Subclinical hypothyroidism is a well-known secondary reversible cause of hypercholesterolemia. Unspecific cardiac alterations have been associated with overt and subclinical hypothyroidism, such as impaired systolic function and left ventricular diastolic filling, increased peripheral vascular resistance, diastolic hypertension, increased arterial stiffness, endothelial dysfunction, pericardial effusion and arrhythmia (5-8). These findings are more likely to be observed in patients with higher TSH levels and in elderly.

Data from observational prospective studies suggest an association between subclinical hypothyroidism and cardiovascular disease (CVD) events, while most of the available evidence derived from the consortium called "The Thyroid Studies Collaboration" (*Figure 1*) (9-11). After a systematic review, all eligible prospective cohorts were identified and their authors were contacted to share their data for an individual participant data (IPD) analysis. This process has the major strength to avoid aggregation-bias, as it might occur by study-level meta-analysis, as well as the following advantages: (I) increased statistical power; (II) adjustment with standardized confounding factors across studies; (III) definition of uniform TSH ranges; and (IV) use of similar clinical outcomes definition (12). Data from 11 prospective cohorts, including 55,287 patients and 3,450 (6.2%) with subclinical hypothyroidism showed higher rates of total coronary heart disease (CHD) mortality in those with higher TSH levels, especially for TSH levels of 7.0 to 9.9 mIU/L with hazard ratios (HRs) of 1.42 [95% confidence intervals (CI), 1.03–1.95] and for TSH levels ≥10.0 mIU/L with HRs of 1.58 (95% CI, 1.10–2.27, P for trend =0.005, *Figure 2*) (9). The HRs for CHD events were 1.17 (95% CI, 0.96–1.43) for TSH levels of 7.0 to 9.9 mIU/L and for TSH levels of 10 to 19.9 mIU/L (HR =1.89; 95% CI, 1.28–2.80; P<0.001 for trend) (10). No significant interaction was found according the presence of CVD at baseline. Using the same data in the assessment of heart failure (HF) events, the IPD of 6 prospective cohorts including 25,390 subjects (22,674 with euthyroidism and 2,068 with subclinical hypothyroidism) showed also higher risk of HF events: HR was 1.65 (95% CI, 0.84–3.23) for TSH levels of 7.0 to 9.9 mIU/L and 1.89 (95% CI, 1.23–2.80) for TSH 10–19.9 mIU/L (P for trend <0.01). No interaction was found also according to the presence of CVD at baseline.

These findings derived mainly from community-dwelling cohorts and few data were available in high-risk patients, such as those who were treated with percutaneous

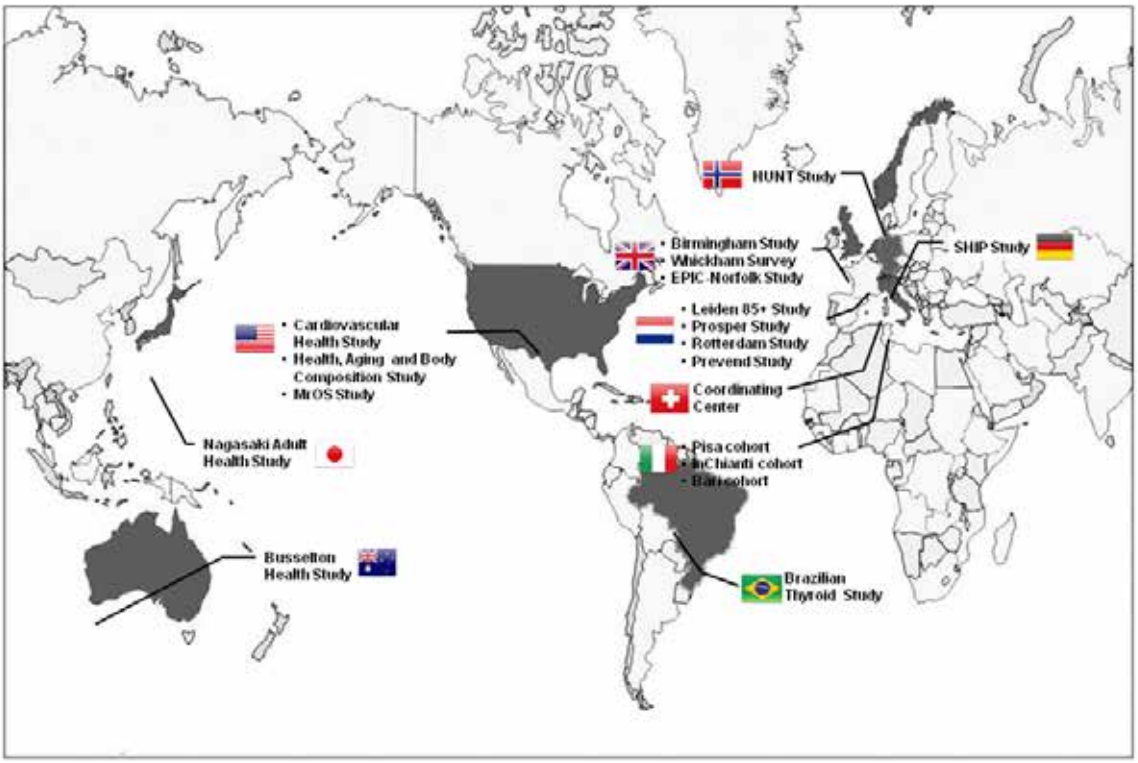

Figure 1 Prospective Cohort Studies Constituting the Thyroid Studies Collaboration.

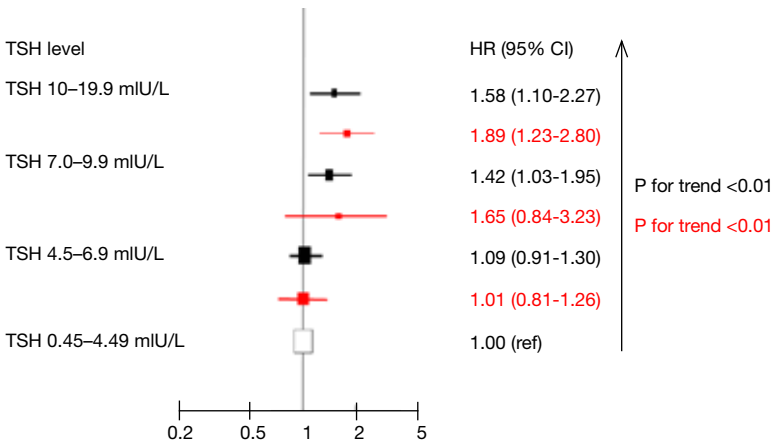

Figure 2 HRs for coronary heart disease mortality (black) and heart failure event (red) according to TSH levels [adapted from (9,10)].

coronary intervention (PCI) (13). Revascularization with PCI remains the recommended therapies of acute coronary syndromes (ACS) or in patients with stable CAD presenting angina and with documented large ischaemia or significant coronary disease (14,15). Secondary prevention is especially important in this setting as the identification of emergent CVD risk, such as subclinical hypothyroidism, was poorly studied. In their article, Zhang *et al.*, from the Mayo Clinic, reported among 2,430 patients treated with PCI an association between subclinical hypothyroidism and the occurrence of major adverse cardiovascular and cerebral events (MACCE) (13). Adjusted HRs were 1.28 (95% CI, 1.13–1.45; P=0.0001) for MACCE, HR 1.14 (95% CI, 0.75–1.69; P=0.54) for cardiac death, HR =1.25 (95% CI,

1.01–1.53; P=0.037) for myocardial infarction, HR =1.46 (95% CI, 1.13–1.88; P=0.004) for HF, HR =1.26 (95% CI, 1.10–1.43; P=0.0008) for revascularization and HR =1.62 (95% CI, 1.04–2.49; P=0.04) for stroke. Prevalence of subclinical hypothyroidism was quite high (28.2%) compared to data from the Thyroid Studies Collaboration, but the magnitude of the risk estimates was similar. In fact, as most patients had missing data for free thyroxine levels, distinguishing overt (low T4 levels) from subclinical hypothyroidism (normal T4 levels) was not feasible. Patients who had an appropriate thyroid replacement therapy with normalization of TSH levels had lower risk of MACCE compared to those with inadequate thyroid replacement (HR =0.78; 95% CI, 0.61-0.99; P=0.045) or those who remained untreated (HR =0.69; 95% CI, 0.52-0.89; P=0.005). Lower risks in patients adequately treated were also observed for cardiac death (P=0.008), myocardial infarction (P=0.004), HF (P=0.02), revascularization (P=0.41) and stroke events (P=0.01). Similarly, Ravzi *et al*. reported an association between thyroid replacement therapy and lower incidence of CHD events (adjusted HR =0.61; 95% CI, 0.39–0.95) among 3,093 patients with subclinical hypothyroidism (16). Although, no causality can be assumed due to the non-randomized design, these data suggest that treatment of subclinical hypothyroidism might be safe and possibly reduce the recurrence of major adverse cardiovascular events.

Currently the evidence to make a recommendation for thyroid replacement is not strong (level B). No adequately powered randomized controlled trial has investigated the impact of thyroid replacement therapy on cardiovascular outcomes. European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines for the management of ACS did not address any specific issues regarding the screening and treatment of subclinical hypothyroidism (15,17). In 2012, AHA guidelines for the management of HF recommended to measure TSH levels in the assessment or progression of HF, but did not mention a specific threshold for thyroid replacement (18). Recently, the 2015 US Preventive Services Task Force for screening for thyroid dysfunction concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening and treatment for thyroid dysfunction in asymptomatic adults, mainly due to the absence of large randomized controlled studies with clinical endpoints (19). Given the recent data, it seems appropriate to screen patients with established CVD for subclinical hypothyroidism, as risk factor or worse prognosis. However, evidence from observational studies should be carefully evaluated until corroboration with randomized controlled studies. In analogy to screening, treatment of subclinical hypothyroidism is a source of controversies. Based on epidemiological studies suggesting higher risks, thyroid replacement therapy should be considered for TSH ≥10.0 mIU/L and might be considered for those with TSH between 7.0–9.9 mIU/L. As the risk is not increased for the majority of patients with TSH between 4.5 and 7.0 mIU/L, the benefit of thyroid replacement therapy would be probably less pronounced. However, an argument for therapy at low TSH threshold is to prevent early the progression to overt hypothyroidism. A counterargument is a chronic and probably life-long daily therapy in asymptomatic individuals requiring frequent medical controls. In the assessment of risks and benefits, overtreatment is an issue in the elderly with potential adverse events, such as atrial fibrillation or osteoporosis with hip fracture (20,21).

In this area of uncertainties and lack of evidence, the TRUST (Thyroid hormone Replacement for Untreated older adults with Subclinical Hypothyroidism a randomized controlled Trial among older adults), supported by the FP-7 EU funding (Specific Program Cooperation—Theme Health, Proposal No: 278148-2, NCT01660126), is currently assessing the impact of thyroid replacement therapy on quality of life, potential symptoms, cardiovascular risk factors, and biomarkers. In addition, further studies should investigate the impact of thyroid replacement of cardiovascular imaging endpoints, such as echocardiography (22). Echocardiography is the most used diagnostic tool for the diagnosis and risk stratification of heart disease, such as the measurement of left ventricular ejection fraction for systolic function, and assessment of Doppler transmitral pulsed-wave flow pattern, such as isovolumic relaxation time, a wave and E/A ratio, or tissue Doppler for the E/é ratio, for the diastolic function (23,24). Recently, other methods using three-dimensional echocardiography and longitudinal strain improved the detection of subclinical abnormalities with higher accuracy (25). Such mechanistic trial will provide strong evidence regarding the potential benefit of thyroid replacement therapy in term of HF endpoints. Regarding atherosclerosis, surrogate endpoints, such as carotid intima media thickness, computed tomography with the estimation of calcium score or intravascular ultrasound (IVUS) or optical coherence tomography (OCT) of coronary arteries. Given that thyroid replacement is not an emergent target for pharmaceutical companies, academics should initiate such

clinical trials in order to strengthen evidence and address a condition that concern 10% of the elderly population (22).

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Footnote

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