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INTERVENTIONAL CARDIOLOGY

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INSIDE

Review of

EuroPCR 2016

Paris, France

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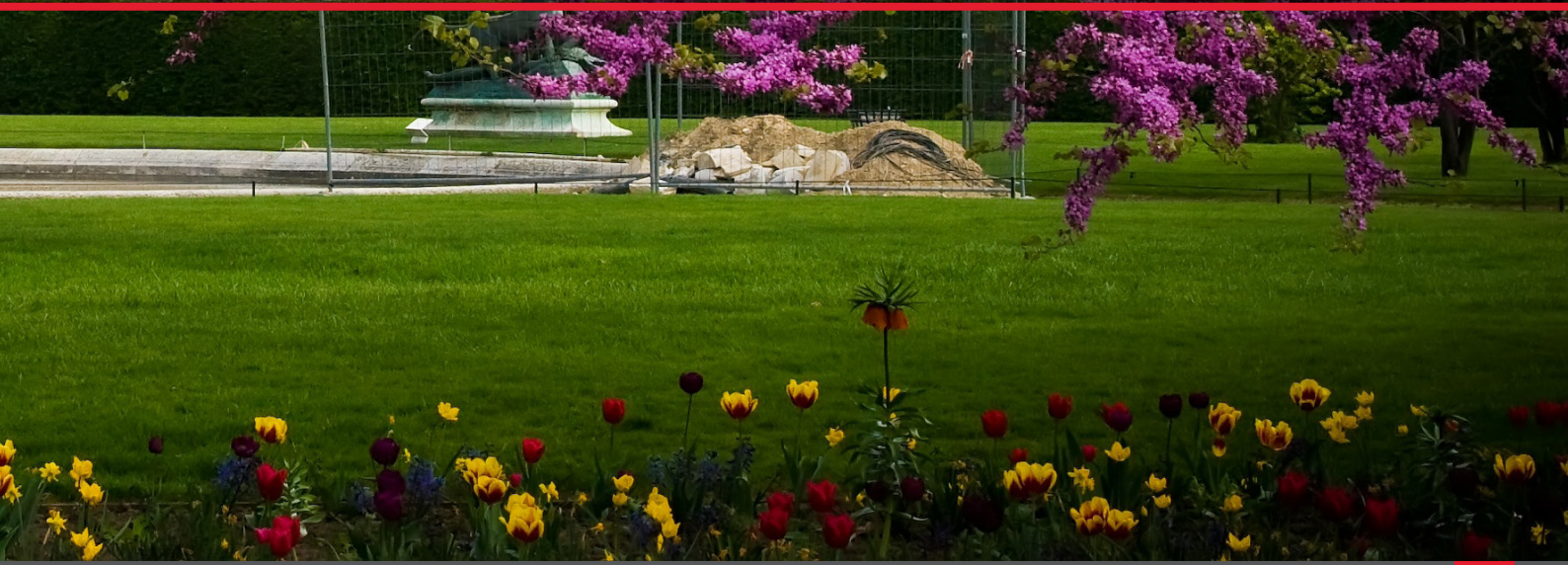

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Welcome

A warm welcome to this year's edition of *EMJ Interventional Cardiology*, within which you will find numerous resources designed to aid your research, stimulate your mind, and expand your perspective. Alongside our 2016 collection of peer-reviewed papers you will find interviews, abstract reviews, and an analysis of the most exciting presentations from this year's renowned interventional cardiology event, EuroPCR.

This year's EuroPCR, hosted in Paris, France, from 17th–20th May, proved to be the most comprehensive and exhilarating interventional cardiology congress our team have visited so far. With an extensive array of learning objectives and an even greater variety of approaches to achieving them, no interventionists were left behind in this monumental meeting of specialists and academics. Inside this issue you will find coverage of some of the most impressive research presented at the congress, including innovations in stent technology and long-term follow-up studies, development of less invasive diagnostic techniques, and analysis of current progress and challenges in cardiovascular treatments.

Alongside a review of the news from EuroPCR, *EMJ Interventional Cardiology* contains abstract reviews direct from the researchers themselves, giving you a personal insight into the new frontiers of the field. Covering a number of topics including aortic valve implantations and replacements, techniques for treating ischaemic stroke, and the use of drug-eluting stents in the context of diabetic patients, we hope these reviews will enthuse and motivate your interests.

Regarding articles, our Editor's Pick this year comes from Sidhu and Gerber, who offer a thoughtful overview of the paradigm of percutaneous coronary intervention for coronary artery disease, providing advice on the utility of various bifurcation devices. Also available is an update on transcatheter aortic valve implantation by Biagioni et al., and an evaluation of the long-term risks and benefits of the use of manual thrombus catheters in the context of coronary and myocardial circulation by Jamil et al. From Umemoto et al., we bring you an article concerning endovascular treatment for spontaneous carotid artery dissection.

It is our intention that this edition serves as a gateway to a wealth of relevant research that is both conceptually thought-provoking and practically applicable. By providing peer-reviewed articles, congress coverage, interviews, and more, we hope to have achieved this. Interventional cardiology is progressing rapidly and dynamically as a field, and we hope that we have presented these developments in this issue.

Spencer Gore

Director, European Medical Journal

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Front cover and contents photograph: Paris, France, home of EuroPCR 2016.

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Featured inside:

The Rise and Fall of Routine Manual Thrombectomy for ST-Elevation Myocardial Infarction

- Vincent Floré, Stephen P. Hoole

Foreword

Prof Ran Kornowski

Chairman, Department of Cardiology,
Rabin Medical Center, Beilinson and Hasharon Hospital, Petah Tikva, Israel.

Dear Friends and Colleagues,

It is with great pleasure that I welcome you to this edition of *EMJ Interventional Cardiology*.

Now in its fourth year of publication, this issue of *EMJ Interventional Cardiology* once again comprises a collection of exceptional papers, peer-reviewed for quality and chosen to provide you with a strong platform of stimulating ideas to apply in your work, whether interventional or academic. Included is a state-of-the-art review of bifurcation percutaneous coronary intervention by Sidhu and Gerber, and a discussion of endovascular treatment of spontaneous carotid artery dissection by Umemoto et al. A review encompassing in-stent restenosis following carotid artery stenting by Di Gioia et al. covers all aspects from diagnosis to treatment, and Jamil et al. provide an evaluation of the long-term outcomes of manual thrombus aspiration catheters for interventional use.

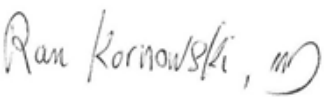
> "With oral presentations, workshops, symposiums, and case studies, the congress covered all aspects of interventional cardiology."

'A world in itself', the EuroPCR congress, held in Paris, France, from 17th–20th May 2016, offered an opportunity to learn, network, and innovate in a setting ripe for scientific advancement. With oral presentations, workshops, symposiums, and case studies, the congress covered all aspects of interventional cardiology. In this edition, you will find a selection of abstract reviews and summaries presented at EuroPCR 2016, offering an insight into the most relevant and inspiring research within the field.

The ultimate aim of the European Medical Journal is to provide the resources for interventional cardiologists to develop their approach and perspective, by offering a robust and high-quality selection of research papers and abstracts. It is with this in mind that I invite you be a part of this endeavour, and to contribute your work to be published in the 2017 edition of *EMJ Interventional Cardiology*.

I hope you enjoy reading this issue!

Kind regards,



Ran Kornowski

Chairman, Department of Cardiology, Rabin Medical Center, Beilinson and Hasharon Hospital, Petah Tikva; Professor of Cardiovascular Medicine, The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.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EUROPCR ANNUAL CONGRESS 2016

PALAIS DES CONGRÈS,
PARIS, FRANCE
17TH-20TH MAY 2016

Welcome to the *European Medical Journal* review of the Annual Meeting of the EuroPCR Congress

Paris, France, played host to EuroPCR again this year; the city has a rich medical history from Paré to Pasteur and the innovations seen at this year's congress are also likely to be talked about for years to come. It has been hailed as the year of interaction for EuroPCR with more engagement, sharing, and reaction than ever before.

The congress had 11,588 participants this year, with more than 510 abstracts integrated into the programme, more than 50 hours of live demonstrations, and 10 new sessions covering over 65 clinical trials. A brand new structure to the course this year saw the events categorised by theme, focus, and format. The themes covered the four main categories of interventional cardiology; the focusses split the categories into areas concentrating on research, daily practice, essentials for young practitioners and allied health professionals, and imaging. Finally, there was a diverse range of session formats this year from informal discussions to formal lectures. William Wijns, course director, commended these various sessions as "relevant for the entire community," going on to say that they encompass "a self-directed, new learning experience."

The Innovators Day brought together clinicians, researchers, industry innovators, and financiers to aid development in the current issues at the forefront of interventional cardiology. The day built upon three key areas: mitral and transcuspid valve interventions; heart failure interventions and technologies; and applications of e-health solutions in the cardiovascular space. Nicolo Piazza, Department of Interventional Cardiology, McGill University Health Centre, Montréal, Québec, Canada commented, "It was a truly fascinating day, full of new ideas and challenges, and I think it is the challenges that fuel innovation. As physicians and engineers, it is these challenges that gives us the opportunity to help our patients."

The last day of EuroPCR saw the final of the abstract competition, the coveted Best Abstract Award, in which contestants had to present their abstract in 5 minutes followed by 3 minutes of questioning. The winners of this competition were Ziad Ali, whose abstract presented 'Imaging and physiology-guided PCI

without contrast administration in advanced renal failure: A feasibility, safety, and outcome study', and Dejan Milasinovic, who presented the results from 'Clinical outcomes after immediate vs. delayed invasive intervention in patients with NSTEMI: long-term follow-up of the randomized RIDDLE-NSTEMI study'.

> "As physicians and engineers, it is these challenges that gives us the opportunity to help our patients."

Further to this, training and research awards were given by the European Association of Percutaneous Coronary Intervention (EAPCI). Alberto Polimeri received the first award for research into 'Echocardiographic parameters for prediction of clinical responsiveness to MitraClip implantation'. Celestino Sardu was awarded the second for '*In vivo* and *in vitro* research protocol – Non-ST-Elevation Myocardial Infarction (NSTEMI) outcomes in Type 2 diabetic patients with non-obstructive coronary artery stenosis. DIAbetic Myocardial infarction Coronary Non-Obstructive Stenosis: DIA-MYCONOS STUDY'. The last award went to Nader Zaki-Nazmi, for work in 'A head-to-head comparison: Aspirin plus clopidogrel versus rivaroxaban following transcatheter aortic valve implantation regarding post-procedural silent left main compromise and early hypoattenuated leaflet thickening'.

In this review, you will find a selection of articles summarising the most recent and impactful research from EuroPCR, with important topics such as transcatheter aortic valve implantation and percutaneous coronary intervention featuring heavily. We have also included work which comes directly from the daily sessions with a number of abstract reviews written by the presenters themselves. We hope this review will give you all the information you need to know to keep up-to-date within the interventional cardiology sphere. EuroPCR 2017 will return to Paris on the 16th–19th May, and we hope to see you there!

Optical Imaging Achieves Clinical Value in Guiding Percutaneous Coronary Intervention

PROMISING results from the OPINION Study regarding optical imaging for guiding percutaneous coronary intervention (PCI) were discussed in a EuroPCR press release dated 17th May 2016. The study results showed that optical frequency domain imaging (OFDI) with second-generation drug-eluting stents (DES) used to guide PCI matched the clinical and angiographic outcomes achieved by intravascular ultrasound (IVUS)-guided PCI at 12-month follow-up.

Eight hundred patients requiring PCI using DES (mean age 68 years) were selected for the non-inferiority study, randomised to either OFDI-guided PCI or IVUS-guided PCI at 42 centres in Japan. The procedure involved inserting resorbable polymer DES in *de novo* native coronary artery lesions, followed-up with angiography at eight months. The study's primary endpoint was assessment of target-vessel failure at 12-month clinical follow-up. The results demonstrated low rates of target-vessel revascularisation (cardiac death, target-vessel related myocardial infarction, and clinically driven target-vessel revascularisation) in both imaging strategies at 12 months; OFDI-guided PCI amounted to only 5.2% while IVUS-guided PCI had a rate of 4.9%.

OFDI, the newest optical coherence tomography (OCT) technology, is a non-invasive imaging test that uses light instead of ultrasound. "OPINION is the first study to compare clinical outcomes with OFDI and IVUS to assess lesion morphology during PCI with second-generation DES," said the author of the study Dr Takashi Kubo, Wakayama Medical University, Wakayama, Japan.

The results of the OPINION Study represent the first instance of comparative OFDI and IVUS-guided PCI. Dr Kubo was positive about the findings and their contribution to identifying OCT-guided PCI as a strategy of clinical value. "The clinical outcome in both OCT-guided PCI and IVUS-guided PCI was excellent. Our results might influence the next ESC guidelines, which currently give a Class IIb recommendation for OCT. OCT use during PCI should have a Class IIa recommendation."

> "The clinical outcome in both OCT-guided PCI and IVUS-guided PCI was excellent. Our results might influence the next ESC guidelines, which currently give a Class IIb recommendation for OCT."

Leaders Free Trial Considers Acute Coronary Syndromes in Interventional Procedures

SIGNIFICANTLY lower rates of target-lesion revascularisation in patients with acute coronary syndromes (ACS) have been reported in those undergoing percutaneous coronary intervention (PCI) with a polymer-free biolimus-A (BA9) drug-coated stent (DCS) over those receiving a bare-metal stent (BMS).

According to a EuroPCR press release dated 17th May 2016, the results were attained in a sub-study of the LEADERS FREE trial. The trial investigated the use of polymer-free and carrier-free DCSs that transfer BA9 into the blood vessel wall over a 1-month period.

> "The information from this sub-study is key because this specific population has not been included in previous clinical studies and, until now, treating these patients was like working in a 'data-free' zone."

The sub-study assessed 659 patients with ACS: 554 diagnosed with a non-ST-segment elevation myocardial infarction and 105 with an ST-segment elevation myocardial infarction, who were randomised to receive either a polymer-free BA9-coated stent or a BMS, along with 1 month of dual antiplatelet therapy for all patients to minimise the risk of bleeding.

A 12-month follow-up concluded that patients with polymer-free stents had less than half the rate of clinically driven target-lesion revascularisation than those with BMSs (3.92% versus 8.96%, p=0.009). Risk of adverse events (cardiac death, myocardial infarction, and stent thrombosis) was also considerably lower in the group receiving DCSs (6.92% versus 9.32%, p=0.049), while BMSs increased the possibility of restenosis and thus, further intervention.

The results may have a substantial effect on future PCI procedures for patients with high-risk of bleeding. "Current guidelines may need to be revised and BMSs can no longer be recommended for these patients," suggests study author Prof Christoph Naber, Contilia Heart and Vascular Center, Clinic for Cardiology and Angiology, Essen, Germany.

Prof Thomas Cuisset, from University Hospital, La Timone, Marseille, France, commented on the findings: "The information from this sub-study is key because this specific population has not been included in previous clinical studies and, until now, treating these patients was like working in a 'data-free' zone." However, despite promising results, more research is required and the study's specifications should not yet be extrapolated to other populations.

Developments in Less Evasive Surgery for Ischaemic Cardiomyopathy Treatment

VAST developments have been reported in two European studies that used the Revivent™ system to reduce the severity of heart failure in patients with ischaemic cardiomyopathy, and anteroapical left ventricular aneurysms.

> "This technique represents a less invasive intervention to exclude apical aneurysm instead of the usual surgical approach that requires cardiopulmonary bypass and ventriculotomy."

Researchers investigated a total of 71 patients classified under New York Heart Association (NYHA) Functional Classification as having

symptoms greater than Class II including anteroapical large post-myocardial infarction scarring, dilated left ventricle, and heart failure. Whilst 51 patients were treated using the surgical approach with the new system, the remaining 20 were treated with a hybrid transcatheter. The results demonstrated an overwhelming procedural success rate for implantation of the Revivent of 97.2%. Furthermore, the results indicated an operative and 30-day mortality of 5.6% as well as improvements in ejection fraction and NYHA Functional Class.

The new transcatheter procedure involves an anchoring system which excludes the need for more invasive surgery. Small titanium anchors are implanted on the left ventricular epicardium and the right ventricular septum, which are pulled toward one another, effectively reconfiguring abnormal cardiac geometry that causes dysfunction.

In a EuroPCR press release dated 19th May 2016, Marco Hernández Enríquez, Interventional Cardiology Fellow, Hospital Clínic de Barcelona, Barcelona, Spain, summarised, "This technique represents a less invasive intervention to exclude apical aneurysm instead of the usual surgical approach that requires cardiopulmonary bypass and ventriculotomy. This could open a new option to treat heart failure in a high-risk population." He went on to say, "it may reduce left ventricle volumes with improvement in ejection fraction and quality of life for up to 1-year follow-up."

Future deployment of the Revivent system for patients who are categorised as more high-risk would mean avoiding the use of more invasive surgeries. The findings are encouraging to both patients and healthcare professionals alike as they present a lower-risk alternative to the conventional surgical approach.

More than 50 hours of live demonstrations

Research into Alternatives to Desolve® 150 for Treating Coronary Artery Lesions

RESEARCHERS at the University of Giessen, Giessen, Germany, have compiled findings regarding the differences between the novolimus-eluting, bioresorbable scaffold DESolve® 150 and a brand new DESolve 100 scaffold according to a EuroPCR press release dated 19th May 2016. Although DESolve 150 has been approved for use in treatment of coronary artery lesions, the new scaffold has a strut profile of just 100 µm that scientists hope will reduce the incidence of scaffold thrombosis, which is associated with the shear stress caused by the struts following surgery.

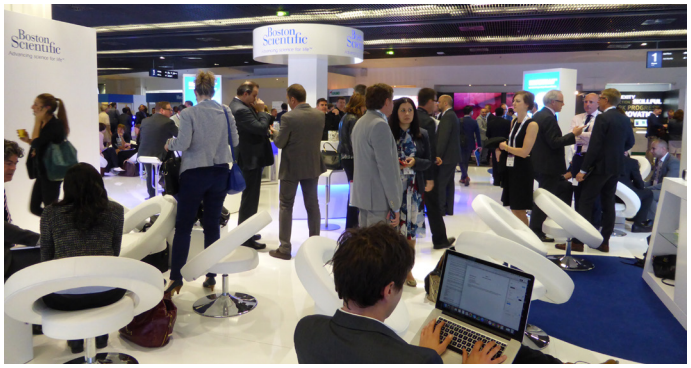
The team compared the performance of the two scaffolds over a short-term period. This was measured using optical coherence tomography in a total of 57 patients who had undergone percutaneous coronary intervention, most of whom had stable angina as the indication for surgery. A total of 62 DESolve 150 scaffolds were implanted in 42 patients, whilst 17 DESolve 100 scaffolds were implanted in the remaining 15 patients.

In the results, the researchers noticed a trend toward a higher rate of residual stenosis with DESolve 100 compared with the 150 µm strut profile (21.3% versus 15.3%, p=0.22), with a trend toward a smaller lumen and stent area. The two devices had a very similar mean eccentricity index, however strut fractures were more common in the DESolve 100 group (30.8% versus 14.0%).

The team, led by Niklas Boeder, University Clinic of Giessen, Giessen, Germany, stated "We report the first real-world *in vivo* comparison of novolimus-eluting scaffolds with two different strut thicknesses. Although DESolve 150 and DESolve 100 showed similar mechanical characteristics there is a trend for less mechanical support with the DESolve 100. We need further outcome data to assess the relevance for daily clinical use," although he counselled that "the attempt to reduce the strut thickness should not result in loss of radial strength of bioresorbable stents."

Study Suggests Alternatives Needed to Using Drug-Eluting Stents for Coronary Artery Lesions

RESULTS from a recent study which attempted to diffuse coronary artery lesions with newer-generation drug eluting stents have fallen short. From the results, researchers demonstrated that only a suboptimal fractional flow reserve (FFR) is achieved in patients who have undergone percutaneous coronary intervention (PCI) in comparison to blood flow of a healthy artery.



> Knowing that the optimal functional result is rarely achieved after stenting long coronary lesions in patients with diffuse coronary artery disease, particularly when the total stent length exceeds 5 mm, suggests other revascularisation options should be considered.

The study involved 74 patients who received second or newer-generation drug-eluting stents that were ≥30 mm in length and who had FFR rates ≤0.8. They underwent angiographic and FFR evaluation both before and after PCI, and at 9-month follow-up.

Following the study, the team found that an FFR of >0.95, the optimal post-PCI value, was only achieved in 12.2% of the patients (9 out of 74). None of the patients who received ultra-long stents (>50 mm) achieved the optimal FFR. Only 16.2% of the patients achieved FFR values of 0.91–0.95, and just 10.8% of the cohort achieved FFR <0.8, meaning that they were still considered ischaemic. Patients who received the ultra-long stent had a higher FFR gradient across the stent than those with long stents (0.07 versus 0.04, p=0.001). Angiographic restenosis rate at 9-month follow-up was 4.7%, with functional restenosis rate measured at 15.1%.

In a EuroPCR press release dated 18th May 2016, Dr Arvydas Baranauskas, Department of Cardiology, Center of Cardiology and Angiology, Vilnius University Hospital, Vilnius, Lithuania, commented, "the study shows that in the majority of cases diffuse coronary artery disease cannot be effectively treated using long drug-eluting stents because the FFR post-PCI is suboptimal." He also added that "knowing that the optimal functional result is rarely achieved after stenting long coronary lesions in patients with diffuse coronary artery disease, particularly when the total stent length exceeds 5 mm, suggests other revascularisation options should be considered."

Stem Cells Unable to Significantly Improve Ischaemia for Angina

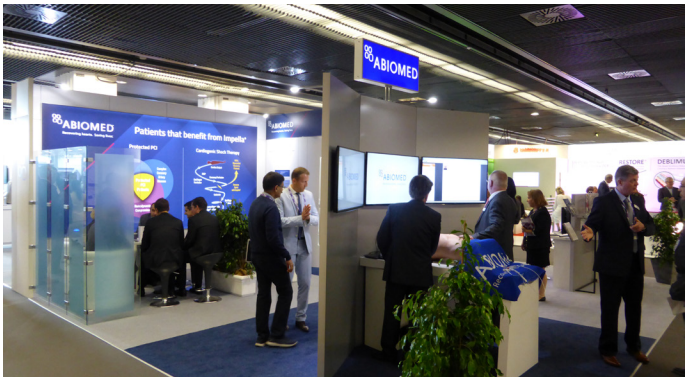
DRUG-RESISTANT angina patients injected with stem cells demonstrated no significant improvement in inducible angina, reported an EuroPCR press release dated 17th May 2016.

> The study suggests that we probably need standardised second-generation cell products, such as expanded, pre-differentiated, or allogeneic cells, in order to obtain clinical improvement.

Patients with inducible ischaemia or perfusion deficit experience a diminished blood flow, and thus oxygen supply, to the heart or a region of the heart, respectively. The recent REGENT-VSEL study explored the therapeutic effects of stem cells in 31 treatment-resistant patients presenting with stable angina and for whom vascularisation for myocardial ischaemia had been unsuccessful. The study randomised each of the patients to either autologous CD133+ cell or placebo treatment, which was injected into non-functioning regions of the left ventricle. A 4-month follow-up enabled comparison of the treatment outcomes in this group of patients.

Myocardial perfusion in each individual was evaluated at follow-up using single-photon emission computed tomography. The results suggested a lower level of inducible ischaemia

activity and total perfusion deficit in those treated with CD133+ cells compared with the placebo group, with summed difference scores of 2.60 versus 3.63, and 3.60 versus 5.01, respectively. However, these differences could not be proven significant at the statistical level of analysis. On the other hand, patients that received CD133+ cell therapy did demonstrate a significant reduction in left ventricular volume when compared with those in the placebo group.



"The study suggests that we probably need standardised second-generation cell products, such as expanded, pre-differentiated, or allogeneic cells, in order to obtain clinical improvement," elucidated Prof Wojciech Wojakowski, Department of Cardiology, Medical University of Silesia, Katowice, Poland. Nonetheless, no serious adverse events or deaths occurred during the length of the study, a positive finding for the research team. Additionally, the data has contributed new guidelines for three dimensional NOGA® mapping, furthering our understanding of myocardial function and setting the stage for further study.

Advancements in the Treatment of Secondary Mitral Regurgitation

SIGNFICANT developments have been reported concerning mitral valve construction in patients with high-risk secondary mitral regurgitation (MR). The Cardioband® reduces MR and improves function and quality of life in high-risk patients. The reconstruction of the mitral valve by direct annuloplasty is delivered transfemorally, eradicating the need for open-heart surgery.

Researchers enrolled 49 high-risk patients with significant secondary MR, in which 82% fell into the New York Heart Association (NYHA) heart failure Class III–IV with a mean left ventricular ejection fraction of 33%.

The procedure, which involved implantation of the device, was successful in reducing MR to Grade 2 or lower in 41 out of 47 (87%) of patients. At the 12-month follow-up, 89% of patients (n=22) had an MR of Grade 2 or lower, with just over two-thirds (68%) having NYHA heart failure of Class I–II. At follow-up, a significant improvement in quality of life and tolerance to exercise was also demonstrated.

In a EuroPCR press release dated 17th May 2016, Dr Georg Nickenig, Department of Cardiology, University of Bonn, Bonn, Germany, summarised, "transseptal mitral repair with the Cardioband device resulted in reduction of MR by reconstruction of the mitral annulus." He also reported that "the safety profile is comparable to other transcatheter mitral procedures and the reduction in severity of MR and clinical benefit are stable up to 12 months."

11,588 participants

The results of the study prove incredibly promising, with a high number benefitting from the procedure; giving improved function and quality of life. Experts believe that eventually, these technologies could be applied systematically around the world to patients who suffer from secondary MR as well as showcasing an evolution in technological advancement for heart surgery.

Long-Term Durability of Transcatheter Heart Valves Questioned

LONGER-LASTING transcatheter heart valves (THVs) will be required in the coming years as life expectancy of patients has been extended following surgery. A recent study investigating the long-term durability of transcatheter valves has found that half of them had undergone degeneration within 10 years following implantation.

> “Physicians must be mindful of the limitations of the THV they implant and whether patients can be safely treated by another transcatheter approach, such as valve-in-valve, if a THV fails years later.”

The study evaluated 704 patients (mean age 82 years) from two centres in Canada and France, all of whom underwent a transcatheter aortic valve implantation (TAVI) >5 years earlier; of these patients 378 were followed-up with repeat echocardiograms for up to 10 years. Patients who died within 30 days had device failure immediately after the procedure, and those who had a valve-in-valve procedure were excluded from the analysis. The valves used in the study included the Edwards SAPIEN XT, the Edwards SAPIEN, and the Cribier-Edwards™ valves.

After 5 years, those who had survived (n=100) were assessed for valve degeneration, this was measured by intravalvular regurgitation and/or aortic stenosis (≥20 mmHg). Thirty-five patients were identified as having valve degeneration, mostly occurring between 5 years and 7 years; the majority (two-thirds) of the cases were intravalvular regurgitation and the remaining third were valvular stenosis; there was also a small number of mixed cases.

Dr Danny Dvir, Centre for Heart Valve Innovation, St Paul’s Hospital, Vancouver, Canada, spoke of the need for forethought when performing these procedures in a EuroPCR press release dated 17th May 2016. “Physicians performing TAVI in younger patients and in those expected to survive long after the procedure should be aware that the long-term rate of THV degeneration is not negligible, at least for first-generation THV devices. Physicians must be mindful of the limitations of the THV they implant and whether patients can be safely treated by another transcatheter approach, such as valve-in-valve, if a THV fails years later.” It is hoped that in the newer devices there will be less degeneration and thus reduced need for repeat procedures.

More than 510 abstracts

Surgery Versus Transcatheter Aortic Valve Implantation

HEAD-TO-HEAD debate at this year's EuroPCR focussed on whether or not transcatheter aortic valve implantation (TAVI) is suitable for low-risk patients; currently a heart team decides if a patient receives the conventional surgery or TAVI. The great debate panel was comprised of three cardiac surgeons (Prof Jean Francois Obadia, Prof Gerhard Wimmer Greinecker, and Dr Thomas Walter) and three interventional cardiologists (Dr Darren Mylotte, Dr Lars Sondergaard, and Prof Stephan Windecker).

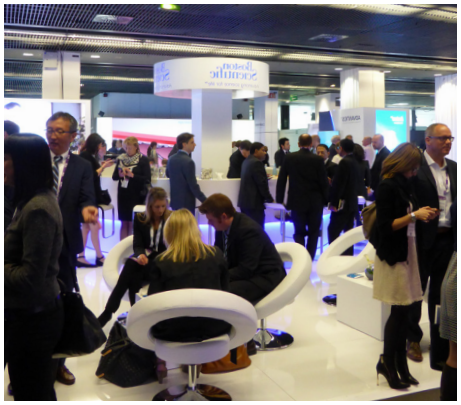
There was mutual agreement that the current practice of a case-by-case approach is the best one and that specific patient clinical data is required. They also all agreed that further data is required for a more evidence-based approach, specifically regarding the durability of bioprosthetic valves. Prof Obadia raised the concern that "we have absolutely no evidence that these valves will last for several years."

Dr Walter raised the point that, at present, conventional surgery can achieve "perfect outcomes" yet there are several aspects in need of consideration, such as valve morphology, in low-risk patients. Prof Greinecker even suggested that "it is time to step a little bit on the brakes" with TAVI procedures. Despite this, Dr Myolette mentioned the evidence from echocardiographic data in randomised trials comparing the interventions which suggests the two are at least comparable and that TAVI may have superiority in terms of haemodynamic performance at 5 years.

Dr Sondergaard discussed the NOTION trials and how they have shown that in younger populations (60–65 years) TAVI is safe and efficient. This idea was supported by Prof Windecker who said: "We have witnessed that TAVI has matured in a very secure and reproducible technique and we have a sound body of evidence that truly justifies that this intervention can be extended to low-risk patients."

Further discussion brought about the idea of how a younger patient may in fact be a 'sicker' patient with increased comorbidities. The take-home message from the debate was that whole decision-making should be used and that further data needs to be collected regarding TAVI in low-risk patients.

> "We have witnessed that TAVI has matured in a very secure and reproducible technique and we have a sound body of evidence that truly justifies that this intervention can be extended to low-risk patients."



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Ronald Krone

Professor of Medicine, Cardiovascular Division, Washington University School of Medicine, St. Louis, Missouri, USA; Fellow of the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions; Director of the International CardiOncology Society.

Q: What inspired you to build a career in cardiology?

A: I had always been interested in physiology and in 1970, when I began working as a cardiologist, I enjoyed managing patients with myocardial infarction (MI) and arrhythmia. As technology improved, the potential to actively intervene in order to limit damage and return a person's life to normal was exciting and very fulfilling, given that in the 1970s the patient would have been severely limited.

Q: How has digital technology influenced the evolution of interventional cardiology practice and care?

A: Digital technology has had an impact in many areas. The area I have been most concerned with and where I have spent much of my time is the development of databases documenting results and techniques. This started with the Society for Cardiac Angiography and Interventions (SCAI) in the 1990s and when the American College of Cardiology (ACC) supported this, these observational databases (NCDR) began to shape practice in a very meaningful way, leading to discussions of optimal use, stratifying outcomes, and helping to sort out worthwhile technologies. By linking to outcomes databases, and in the USA with Medicare outcomes, important decisions can be monitored and evaluated. In the catheterisation laboratory itself, the ability to obtain high quality digital images as well as high quality data storage/archiving of cases has made it possible to simplify the lab, throwing out the film processer with its delay to analysis, as well as avoiding the occasional disaster. This has greatly improved the ability to act fast in emergencies, ST-elevation myocardial infarctions for example. In terms of data analysis, rapid calculations of valve areas, amongst other things, has greatly reduced the burden on the lab and improved the speed of analysis, so the results can be known as soon as the case is done.

Q: Which aspects of the field do you feel have advanced significantly as a result of modern technology?

A: Imaging is a major one; computed tomography angiography, and digital processing of imaging, which permits dose reduction as well as digital storage algorithms. The whole area of outcomes research based on catheterisation lab procedures and results has been greatly simplified, which permits more robust analyses and the ability to query many small but important points.

Q: You are a director of the International CardiOncology Society; in what ways is the society working to develop cardiovascular health awareness and policy?

A: Cardio-oncology is a relatively new field. In actual fact very little is evidence-based and most recommendations are actually 'expert opinion'. This puts a premium on interactions between physicians, cardiologists, and oncologists as well as basic scientists trying to unravel the mechanisms of cardiac damage from cancer chemotherapy or from the stress of cancer itself. It is all new and thus careful monitoring of experience is critical. There are areas where randomised studies can be done, such as strategies to protect the heart during therapy, and these areas need to be supported.

> "By linking to outcomes databases, and in the USA with Medicare outcomes, important decisions can be monitored and evaluated."

> “Smoking is the greatest modifiable risk factor and it is depressing to see a resurgence of smoking among young people and also women.”

Most likely, because of the low event rate and the large numbers of patients required to demonstrate results, this will bring in an era of multicentre studies. Funding for these studies may be a problem which needs to be solved, since many of the drugs are already available and will be repurposed for this protection which limits the payback to industry, a usual source of funding for these projects.

Q: What are the most pressing issues in cancer and cardiovascular disease today?

A: There are two as I see it. Firstly, identifying the persons at risk in order to begin a proactive strategy of protection; identifying patients at risk of coronary disease and treating them to reduce the risk. Secondly, better imaging strategies need to be developed to improve the reliability of the measures of left ventricle function, improving the reliability of the echo or possibly justifying more magnetic resonance imaging.

Q: What is the most important lesson you have learnt from your research in clinical trials?

A: It is very important to develop hypotheses prior to beginning the study so that adequate data can be accrued to answer the question. *Post hoc* analysis is important but can only be hypothesis-generating, leading to a new study, developed to answer the question raised. For example, the initial BARI (Bypass Angioplasty Revascularization Investigation) study showed an important difference between patients with and without diabetes. Unfortunately, the only information about diabetes was a yes/no answer. Data on duration, type of treatment, adequacy of treatment, etc., was not captured, so a second study needed to be developed to capture that information, which was very important in understanding the mechanisms.

Q: Meetings such as the EuroPCR congress bring together professionals from a range of backgrounds and specialties; how does this variety of perspectives benefit your work, and the field of interventional cardiology as a whole?

A: These meetings are critical to disseminate information, let people expand their borders, and reduce the limits of what they are doing. The importance of the discussions, small groups, and opportunities for interactions cannot be overestimated.

Q: You have conducted research into risk stratification after MI; what can people do to reduce their risk, either before or after the event?

A: Some of this is well known. Smoking is the greatest modifiable risk factor and it is depressing to see a resurgence of smoking among young people and also women. Diabetes is another and the consumption of sugary beverages is clearly a major factor. Both of these factors have something in common; that is, the industry looks at the profits from these items and ignores the health consequences. Once a person has the disease, the most important modifiable risk factor is speed of access to a skilled tertiary facility where active intervention can take place. This is also a political problem, since it means that certain hospitals will need to be passed through on the way to the skilled facility. When the studies you refer to, regarding risk stratification after a MI, were done in the late 1970s and early 1980s, management of MI was quite different. Catheterisations and bypass surgery were often delayed for 1 month, and the infarction was over. The big decision was whether or not to catheterise at all. Today, there is not the same problem, at least in the USA. Here everyone with an MI gets a catheter so there is none of that discrimination; the decision point now is whether or not a coronary intervention should be done.

Q: Is there any up-and-coming research that you believe will strongly impact interventional cardiology research in the future?

A: There are a number of new technologies that are being evaluated. Robots, for example, for

interventions, which can substantially reduce radiation to the operator. Perhaps better drugs to limit restenosis without prolonging endothelisation of the stented vessel. I may not be a visionary but at this point I see our progress as developing from incremental improvement in existing technologies. Perhaps the bioabsorbable stent may have a place, but the target keeps moving as metal stents continue to improve.

Q: If you could give one piece of advice to your undergraduate self, what would it be?

A: I have two pieces of advice I would like to give. First, "Ski within yourself. Do not go over your head, do not attempt something you are not comfortable with. If you try, and fail, you will never get another chance but your skills will improve with experience so you can run the moguls in time." The second bit of advice comes from Bernard Lown, MD, and is a key bit of advice for all physicians: "One must not proscribe all life's pleasures lest you be a modern day Savonarola" (Savonarola of course was the monk in Firenze, Italy, who orchestrated the 'Bonfire of the Vanities' and then himself was burned 2 years later at the same spot).

Q: You have experience in numerous aspects of interventional cardiology; are there any areas of medical research you are interested in, that you have not yet explored?

A: That is a tough question. One important feature of medicine is that it is expanding so quickly in so many directions that no one person can be an expert in everything. Imaging techniques continue to improve, genetic testing and understanding the role of mutations in human disease are fascinating and in cancer are driving the field, mechanical support for failing hearts, and use of inotropes in ambulatory patients are all areas that are just beginning to lead to results. I think the goal is to find an area that interests you and dive deeply into it. I am diving into cardio-oncology (or oncocardiology) and I am finding it fascinating. I think it is very important to maintain the quality of life promised by the advances in cancer therapy.

Eric Eeckhout

Associate Professor of Cardiology, University of Lausanne Medical School; Director of the Catheterisation Laboratory, University Hospital of Lausanne, Lausanne, Switzerland; Course Director, AsiaPCR.

On the 31st May 2016, here at EMJ we caught up with our editorial board member and renowned interventional cardiologist Prof Eric Eeckhout from the University of Lausanne Medical School, Lausanne, Switzerland. Amongst many interesting topics, we discussed his career and work in the field, his perspective on some of the challenges that have come about as a result of the emergence and growth of interventional cardiology, and his take on some of the changes and enhancements that he expects to occur in the foreseeable future.

We began by asking Prof Eeckhout about his original motivation to enter the field of interventional cardiology as a young man. "I started cardiology because I wanted to do something where there was a technical aspect," he answered. "I had no feelings or ideas about getting into interventional cardiology, but quite quickly when I started cardiology in the mid-1980s, I was fascinated by the ability to perform images of the heart, by means of coronary angiography, and saw balloon angioplasty for the first time. Stents were around the corner in 1986 but they were not widely available, but I was fascinated to see that balloon technology could treat patients who were suffering from angina. That was long before the era of the boom of primary percutaneous coronary intervention (PCI) and treating acute and myocardial infarction patients with PCI."

> One of the big challenges, of course, is to make these therapies available on a worldwide level. This is a big challenge because in emerging countries there is not access to medical care for a substantial number of people.

Since those early days Prof Eeckhout has become a prominent figure in the field, and this is evidenced by the important positions he has held on the EuroPCR congress committee. In 2009, he helped in the creation of the first PCR meeting outside of Europe in Singapore, and remains a course director of the AsiaPCR congress, which helps to develop the field of interventional cardiology in this region of the world. "It is what we do at EuroPCR, with the same philosophy, in Asia," he explained.

There has been significant expansion of this therapeutic area in parts of Asia, and this is something that Prof Eeckhout has observed ever since his first visit to the continent in the early 2000s. "I have seen tremendous change in terms of expertise and access to healthcare in these countries which are booming together with the economy, so things have changed a lot. If you go to places like Hong Kong or Singapore, the standard of care is extremely high, and I think that economically speaking these regions have become more wealthy than many European countries, so the healthcare is excellent and the facilities are often better equipped than most European countries," he said.

Indeed, the field generally has advanced significantly in recent times: "Interventional cardiology has become quite mature in terms of the coronary field. We have excellent devices, balloons, stents, catheters. We have excellent pharmacological therapy which means we have excellent things to treat our patients [with] and we also have imaging techniques to help us to better understand what is going on in coronary circulation, so it has become quite a mature specialty."

Nevertheless, it is clear that there are a number of challenges that have come about as a result of such advancements. Despite the positive growth of interventional cardiology in some of the emerging regions of the world, there are still many places where such care is simply not available for a lot of people. As Prof Eeckhout pointed out: "One of the big challenges, of course, is to make these therapies available on a worldwide level. This is a big challenge because in emerging countries there is not access to medical care for a substantial number of people."

One topic that the Swiss professor was keen to talk about is the pressure and workload that interventional cardiologists, particularly in Europe, face today, as a result of growth in the field. "The biggest challenge for us is how to ensure working on a day-to-day basis in the catheterisation laboratory, and I think to that charge the night shift for the primary PCI networks because since primary PCI has become, certainly in Europe, the main therapy, there is additional work on top of our daily practice. So I think it creates a lot of fatigue in the long run to be fit in the day, to be fit at night, and on a daily, weekly, yearly basis."

An issue that has emerged as a result of the increase of coronary interventions is the number of complications that arise from such procedures. As such, questions still persist about the safety of the interventions. "I think this is something that will be around for many years to come," commented Prof Eeckhout. "Complications have two major courses. I think you can compare it to the aviation industry. You have human factors and then you have technology factors. Now the human factors are much more predominant than the technology factors, and they are related to many issues: lack of expertise, lack of training, lack of concentration, the inability to have a picture of what is really going on with the patient." He added: "Complications in the field of cardiovascular medicine are present and are underreported. There is still a lot of work that could be done."

> “Try and go to another country for training and then find the objectives of what you want to do in life.”

Despite the challenges that need to be overcome, there are likely to be many more exciting developments to look forward to in the future which will enhance the treatment of patients with heart conditions, and Prof Eeckhout postulated what some of these may be during our discussion: “In the coronary field first of all, we now have excellent metallic drug-eluting stents so we will see if the vanishing technology, by which I mean the biovascular scaffolds, will hold their promise and we are looking forward to that. It would be great to see in 10 years that the metallic stents would be counterbalanced by vanishing devices; that would be great for our patients and I am looking forward to that! In terms of imaging, I hope that we will be able to further develop less invasive coronary imaging to help us understand better some pathologies. There is a company which can, based on a computerised tomography scan of the human heart, predict if a patient has coronary disease. So I hope that in 10 years to come we will have less invasive and more accurate techniques to learn if a patient has this kind of disease and whether they need the treatment or not. I hope that in terms of the mitral valve, which is a very difficult field, there will be a percutaneous solution other than the current MitraClip, edge-to-edge, or other techniques that are available.”

Finally, the pre-eminent professor had some wise words and advice for those thinking about starting a career in interventional cardiology: “Find yourself a mentor, a person who is behind you. It is very important to have a mentor in life who you can talk to and who gives you advice. Try and go to another country for training and then find the objectives of what you want to do in life.”

While Prof Eeckhout outlined how difficult and demanding such a role can be, he also described exactly why interventional cardiology can be such a rewarding and fulfilling area of medicine to work in. “Treating a patient with an acute myocardial infarction (MI) in the setting of primary PCI, even if it is at night, you are doing it for the patient. It is quite often a life-saving act. There are not that many acts in medicine that are life-saving, but if you treat a big anterior MI on the occluded left anterior descending artery, you know that your act is life-saving, and I think this is something that is very rewarding to do.”

Nicholas Kipshidze

Director, Innovations and Endovascular Therapy Department, New York Cardiovascular Research, New York City, New York, USA; Consulting Cardiologist, Central University Hospital, Tbilisi, Georgia; Member of Parliament, Tbilisi, Georgia.

Q: Can you pinpoint the moment you decided to pursue a career in interventional cardiology? What inspired you?

A: This goes back to 1973 when I was a fourth year student at Tbilisi State Medical School in Georgia. My father, Nodar N. Kipshidze, Professor of Cardiology, first showed me a coronary angiogram and I became very interested. Later that year the eminent cardiac surgeon Michael Debakey visited our home in Tbilisi and had a lengthy stimulating discussion with my father about the future of the management of coronary artery disease and I became more convinced to get into an invasive cardiology programme. I was lucky to find the right place in Moscow at the Institute of

Cardiovascular Surgery, the premier facility at that time, and start my work under the guidance of Professors Burakovsky and Petrosian.

Q: Throughout your career you have worked in a variety of contexts, including research institutions, laboratories, innovation, and education; in what ways, if any, does the perspective on interventional cardiology vary across these fields?

A: Indeed, the atmosphere and perspectives vary in different facilities and I strongly advise young cardiologists to spend a few years in academic institutions to become familiar with basic and clinical research in cardiology before entering private practice.

Q: You have championed the development of novel interventional techniques; are there any recent changes in surgical technology that you believe have fundamentally changed the trajectory of the discipline? Can you predict how the next 10 years will be influenced by technological advancement?

A: Structural heart interventions, endovascular treatment of stroke, and biodegradable scaffolds will change the face of interventional medicine. Additionally, metabolic interventions can aid in untouched territories, such as the treatment of diabetes. We need to remember that when using arteries and/or veins we have access to, and can modify the function of, every organ in the human body; I predict that in 10 years we will be able to treat many conditions.

Q: As well as your range of experiences within different research environments, you have also worked in Moscow, Wisconsin, and most recently New York. How do the approaches to interventional cardiology compare internationally? Are there any countries in particular that you believe are leading the field, or is research becoming a global initiative?

A: I was lucky to work in many different countries and have to admit that the USA, Western Europe, and Israel are leading cardiovascular research; however, many interesting ideas and first-in-human studies come from the former USSR, India, and China.

> “I was lucky to work in many different countries and have to admit that the USA, Western Europe, and Israel are leading cardiovascular research...”

Q: What do you think are the most valuable outcomes of scientific meetings such as the European Association of Percutaneous Coronary Interventions (EuroPCR) congress? What effect have these meetings had on your research during your career?

A: Meetings are very important and they have influenced my research during my long career. PCR is one of the best meetings in interventional medicine. However, during the last decade there has been an oversaturation of meetings, with too many major meetings per year and with duplicate topics or themes. Therefore, I strongly believe we need to reconsider having yearly meetings such as TCT, PCR, SCAI, ACC, AHA, and ECC. It is impossible to come up with new findings, conduct clinical trials, and produce meaningful results at such regular intervals even in such a dynamic era.

Q: If you could offer one piece of advice to an aspiring interventional cardiologist, what would it be?

A: Attempt to think outside of the box and innovative ideas will come to you.

Q: Currently, >11% of the American population has been diagnosed with heart disease. What, in your opinion, is the single most important factor in reducing this figure, in both America and the world?

A: Prevention is the key. A healthy lifestyle with regards to both diet and exercise will dramatically reduce cardiovascular burden.

Q: What exciting elements of cardiovascular research and therapy are you currently working on?

A: Currently, I am working on several interesting projects. Most interesting, in my opinion, is an endovascular metabolic intervention. It is a brand

new approach to treating obesity and its associated diseases. Early animal experiments from a Johns Hopkins University, first-in-human study that I conducted demonstrated that embolisation of the left gastric artery reduces the production of the 'hunger' hormone ghrelin and induces weight loss. Another interesting project I am involved in is chemical denervation for the treatment of hypertension. A new drug-eluting stent concept is at a very early stage of research in collaboration with George Dangas from Mount Sinai, New York City, New York, USA. Finally, I am also working on an interventional treatment of sepsis with a start-up company from the west coast.

Q: In addition to clinical research, in the past decade you have expanded into public health initiatives, tell us about these initiatives?

In 2006 the President of Georgia, Mikheil Saakashvili, invited me to oversee the process of radical reforms of the healthcare sector in Georgia. It was an interesting challenge for me to try and help my country and of course I was honoured by this invitation. So I went there, and with great support from the Government of Georgia, the U.S. Agency for International Development, GE Medical, and my dear friends, the late Dr John R. Petersen, Director, Milwaukee County Regional Medical Center, Wauwatosa, Wisconsin, USA, Dr Ken Walker, Professor of Medicine and Neurology at Emory University School of Medicine, Atlanta, Georgia, USA and Executive Director of Partners for International Development, and Brue Chandler, Senior Director at Galloway Consulting, developed the first modern emergency medical services programme in Georgia, and later the first residency programme there specialising in emergency medicine. Additionally, the group also rebuilt Central University Hospital in Tbilisi, Georgia, including a state-of-the-art cardiovascular centre. I plan to continue my efforts in this direction and work on establishing a Georgia-US Centre for Medical Innovations as a platform for basic and clinical research in the area of vascular medicine. A similar project is in work in Ukraine as well.

> "Meetings are very important and they have influenced my research during my long career. PCR is one of the best meetings in interventional medicine."


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SLOW-SPEED ROTATIONAL ATHERECTOMY IN ACUTE CORONARY SYNDROME: A SINGLE-CENTRE EXPERIENCE IN 78 HIGH-RISK PATIENTS

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Due to the expansion of percutaneous coronary intervention (PCI) indications to more challenging settings, the problem of referral of patients with complex and heavily calcified coronary lesions is growing. Despite the development of more supportive catheters, balloons, and alternative plaque-modifying technology, many calcified lesions may require rotational atherectomy (RA). However, universal adoption of the RA technique has been hampered by many factors such as concerns regarding the complexity of RA procedures and potential procedure-related complications, lack of standardised protocols, and lack of structured and widely available training programmes.

On the other hand, according to the data published in different studies and the widespread use of RA in the general population, current indications, complication rates, and outcomes inherent to RA have been changed and some of them should now be considered obsolete. In fact, despite the recommendations reported in its technical sheet, up to 50% of rotablations were performed in unstable patients for lesions that cannot be crossed by a balloon or adequately dilated before stenting. There are few data available regarding RA performed in acute coronary syndrome (ACS), and many of them were collected from subgroups of patients of other studies not designed for such a purpose. Thus, real-world data encourage us to study the role, safety, and usefulness of rotablation performed in ACS in a real scenario, in a controlled setting.

We conducted a prospective single-centre analysis of 78 consecutive patients with ACS in which RA was used to treat the culprit lesion. Demographic, clinical, angiographic, and PCI parameters were included and outcomes were collected.

The findings were as follows: Mean age was 77 years with a very high cardiovascular risk profile. Concomitant comorbid conditions were also high, as reflected by the prevalence of prior myocardial infarction and left ventricular ejection fraction dysfunction, present in 59% and 26% of the patients, respectively. Clinical onset was ST-segment elevation myocardial infarction (STEMI) in 36%, unstable angina or non-STEMI in 52%, and other causes such as cardiac arrest, syncope, or malignant arrhythmias in the remaining 12%.

Angiographic findings showed that the prevalence of multivessel disease was 70.2%, the left anterior descending artery being the most commonly diseased and the most frequently treated with RA, followed by left main disease.

PCI and RA procedures showed some interesting findings. Firstly, the majority of lesions were approached with a 1.5 mm burr with a mean rotational speed <140,000 rpm. Secondly, in 76% of rotablations a bifurcation was involved (22% of them were 1,1,1 according to the Medina classification). In accordance with current guidelines, drug-eluting stents were the most used, with a median stented lesion length of 60 mm.

The rate of achieved clinical and angiographic success was >98%. Cardiovascular death during hospitalisation was 1.2% (one patient, a cardiac rupture 4 days after primary PCI). No side-branch closures, burr entrapment, coronary perforations, or stent thrombosis were recorded. At 1.5-year follow-up the overall cardiovascular death was 3.8% (three patients, mainly due to heart failure) and target-lesion revascularisation rate was 2.4%.

In conclusion, currently RA is mainly recommended for preparation of calcified lesions in stable coronary ischaemic disease. However, in current

daily practice the majority of patients referred for PCI are unstable patients. Our data support the use of slow-speed RA in combination with drug-eluting stents as an effective method to treat complex coronary lesions during ACS, even if a bifurcation is involved, with a low incidence of clinical and angiographic complications during index PCI and follow-up. Further study is therefore required.

THE FAILING RIGHT HEART: IMPLICATION AND EVOLUTION IN HIGH-RISK PATIENTS UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT

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Transcatheter aortic valve replacement (TAVR) is an effective therapeutic option in patients with severe aortic stenosis deemed at high or prohibitive-risk for conventional surgical aortic valve replacement.[1,2] Despite a large amount of literature concerning possible factors associated with or predictive of an adverse prognosis,[3-6] the impact of coexisting right ventricular (RV) dysfunction on TAVR outcome is unclear. On the other hand, it is also uncertain whether the improved left heart haemodynamics after TAVR could exert a beneficial effect on RV dysfunction. We thus evaluated, in a multicentre registry of high-risk patients undergoing TAVR, the prognostic impact of different grades of RV dysfunction on TAVR, and the possible impact of TAVR on RV dysfunction. From January 2010–April 2013, a total of 870 consecutive patients affected by severe aortic stenosis were treated with the third-generation 18 Fr CoreValve Revalving System device. This registry has been approved by local ethics committees and all the data are fully available to the enrolling centres. All patients were evaluated for TAVR by the local 'heart team' which included: a clinical cardiologist, an interventional cardiologist, a cardiac surgeon, and a cardiac anaesthesiologist. The evaluation of the heart team led to the indication for TAVR after careful assessment of all the clinical/anatomical conditions determining a higher risk of mortality/morbidity after surgery. All patients scheduled for TAVR and that gave written consent for the procedure and registry were enrolled. Transthoracic echocardiography was performed before TAVR, within 3 days following TAVR, and at the 1, 6, and 12-month follow-up by a senior cardiologist. RV function by means of tricuspid annular motion or tricuspid annular plane systolic excursion, and RV size were determined and categorised according to the American Society of Echocardiography (ASE), the European Association of Echocardiography (ESE), and the Canadian Society of Echocardiography (CSE) recommendations.[7]

The results of our study added several ideas to current knowledge: the presence of concomitant RV dysfunction is relatively frequent in these patients; severe RV dysfunction and severe RV dilation independently predict overall mortality; a severe RV dysfunction is a stronger predictor of 1-year mortality compared with a severe left ventricular dysfunction; in patients with severe RV dysfunction, an improvement in RV function can be expected in a minority of the patients; in patients with moderate RV dysfunction, this improvement is more likely to occur in the absence of atrial fibrillation, severe pulmonary hypertension, and severe renal failure; and the improvement in RV function does not independently predict mortality. On a broader perspective, our results advocate for the first time the inclusion of the RV evaluation in a more complete pre-TAVR evaluation work-up.

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A RANDOMISED COMPARISON BETWEEN DRUG-ELUTING BALLOON AND CONVENTIONAL BALLOON ANGIOPLASTY FOR LESIONS IN THE PENILE ARTERY IN PATIENTS WITH ERECTILE DYSFUNCTION: THE PERFECT-4 STUDY

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BACKGROUND

Pelvic arterial insufficiency is present in >70% of patients aged >50 years with erectile dysfunction. One-third of the pelvic arterial lesions are present in penile artery segments. We have previously shown that penile artery balloon angioplasty could achieve ~80% early improvement in erectile function in patients with erectile dysfunction and isolated penile artery stenoses. However, an approximately 40% restenosis rate was found. In this study, we assessed the efficacy of a paclitaxel drug-eluting balloon (SeQuent® Please), compared with balloon angioplasty alone, for the reduction of restenosis in patients with erectile dysfunction undergoing endovascular intervention for lesions in penile artery segments.

METHODS

Patients with erectile dysfunction and obstructive penile arterial lesions (diameter stenosis ≥50%) with a reference vessel diameter ≥1.5 mm identified by multi-detector computed tomography (CT) were enrolled. A total of 44 consecutive patients (mean age 62 years [range: 49–83 years]) with 50 lesions were randomised to either drug-eluting balloon group or conventional balloon angioplasty group in a 1:1 manner. The primary endpoint was binary in-segment restenosis (≥50% diameter stenosis) assessed by CT angiographic at 8-month follow-up. The secondary endpoints include diameter stenosis at follow-up and 12-month clinical success defined as the change of International Index for Erectile Function-5 (IIEF-5) from baseline by ≥4 points or IIEF-5 ≥22 points.

RESULTS

There were no significant differences in baseline angiographic characteristics of target lesions between the two groups. However, lesions treated with drug-eluting balloons were associated with a smaller post-intervention diameter stenosis (7.2±4.0% versus 10.2±4.2%, p=0.011), together with a greater averaged maximal balloon catheter size (2.1±0.3 mm versus 1.7±0.3 mm, p<0.001). Binary

restenosis occurred in 12 of 25 lesions (48%) in the drug-eluting balloon group compared with 10 of 25 lesions (40%) in the balloon angioplasty group (p=0.569), with the corresponding average follow-up diameter stenosis of 52±36% and 37±41%, respectively (p=0.200). Clinical success was achieved at 12 months in 11 of 22 patients (50%) in the drug-eluting balloon group compared with 13 of 22 patients (59%) in the balloon angioplasty group (p=0.545), with the corresponding IIEF-5 score changes of 4.2±5.2 and 5.2±4.2, respectively (p=0.507).

DISCUSSION

The use of drug-eluting balloons, compared with conventional balloon angioplasty, achieved similar rates of 8-month restenosis (40–50%) and improvement in erectile function (50–60%) at 12 months in patients with erectile dysfunction and penile artery stenoses. Both the vessel factors (dissections underestimated) and instrument factors (small-profile stents required to keep vascular integrity) may explain the suboptimal mid-term results of drug-eluting balloons and should be meticulously dealt with in future penile artery intervention studies.

Endovascular intervention for obstructive penile artery stenosis provides a breakthrough management technique for patients with erectile dysfunction and obstructive penile artery stenosis. However, it should be emphasised that the success of endovascular intervention must come along with optimal medical treatment, including vascular risk factor control, normalisation of serum testosterone level, and use of phosphodiesterase 5 inhibitors. Given the friable nature of the penile artery and its tendency to develop dissection, it is reassuring that there were no adverse events in this PERFECT-4 study.

THE LATEST CRE8 CLINICAL EVIDENCE IN DIABETICS EMPOWERS UNIQUE AMPHILIMUS FORMULATION EFFICACY: THE INVESTIGATE REGISTRY

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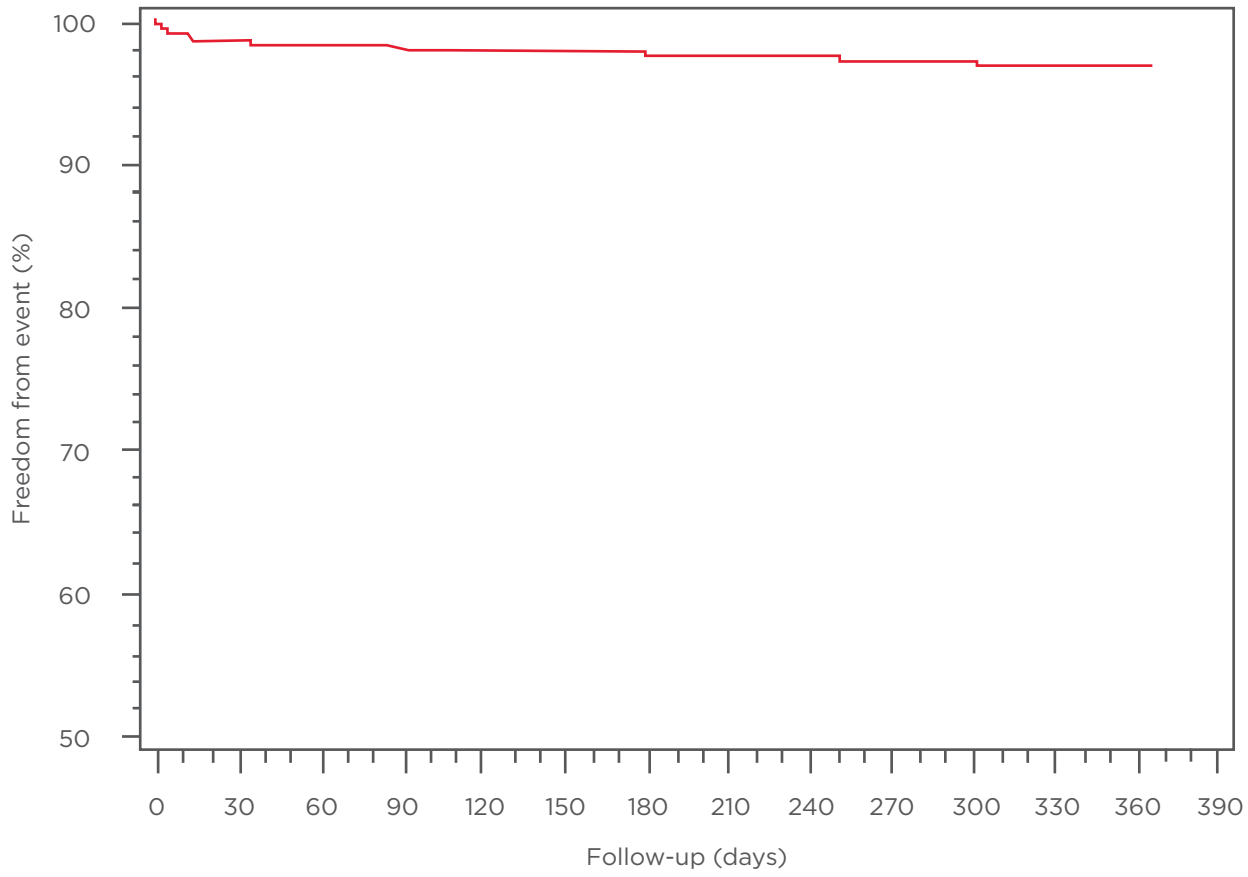
The utilisation of drug-eluting stents (DES) has reached a large diffusion for treatment of coronary artery disease.[1] However, patients with diabetes mellitus remain a challenge for in-stent restenosis and adverse cardiovascular events such as late stent thrombosis (ST).[2] This is particularly the case after discontinuation of thienopyridine therapy. Despite this, the most recent generation of DES, with the introduction of biodegradable polymers and bioresorbable structure, has reduced the incidence of restenosis in diabetics and cases of ST and is thus confirmed to be the best strategy.[3-5] The polymer-free drug-eluting Cre8™ stent (CID, Saluggia, Italy) has three distinctive features: abluminal reservoir technology, bio-inducer surface, and amphilimus formulation (sirolimus and organic acid). The lack of a polymer avoids inflammatory triggers and the drug elution is controlled and directed exclusively towards the vessel wall; the bio-inducer surface is a second-generation pure carbon coating covalently bonded to the thin cobalt-chromium platform, minimising prothrombotic stimuli and promoting a fast stent-strut coverage. The amphilimus formulation (sirolimus and organic acid eluted together) results in a more efficient combined effect, enhanced drug bioavailability, permeability, and maximised product safety and efficacy. This effect is more evident in diabetic cells, due to the overexpression of membrane protein that leads to higher fatty acid binding and translocation.



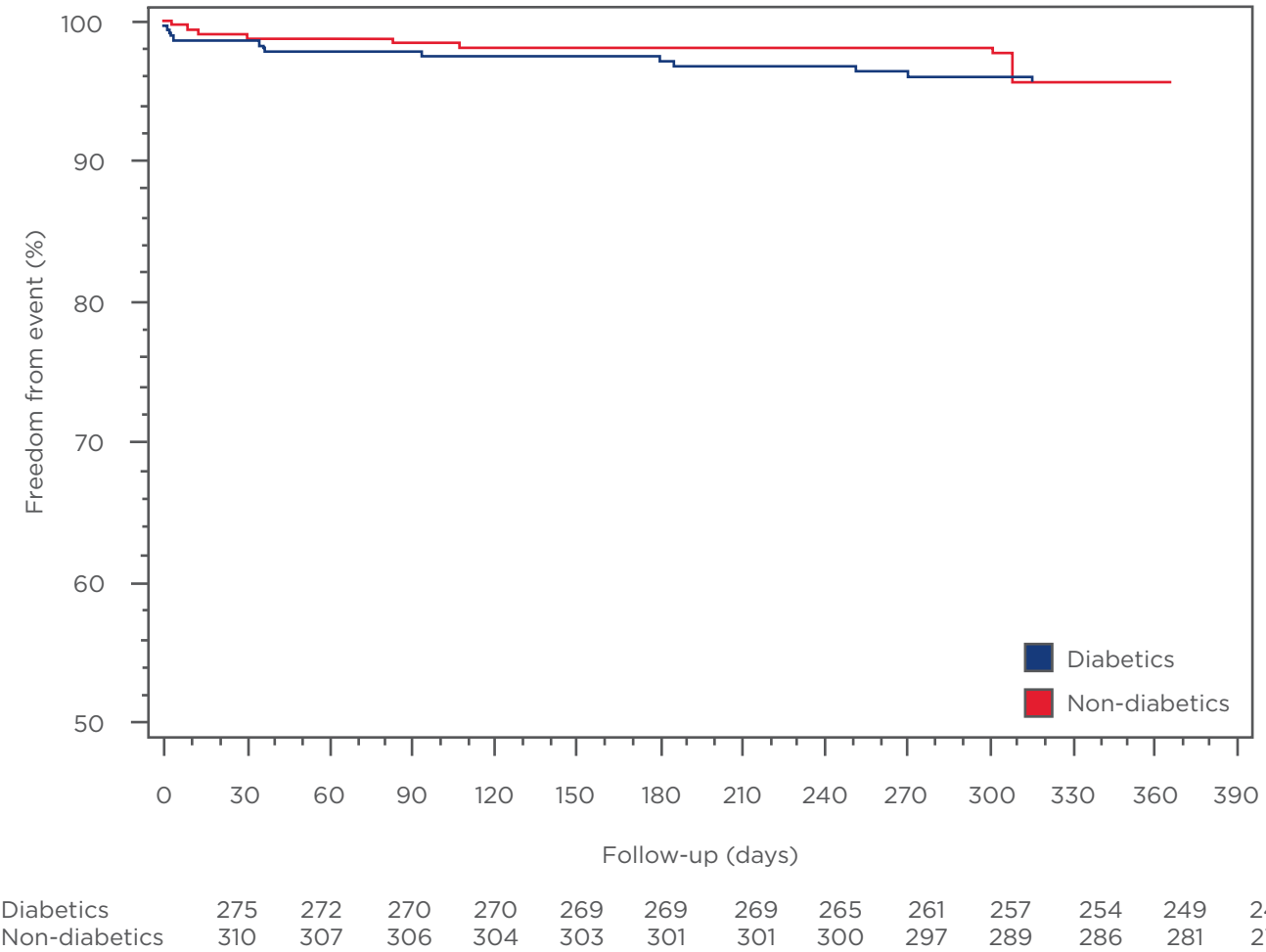
Period	Freedom from event	95% CI
1 year	95.7%	93.8-97.1%

Figure 1: In overall population, Kaplan–Meier analysis estimated the rate of survival free of events of 95.7% at 1 year.
CI: confidence interval.

In the NEXT randomised study, patients treated with the Cre8 stent showed a significantly lower rate of in-stent late lumen loss (LLL) at 6 months compared with Taxus Liberté®, with a trend toward better 12-month clinical safety and efficacy results.[6] In the diabetic subgroup the absolute difference in LLL reduction was 72% (0.12±0.29 versus 0.43±0.41). In the PARTICIPATE study the objective was to evaluate the safety and efficacy performances of Cre8 in patients compared with everyday clinical practice, with a specific focus on diabetic individuals.[7] The device-oriented major adverse cardiac events rate at 1 year was low and similar in non-diabetic and diabetic groups (coronary intervention target-lesion revascularisation (TLR) 1.0% versus 1.4%) with a LLL of 0.16±0.13. The RESERVOIR trial compared the efficacy of amphilimus-eluting stents (AES) with that of everolimus-eluting stents (EES) in patients with diabetes mellitus.[8] The primary endpoint, neointimal (NI) volume obstruction, was 11.97±5.94% for AES versus 16.11±18.18% for EES, meeting the non-inferiority criteria (p=0.0003). By quantitative coronary angiography, in-stent LLL was 0.14±0.24 for AES versus 0.24±0.57 mm for EES (p=0.27), with a larger minimal lumen diameter at follow-up for AES (p=0.02). The multicentric and retrospective registry of polymer-free

DES (INVESTIG8 registry) enrolled all consecutive patients who had undergone percutaneous coronary intervention with the Cre8 stent.[9] The safety and efficacy of the Cre8 stent were evaluated in an all-comer patient population in terms of incidence of clinical composite endpoint (cardiac death, target-vessel myocardial infarction [MI], and TLR clinically driven) at 12-month follow-up. Secondary endpoints were the incidence of clinical composite endpoint (all deaths, all MI, any revascularisation) and ST (according to an Academic Research Consortium [ARC] definition) at 12-month follow-up. Moreover, a pre-specified analysis in diabetic patients was performed. No inclusion or exclusion criteria were used.

Out of 647 patients from six centres who received the Cre8 stent, 589 patients completed a 1-year follow-up. Forty-five point five percent of patients were found to have acute coronary syndrome and the remainder had stable angina or silent ischaemia.



Non-diabetics			Diabetics		
Period	Freedom from event	95% CI	Freedom from event	95% CI	Log rank test p-value
1 year	97.8%	95.4-98.9%	95.6%	92.4-97.5%	0.1582

Figure 2: Kaplan–Meier curves estimated the rate of survival free of events of 95.6% versus 97.8% (p=0.15) at 1 year in diabetic and non-diabetic patients, respectively.
CI: confidence interval.

The cardiovascular risk factors were largely diffuse; of particular importance, 21.9% of the diabetic patients (who made up 47.4% of the total patient cohort) required insulin treatment. B2-C coronary lesions were found in 57.8% of patients. In the overall population, at 1-year follow-up, the incidence of the composite endpoint was 4.2% and cardiac death, target-vessel MI, and clinically-driven TLR were 2%, 0.7%, and 1.5%, respectively. The incidence of definite ST was 0.3% (acute ST 0.1% and subacute ST 0.1%) and the probable ST was 0.7% (subacute 0.3% and late ST 0.3%). Kaplan–Meier analysis estimated the rate of survival free from events at 95.7% at 1 year (Figure 1).

The subanalysis in diabetic patients (n=278) showed a more complex clinical risk profile than in non-diabetic patients. At 1-year follow-up, the incidence of composite endpoint was 5% versus 3.5% (p=0.48), cardiac death (2.5% versus 1.6%, p=0.56), target-vessel MI (1.1% versus 0.3%, p=0.34), and clinically driven TLR (1.4% versus 1.6%, p=1), respectively in diabetic and non-diabetic patients. The rates of definite and probable ST did not present a significant difference (definite ST was 0.3% versus 0.3%, p=1; probable ST was 1.1% versus 0.3%, p=0.35). Kaplan–Meier curves estimated a rate of survival free from events of 95.6% versus 97.8%, p=0.15) at 1 year, respectively in diabetic and non-diabetic patients (Figure 2).

In conclusion these data demonstrated the low incidence of adverse events confirming the safety and efficacy of Cre8 in a non-selected population at 1-year follow-up. In the diabetic patient subgroup, results showed a good safety profile with the same incidence of clinically driven TLR, even in the presence of a more complex angiographic profile and comparable composite endpoint and ST values.

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TRANSCATHETER AORTIC VALVE IMPLANTATION IN HOSPITALS WITH AND WITHOUT ON-SITE CARDIAC SURGERY DEPARTMENT: INSIGHTS FROM THE PROSPECTIVE GERMAN AORTIC VALVE REPLACEMENT QUALITY ASSURANCE REGISTRY (AQUA) IN 17,919 PATIENTS

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Performing transcatheter aortic valve implantation (TAVI) at hospitals with a cardiology, but no cardiac surgery (CS), department on-site is at great odds with current guidelines. In some German hospitals without CS on-site, TAVI is performed by interdisciplinary heart teams comprising in-house cardiologists and external visiting CS teams from collaborative hospitals.

We analysed the 2013 and 2014 datasets on transfemoral TAVI from the prospective German Aortic Valve Replacement Quality Assurance Registry (AQUA). Participation is compulsory for all hospitals and is linked to reimbursement for the procedure ensuring accurate reporting of all TAVI and surgical aortic valve replacement cases performed in Germany. Overall 97 hospitals performed TAVIs, with 22 having no CS department on-site. In all hospitals a heart team was available, made up of either internal staff physicians or internal cardiologists, and external visiting cardiac surgical teams.

Of 17,919 patients (81.2±6.1 years, 55% female, logEuroSCORE 21.1±15.4%) undergoing transfemoral TAVI in 2013 and 2014, 1,332 (7.4%) were treated at hospitals without a CS department on-site. Patients in hospitals without CS were older, with higher New York Heart Association (NYHA) symptom Class and a greater prevalence of coronary artery disease, peripheral vascular disease, and previous neurological events, and thus had higher predicted peri-procedural death risk (as per logEuroSCORE). Reasons for selecting TAVI over conventional surgery were similar in the two groups. Overall, complications were similar in both groups including rates of stroke (2.6% versus 2.3%, p=0.452) and in-hospital mortality (3.8% versus 4.2%, p=0.396). Analysis of age, sex, and German Aortic Valve risk-score matched patients (n=1,110) confirmed similar complication and death rates (1.8% non-CS versus 2.9% CS hospitals, p=0.234) in the two groups.

These data show that the heart team approach at non-CS sites results in appropriate patient selection and similar outcomes compared with CS hospitals, suggesting the feasibility and safety of a heart team-based TAVI at non-CS sites. These findings need confirmation in future randomised studies. Until then, the lack of CS department on-site should not be regarded as a contraindication for TAVI.

SIX-MONTH INVASIVE SAFETY ASSESSMENT IN HUMANS OF RENAL ARTERY DENERVATION USING SYMPLICITY SPYRAL™ APPLIED IN THE MAIN TRUNK AND BRANCHES

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Catheter-based renal denervation is a technique which aims to denervate the renal sympathetic nerves through the lumen of the renal artery to reduce systemic blood pressure. Recent preclinical data have suggested that the efficacy of denervation may be improved by performing renal denervation in distal renal arterial branches where the mean distance from renal artery lumen to nerve is smallest with a predominance of efferent nerve fibres. Although damage to the renal sympathetic nerves is desirable through this approach, the safety of applying radiofrequency energy to the vascular lumen as well as the surrounding anatomical structures needs to be thoroughly assessed.

At EuroPCR 2016 we presented the results of a prospective study designed to evaluate the safety of the multi-electrode radiofrequency Symplicity Spyral™ ablation catheter for performing distal denervation. Sixteen patients underwent bilateral selective invasive renal angiography followed by renal denervation performed using the Symplicity

Spyral catheter, denervating in the main renal arteries and each distal branch >3 mm diameter. Invasive renal arterial angiography was performed immediately pre-procedure (to check for any stenosis which might prevent denervation being performed), immediately post-procedure (to assess short-term vascular integrity), and at 6-month follow-up in all 16 patients. Images were subsequently anonymised and quantitative analysis was performed by triple-blinded reviewers.

The main findings of our study were that in patients undergoing distal vessel renal artery denervation using the Symplicity Spyral catheter, there was no significant difference in post-procedural vessel dimension, no formation of *de novo* stenosis, and no worsening of pre-existing atheroma either acutely after denervation or at 6-month follow-up. In addition, there was no deterioration in renal function at 6-month follow-up using distal renal denervation.

SHEAR STRESS ANALYSIS AFTER PERCUTANEOUS CORONARY INTERVENTION WITH BIORESORBABLE SCAFFOLDS: A CONVINCING TOOL FOR SEEING RESULTS OF OPTIMISATION AT FOLLOW-UP

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There are three main physical forces acting on the walls of the blood vessels; the blood pressure, circumferential stretch of the vessel wall caused by the action of the blood pressure, and the endothelial shear stress (ESS). ESS exerted by the blood flow is determined by the shear rate (i.e. velocity gradient) at the wall multiplied by viscosity.[1] Local ESS is sensed by several types of luminal endothelial mechanoreceptors. Physiological ESS activates various signalling pathways within the endothelial cells (EC) that provide structural cytoskeleton remodelling, suppressing reactive oxygen species, nitric oxide production, etc.[1] Steady laminar flow with high shear stress upregulates expressions of EC genes and proteins that are protective against atherosclerosis, whereas disturbed flow with associated reciprocating low ESS upregulates the EC genes (*MCP-1* and *PDGFs*) and proteins that promote atherogenesis.[1]

In order to demonstrate the acute-term effect of optimal bioresorbable scaffold (BRS) implantation on the local coronary haemodynamics, we designed the Mirage Animal Shear Stress Study to reveal the effect of two differently designed BRSs: Absorb everolimus-eluting bioresorbable vascular scaffold (Absorb BVS) and Mirage sirolimus-eluting bioresorbable microfiber scaffold (Mirage BRMS). Both BRSs are poly-L-lactic acid-based. The Absorb BVS has zig-zag hops linked by bridges, 157 µm strut thickness, 27% vessel surface coverage, and a long degradation time (36 months). The Mirage BRMS has a helix coil design, 125 µm strut thickness, 47% vessel surface coverage, and a relatively short degradation time (14 months).

The lumen and the scaffold borders were detected in the optical coherence tomography images and fused with angiographic data to reconstruct the coronary artery anatomy in 3D. Blood flow simulation and local ESS were computed

with computational fluid dynamic software (ANSYS Fluent). Average ESS was estimated for each of the 17 scaffolds to account for the interdependency of individual ESS values at each 5° subunit (sector) within each cross-section. Strut type, the treated vessel, and slice lumen area were recorded to evaluate a possible relationship with ESS. The ESS was lower in the Absorb BVS compared with the Mirage BRMS for the steady flow simulation (0.891±0.783 Pa versus 1.055±0.675 Pa, respectively; p<0.001). Seventy percent of the scaffolded surface in the Absorb BVS and 52% in the Mirage BRMS was exposed to a low (<1 Pa) athero-promoting ESS environment.

The long-term effect of BRS implantation has been investigated in the study by Bourantas et al.[2] Low ESS values between the struts were normalised and increased at 2-year follow-up compared to baseline. In our long-term designed study, we investigated the ESS change in the absorb Cohort B2 population. In preliminary results of the first two cases, we found that in well-expanded and symmetric apposed scaffolds, ESS values were improving. In the first case, which had an expansion index (EI) of 0.92 and symmetry index (SI) of 0.24, average ESS changed from 1.54±0.39 Pa (after implantation) to 1.43±0.14 Pa (at 5-year follow-up). Visually, the area with low and heterogeneous ESS at baseline after implantation normalised and homogenised. On the other hand, in the second case, which had an EI of 0.83 and an SI of 0.42, baseline average ESS was 1.97±0.84 Pa and at 5-year follow-up average ESS was 4.16±1.53 Pa. In concordance with the ESS results, the heterogeneous nature of ESS distribution remained at 5-year follow-up due to poor implantation indices at baseline.

In conclusion, we can say that intravascular imaging-based computational models can be used in evaluation of the haemodynamic performances of bioresorbable scaffolds. Regarding the optimal implantation, well-embedded scaffolds induce less flow disruption and fewer incidences of lower ESS at the acute phase of post-implantation. ESS is a valuable tool for demonstrating the optimal scaffold implantation results at longer follow-up and may have a value in the future for the optimisation of scaffold configuration.

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POST-RESUSCITATION ELECTROCARDIOGRAM FOR SELECTION OF PATIENTS FOR EARLY INVASIVE CORONARY TREATMENT STRATEGIES IN COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST

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There is considerable variability in the selection of comatose survivors of out-of-hospital cardiac arrest (OHCA) for immediate coronary angiography. The post-resuscitation electrocardiogram (ECG) is used by some individuals and institutions as a gatekeeper for selecting patients but it is unclear whether it accurately predicts myocardial ischaemia, particularly in the absence of ST-elevation. The aim of this study was to investigate the correlation between the post-

resuscitation ECG and coronary angiographic findings in a large unselected cohort of comatose OHCA survivors.

We identified 192 comatose survivors of OHCA who underwent an immediate invasive coronary strategy at our institution between 1st October 2012 and 31st July 2015. Survivors were grouped according to their post-resuscitation ECG into four categories; 1) ST-elevation, 2) presumed new left bundle branch block (LBBB), 3) other ECG signs indicating myocardial ischaemia, and 4) no ischaemia. Coronary angiographic images were reviewed for evidence of an acute coronary occlusion (ACO), which was defined as acute total or subtotal (>95%) occlusion with Thrombolysis in Myocardial Infarction flow grade 0–2 or presence of thrombus.

The prevalence of coronary disease (angiographic stenosis >70% in at least one vessel) was 77% in our cohort. An ACO was found in 42%. Figure 1 shows the proportion of patients in each ECG group who were found to have an ACO. The majority of patients with ST-elevation (89%) had an ACO. However, an ACO was also present in 12% of patients with a non-ischaemic ECG and 26% of patients with an initial non-shockable rhythm. ST-elevation/LBBB identified patients with an ACO with 83% sensitivity and 80% specificity. Percutaneous coronary intervention (PCI) was attempted in 109 patients (57%) with a 96% success rate. A significant proportion of patients without ST-elevation had PCI (Figure 2), including 21% of patients with no ECG evidence of ischaemia. The overall survival to discharge rate was 58%, with 54% of patients achieving good neurological recovery (cerebral performance category 1 or 2).

We conclude from this study that the post-resuscitation ECG does not accurately predict the presence of an ACO. Even in the absence of ECG ischaemia, comatose survivors of OHCA may benefit from emergent revascularisation. These findings are consistent with a recent Norwegian observational study[1] and support the European consensus statement on invasive coronary treatment strategies for OHCA,[2] which advocates early coronary angiography irrespective of ECG findings in the absence of an obvious non-coronary cause.

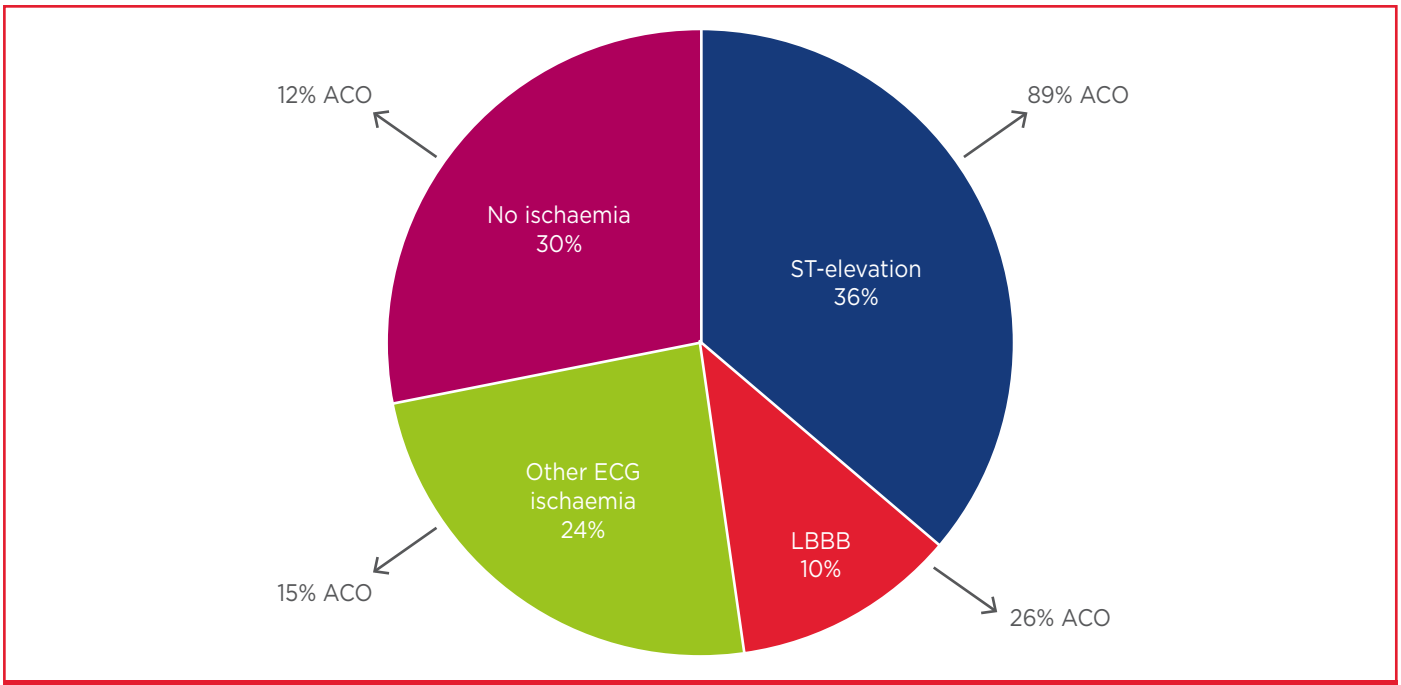

Figure 1: Proportion of out-of-hospital cardiac arrest survivors with an acute coronary occlusion by post-resuscitation electrocardiogram group.
ACO: acute coronary occlusion; ECG: electrocardiogram; LBBB: left bundle branch block.

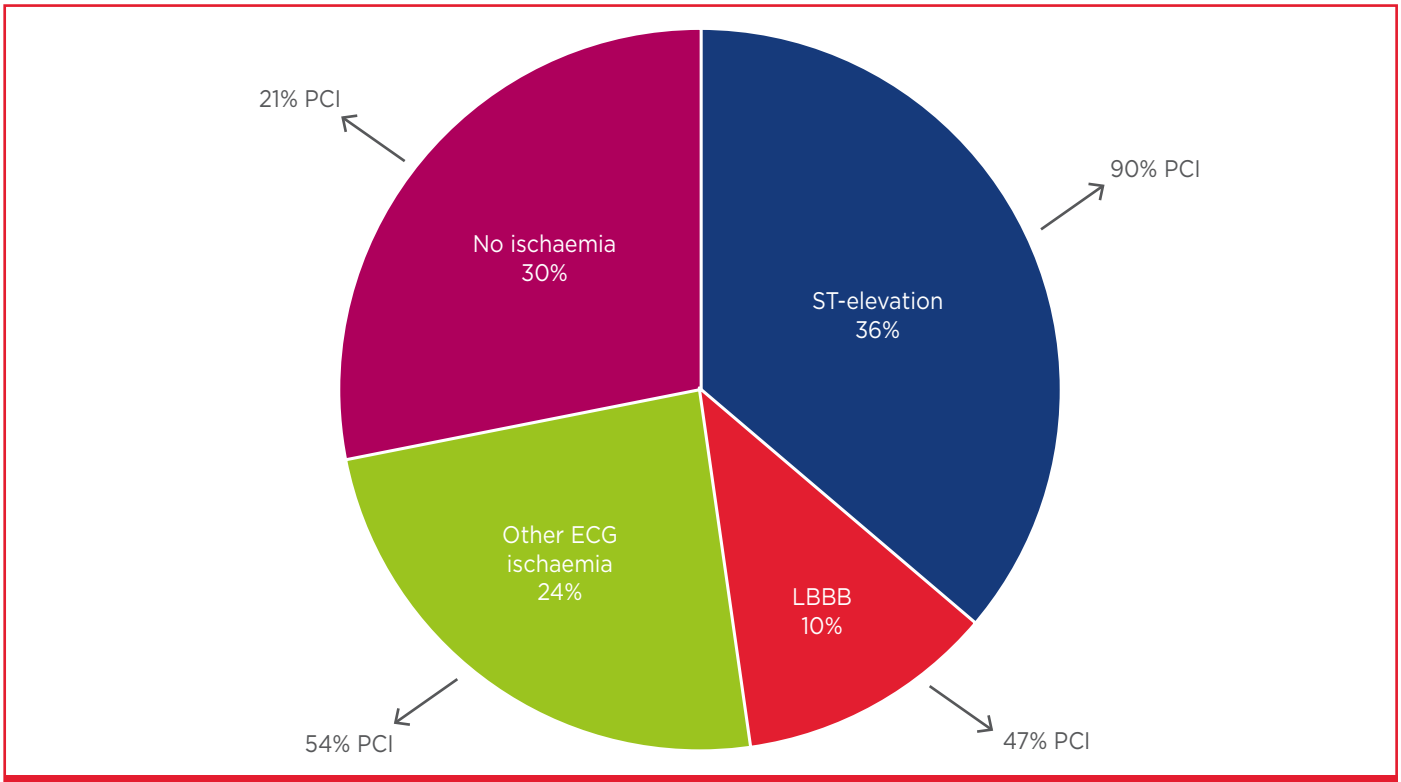

Figure 2: Proportion of out-of-hospital cardiac arrest survivors who had percutaneous coronary intervention by post resuscitation electrocardiogram group.
PCI: percutaneous coronary intervention; ECG: electrocardiogram; LBBB: left bundle branch block.

The discussion led by the chairperson focussed initially on the variability in OHCA care pathways adopted by different institutions. Despite differing practices, there was agreement that interventional cardiologists should become an essential part of the 'chain of survival' for patients with OHCA. The utility and timing of coronary angiography and PCI for all OHCA survivors was predictably debated. Although a growing body of evidence points towards a survival benefit,[3,4] some cardiologists remain unconvinced that an immediate invasive coronary strategy is beneficial or needed, particularly in the absence of ST-elevation on the post-resuscitation ECG. We hope that the randomised controlled trials currently recruiting (ARREST,[5] PEARL,[6] and DISCO[7]) will definitively determine the role of immediate coronary angiography in post-resuscitation care.

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TRANSCUTANEOUS TRANSCATHETER TECHNIQUE IN TREATMENT OF ISCHAEMIC STROKE

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AIMS

Due to the difficulty of accessing small diameter vessels, modern transcatheter technologies remain problematic in the treatment of ischaemic stroke resulting from intracerebral atherosclerotic lesions. This research is dedicated to the possible treatment of patients with ischaemic stroke by means of transcutaneous transcatheter endovascular surgery.

METHODS AND RESULTS

The research involved 798 patients aged 29–81 years (mean age 73 years), predominantly with intracerebral atherosclerosis, after ischaemic stroke: males 591 (74.06%), females 207 (25.94%). The evaluation of the clinical dementia rating, mini-mental state examination, and the Barthel index (BI) were conducted using the following methods; computed tomography, magnetic resonance imaging, magnetic resonance angiography, scintigraphy, rheoencephalography, and cerebral multigated acquisition scan:

- macrofocal strokes were detected in 134 (16.79%) patients
- midfocal strokes were detected in 390 (48.87) patients
- microfocal strokes were found in 274 (34.34%) patients

Transcatheter interventions were conducted in 487 (61.03%) patients in a test group. To perform transcatheter revascularisation of the main intracerebral arteries, high-energy pulsed lasers were used for revascularisation of distal intracerebral branches (continuous low-energy lasers [Patent US 7490612]). By transfemoral access and with the use of multiple conductive catheters, a flexible fibre-optic laser instrument with a diameter of 50–200 µm was guided through the carotid artery to the territory of the intracerebral atherosclerotic lesions, which was then followed by laser irradiation. While the laser apparatus was at work, the fibre-optic instrument was washed with physiologic saline thereby eliminating the blood and creating a transparent environment for laser irradiation. Conservative treatments including desagregate, anticoagulant, vasodilatory, antioxidant, and nootropic therapy were conducted in 311 (38.97%) patients in a control group.

Test Group

After the intervention, a good immediate outcome was achieved in 477 (97.95%) test group patients due to the restoration of patency and lumen of the affected vessels, as well as to the collateral circulation revascularisation. Twelve months after the treatment, the results depended on the size of the ischaemic lesion and the timing of the intervention.

- Good clinical outcome (complete recovery of mental and motor functions; BI: 90–100) was obtained in 175 (35.93%) patients
- Satisfactory clinical outcome (incomplete recovery of mental and motor functions; BI: 75–85) was obtained in 228 (46.82%) patients
- Relatively satisfactory clinical outcome (partial restoration of mental and motor functions; BI: 60–70) was obtained in 84 (17.25%) patients
- Relatively positive clinical outcome (absence of negative dynamics with insignificant reduction of mental and motor functions; BI: <60) was not obtained in any case

Control Group

The following results were obtained from the control group:

- good clinical outcome was not obtained in any case
- satisfactory clinical outcome was obtained in 46 (14.79%) patients

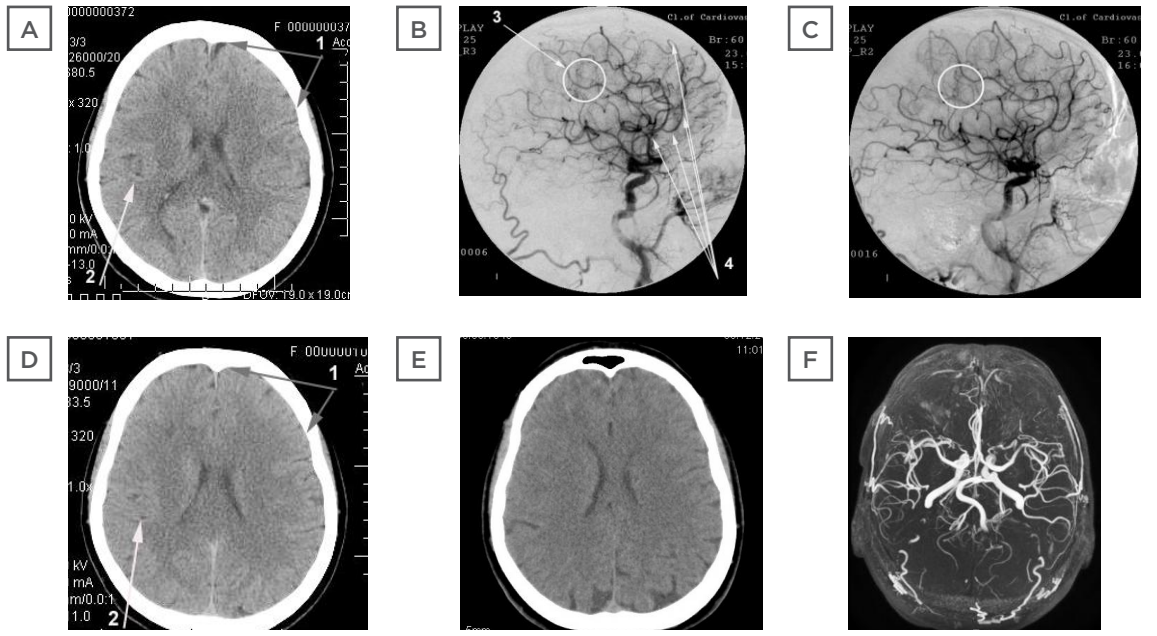

Figure 1: Patient H., 60 years old, female, suffered a small ischaemic stroke in the right hemisphere resulting in partial left-sided hemiparesis.

A) Computed tomography of the brain before intervention: 1) Moderate expansion of the subarachnoid space; 2) moderate heterogeneous post-ischaemic cyst in the right middle cerebral artery region.

B) Right-sided carotid multigated acquisition scan before intervention: 3) occlusion of distal branches of the right middle cerebral artery; 4) multiple stenosis of intra-cranial branches.

C) Right-sided carotid multigated acquisition scan after intervention: Restoration of the lumen and permeability of distal branches of the right middle cerebral artery; improvement of collateral blood flow.

D) Computed tomography of the brain 12 months after intervention: 1) Subarachnoid space restoration; 2) reduction in the size of the post-ischaemic cyst with signs of cerebral tissue structure recovery.

E) Computed tomography of the brain 6 years after intervention: No signs of residual effects of the post-ischaemic cyst, the structure of the right hemisphere cerebral tissue is restored.

F) Magnetic resonance angiograph of the brain 6 years after intervention: The permeability and lumen of the distal branches of the right internal carotid artery are completely preserved, there is further progression of collateral revascularisation.

- relatively satisfactory clinical outcome was obtained in 96 (30.88%) patients
- relatively positive clinical outcome was obtained in 169 (54.34%) patients

CONCLUSION

Evaluating the data obtained it can be concluded that the method of transluminal laser revascularisation of cerebral blood vessels is effective in treating intracerebral atherosclerotic lesions. Transcatheter laser revascularisation in the treatment of ischaemic stroke with intracerebral atherosclerotic lesions is more effective than therapies. Restoration of intracerebral blood flow can significantly reduce the level of mental, cognitive, and motor disorders and return patients to their active daily life.

EDITOR'S PICK

Since its inception in the 1970s, percutaneous coronary intervention has become one of the treatments of choice for patients with ischaemic heart disease. Here, Sidhu and Gerber present a comprehensive and up-to-date review on stenting techniques. This includes a look at the evolution of stenting and an evaluation of techniques and devices. This is not like many other reviews, as this one also provides 'tips and tricks' to help deal with difficult situations when performing these interventions.

PERCUTANEOUS CORONARY INTERVENTION FOR BIFURCATION LESIONS: A STATE-OF-THE-ART REVIEW OF TECHNIQUES AND DEDICATED DEVICES

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ABSTRACT

Percutaneous coronary intervention (PCI) has become an integral step in the management of patients with ischaemic heart disease. Bifurcation lesions are commonly encountered in PCI and are regarded as the most technically challenging lesions to treat. The literature is saturated with studies that explore the best way to treat these lesions, with a variety of techniques introduced to enable stenting of both vessels. However, the optimal method is still undetermined. In this state-of-the-art review, we discuss the various strategies that are currently regarded as ideal, particularly those which involve one or two-stent techniques. Moreover, dedicated bifurcation devices have been developed to facilitate bifurcation stenting and improve outcomes. The role of these devices in this context is also uncertain, therefore we will discuss the current evidence for their use. Finally, a road map on the 'tips and tricks' to successfully perform bifurcation PCI is mentioned, which will aid any interventionist performing this procedure in an optimal manner.

Keywords: Bifurcation lesions, dedicated bifurcation devices, percutaneous coronary intervention (PCI).

INTRODUCTION

Dr Andreas Gruentzig performed the first coronary angioplasty in 1977;[1] since then percutaneous coronary intervention (PCI) has become increasingly sophisticated, enabling treatment of complex lesions. PCI has a central role in the management of patients with ischaemic heart disease, as discussed in the recent European Society of Cardiology (ESC) guidelines,[2] and nearly 600,000 PCIs are performed each year in the USA,[3] compared with 96,143 cases performed in 2014 in the UK.[4] Bifurcation lesions are encountered in up to 20% of patients undergoing PCI.[5] They are challenging,

complex, and often encountered in high-risk surgical candidates, such as the elderly or frail, or those with high SYNTAX scores,[6] where bifurcation stenting is the only realistic revascularisation option. In general, a simplified interventional strategy with a 'less is more' approach is regarded as best practice. However, with the introduction of dedicated bifurcation devices, questions have arisen around this belief (Figure 1).

CLASSIFICATION

The European Bifurcation Club (EBC) has endorsed the Medina classification to describe bifurcation lesions, and the MADS (main, across, distal, side) classification to describe the various ways to start bifurcation PCI.[7]

The Medina classification consists of three numbers.[8] Within this, a score of 1 is used to denote a vessel with a stenosis of ≥50%; otherwise a score of 0 is given. The first number describes the proximal main vessel (MV), the second the distal MV, and the third the side branch (SB). A true bifurcation lesion is regarded as either 1,1,1; 0,1,1; or 1,0,1. It is important to appreciate that the Medina classification only provides an anatomical description of the lesion and not a physiological one.

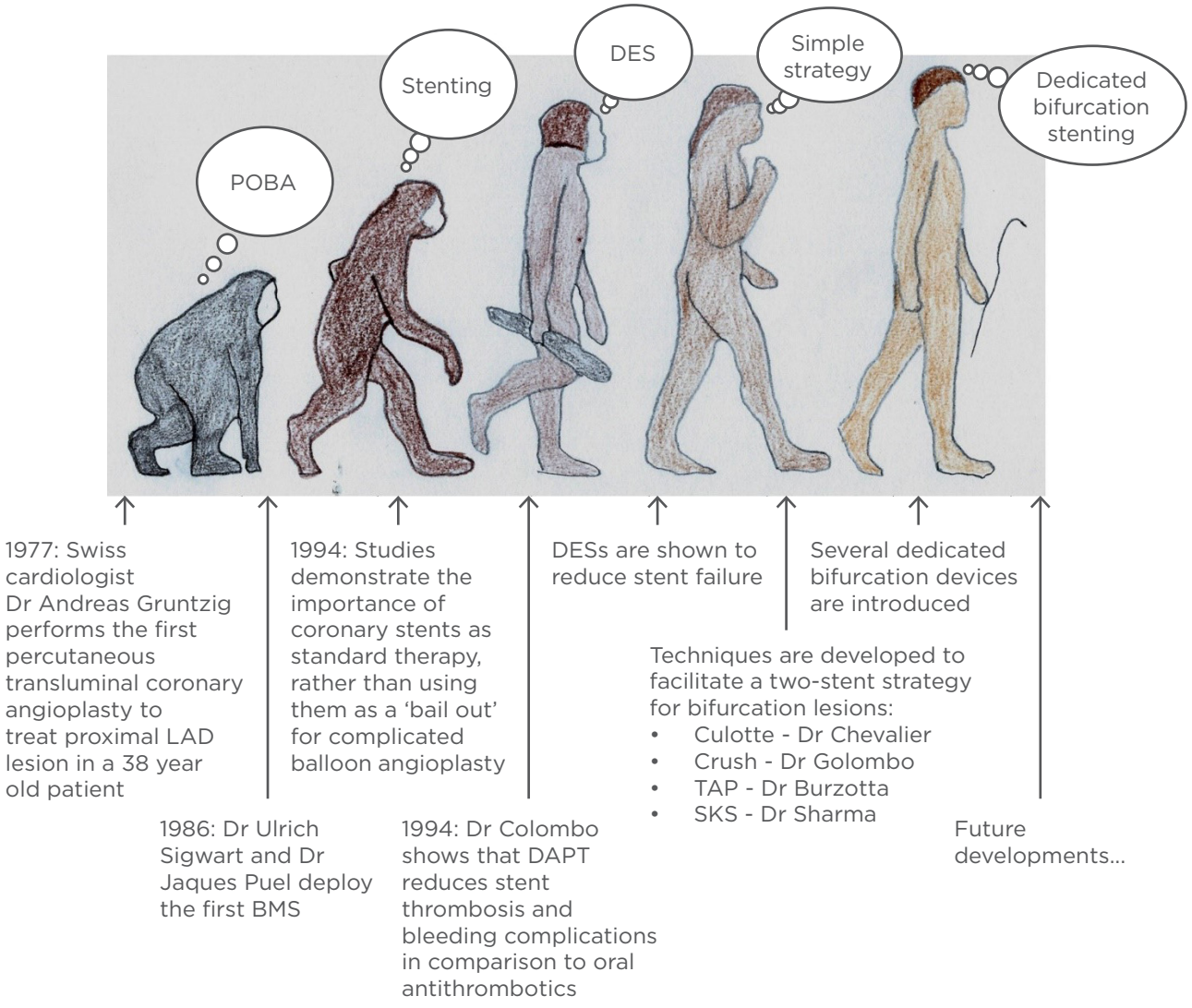

Figure 1: The evolution of percutaneous coronary intervention, from simple angioplasty to complex intervention.

A one (simple) or two-stent strategy can be used to treat bifurcation devices facilitating stenting of both vessels.

BMS: bare-metal stent; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; LAD: left anterior descending artery; POBA: plain old balloon angioplasty; TAP: T and protrusion technique; SKS: simultaneous kissing stent technique.

Studies using fractional flow reserve (FFR) have demonstrated a negative correlation between the percentage stenosis of the SB post MV stenting as determined by quantitative coronary angiography (QCA) and FFR assessment (r=-0.41, p<0.001), with FFR demonstrating that only 27% of lesions deemed significant by QCA are functionally significant.[9] These data support a single stent strategy in the majority of lesions.

Under the MADS classification (as defined previously), 'M' involves stenting of the proximal MV first; 'A' is the placement of the stent across the SB first; 'D' is the placement of the first stent into both distal branches or at the ostium; and finally 'S' indicates when the SB is stented first.[7,10] Whichever technique the operator starts with can lead to further stenting, if required.

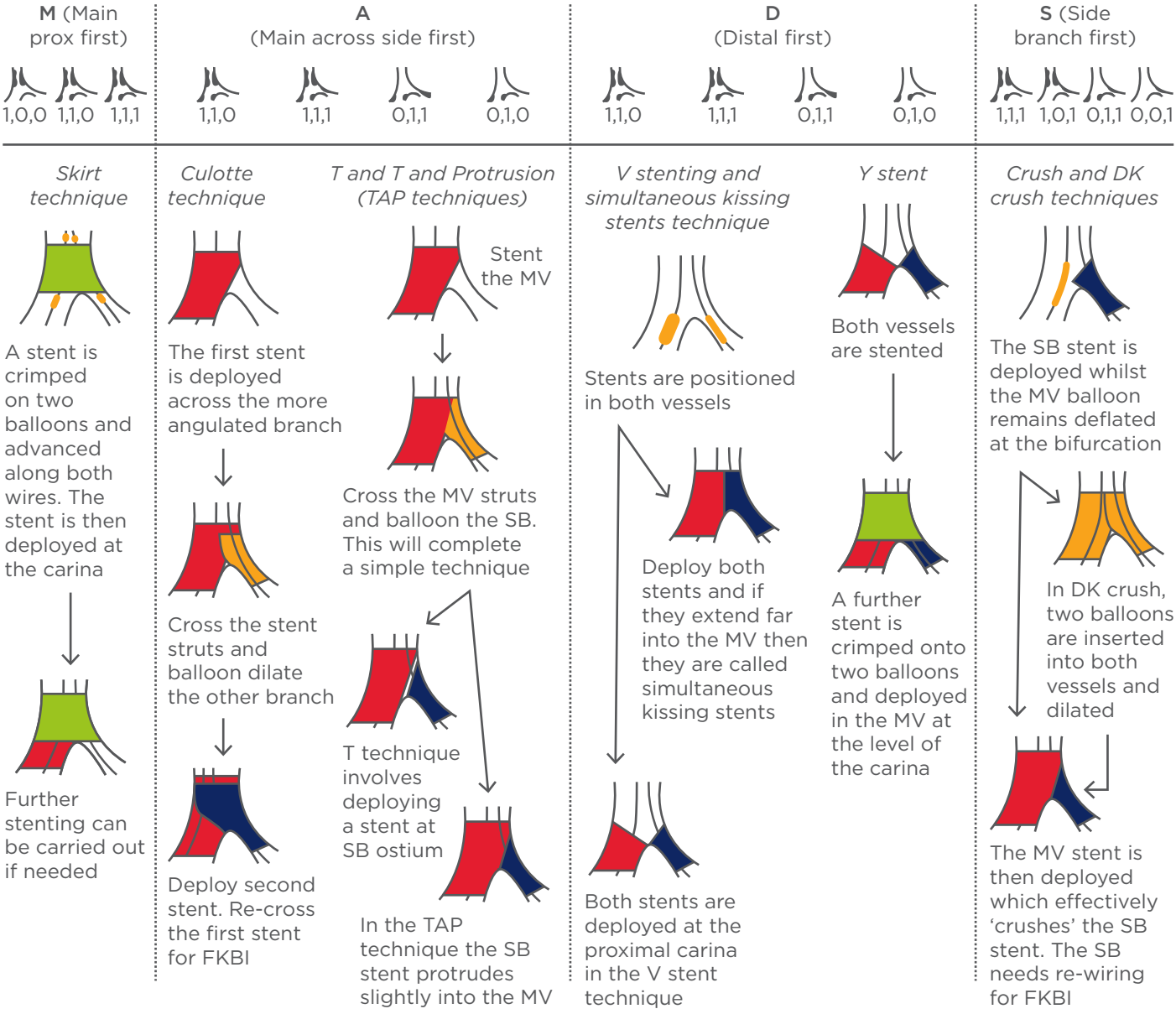

Figure 2: Different complex technique procedures according to MADS (Main, Across, Distal, Side) and how this relates to the Medina classification.

All techniques begin with wiring of both the main vessel (MV) and side branch (SB) followed by balloon dilation. With the complex strategy, the procedures end with a final kissing balloon inflation (FKBI) of both vessels.

Wire on top of a stent means the stent struts are crossed.

Red denotes MV stenting; Blue denotes SB; Green is for proximal MV stenting to the carina; Yellow denotes a balloon.

TAP: T and Protrusion; DK: double kissing.

Table 1: The current studies that compare a simple to a complex strategy using drug-eluting stents.

Trial	No. of patients (simple/ complex)	Complex technique(s)	Baseline SB diameter (mm)	Clinical follow-up (month)	Primary end-point (simple versus complex)	Author comments
Colombo et al.[18] (2004)	85 (22/63)	T-stent V-stent Y-stent 	2.5–3.5	6	Angiographic restenosis of either branch (18.7% vs. 28%; p=NS)	Only true bifurcation lesions were included in this small study. There was a 51% cross-over rate from the simple to complex approach. Also no agreed standard complex strategy, omission of culotte and primary outcome was not clinically based.
Pan et al.[21] (2004)	91 (47/44)	T-stent 	≥2.25	11	Angiographic restenosis of either branch (7% vs. 25%; p=NS) at 6 months	High rates of FKBI but only 86% of true bifurcation lesions were included in this small study.
NORDIC (2006)[22]	413 (207/206)	Crush Culotte other 	≥2.0	6	Cardiac death, MI, ST or TVR (2.9% vs. 3.4%; p=NS)	Trial limited by a small SB diameter, only 59.6% were true bifurcation lesions and the exclusion of peri-procedural myocardial infarction in MACE.
BBK (2008)[23]	202 (101/101)	T-stent 	≥2.25	12	Angiographic restenosis of SB at 9 months (23% vs. 27.7%; p=NS)	An unblinded study with only angiographic and not clinical endpoints. Only 68% of true bifurcation lesions were included but FKBI was used in 100% of cases.
BBC ONE (2010)[20]	500 (250/250)	Crush Culotte 	≥2.25	9	Cardiac death, MI, or TVF (8% vs. 15.2%; p<0.05)	A large study showing higher MACE rates in complex strategy. However, only 82% of true bifurcation lesions were included with no angiographic follow-up and low use of FKBI.
CACTUS (2009)[19]	350 (173/177)	Crush 	2.25–3.5	6	Cardiac death, MI, or TVR (15% vs. 15.8%; p=0.95)	Well conducted randomised trial with angiographic follow-up and FKBI performed in 91% of cases. Only limited follow-up.
Lin et al.[24] (2010)	108 (54/54)	DK crush Culotte T stenting 	≥2.2	8	Cardiac death, MI, ST, or TVR (21% vs. 6%; p<0.01)	All patients had true bifurcation lesions with high rates of FKBI in both groups. Angiographic follow-up carried out.
DKCRUSH-II (2011)[17]	370 (185/185)	DK crush 	2.5–4.0	12	Cardiac death, MI, or TVR (17.3% vs. 10.3%; p=0.07)	Good randomised trial with only true bifurcation lesions included. Large SB, high rate of FKBI, and angiographic follow-up. No functional assessment performed.
NORDIC-Baltic IV (2013)[25]	450 (221/229)	Culotte T-stent other 	≥2.75	6	Cardiac death, MI, TLR, or ST (4.6% vs. 1.8%; p=0.09)	100% of true bifurcation lesions included but only 36% of provisional strategy had FKBI. Low cross-over rate from provisional to complex strategy.

It is important to note that FKBI is associated with better outcomes and a complex strategy should only be considered in a true bifurcation lesion (1,1,1; 1,0,1; or 0,1,1).

FKBI: final kissing balloon inflation; MI: myocardial infarction; MV: main vessel; SB: side branch; ST: stent thrombosis; TVF: target-vessel failure; TVR: target-vessel revascularisation; TLR: target-lesion revascularisation; MACE: major adverse cardiovascular events; NS: not significant.

APPROACH TO BIFURCATION STENTING

The decision to use a one or two-stent strategy ought to be made prior to starting the procedure. With a single stent or provisional technique, the MV is stented first. Then, only if the SB is compromised and judged to be significant is subsequent SB stenting carried out with the T technique. With a two-stent or complex procedure, the operator decides if both MV and SB need stenting from the outset. Following this, we summarise the current literature and evidence for the differing complex approaches (outlined in Figure 2). All techniques begin with the wiring of both vessels, followed by balloon dilation. Procedures should finish with a final kissing balloon inflation (FKBI), which involves ballooning both the MV and SB simultaneously. FKBI has been shown to significantly reduce major adverse cardiovascular events (MACE).[11]

Skirt Technique

The skirt technique involves crimping a stent onto two balloons and advancing them along the two wires until the carina is reached. The stent is then deployed. The main drawback of this procedure is the need to manually crimp the stent as it can disrupt the polymer in drug-eluting stents (DESs).[12]

The T Technique, and T and Protrusion Technique

The T technique involves deploying a stent in the MV and then re-wiring the SB through these struts to place a further stent. It treats proximal MV lesions but leads to incomplete coverage of the ostial SB.[12] A slight modification, called the 'T and Protrusion (TAP) technique' allows the SB stent to protrude slightly into the MV to ensure ostial coverage without significant disturbance to the MV struts.

The Culotte Technique

The culotte stenting technique achieves full coverage of the bifurcation. It involves wiring both vessels and placing a stent across the more angulated branch. The other vessel is then re-wired through these struts and a second stent is deployed. FKBI is performed after re-wiring of the first vessel, again through the struts of the second stent.[13] A culotte can be used in all bifurcation angles but is time consuming, and limited by the creation of a two-stent layer.[12] Additionally, the culotte as opposed to the crush technique requires vessels of similar sizes.

V and Simultaneous Kissing Stent Technique

The V technique involves advancing stents into the SB and distal MV and then inflating them both to create a proximal carina.[14] It can only be used if the proximal MV is free from significant disease. If the carina extends a significant amount into the proximal MV, then it is called the simultaneous kissing stent technique.[15] It is useful in bifurcations with a tight proximal stenosis in the MV. The major advantage of these techniques is that wire access to either branch is maintained; however, treating a proximal lesion after using the V technique can be very difficult and requires re-wiring of the SB.[12]

Y Technique

The Y technique involves deploying a stent in both the distal MV and SB. A further stent is then placed in the proximal MV over two balloons and deployed at the carina.[12] This ensures all three stents are covered.

Crush Technique

The crush technique involves placing un-inflated stents in both vessels and then deploying the SB stent followed by removal of its wire. The MV stent is then deployed and the balloon splays the struts of the SB, effectively 'crushing' them.[16] This enables good coverage of the ostium of the SB; however, re-wiring the SB for FKBI can be difficult and time consuming.[12]

The Reverse Crush Technique

The reverse crush technique is often used when a suboptimal result is achieved with provisional SB stenting; in cases of inadequate ostial SB appearance, another stent is advanced into the SB and retracted 2–3 mm into the MV, with another balloon advanced into the MV at the level of the bifurcation. The SB stent is deployed first followed by inflation of the MV balloon.

Double Kissing Crush Technique

The double kissing (DK) crush stenting technique involves stenting the SB first and then inflation of a balloon in the MV to crush the first stent. A first kissing balloon inflation is performed by placing balloons in both vessels and inflating them. Then the MV stent is deployed followed by an FKBI.[17]

Keep It Open Strategy

Unlike the other strategies described, the keep it open (KIO) strategy does not involve balloon

dilation of the SB or FKBI. With this strategy, the MV is treated whilst the jailed wire is left in the SB to KIO. It is used if the SB is too small to stent, or is clinically irrelevant but has ostial disease.[5]

Whichever technique is used, the patency of vessels needs to be as optimal as possible and they should not be covered with multiple layers of stents.

PROVISIONAL OR COMPLEX STRATEGY

Several studies have assessed which strategy is superior, and these are discussed in Table 1.[17-25] We focus primarily on the use of DESs, as it is well established that a complex approach using bare-metal stents (BMSs) yields much higher rates of MACE and restenosis of the MV and SB than with a DES, hence contemporary practice is to use DESs for bifurcations.[26] A meta-analysis pooled studies that used DESs in order to compare these two approaches. There was a similar risk of cardiac death (odds ratio [OR]: 0.99; 95% confidence interval [CI]: 0.4–2.41, p=0.98), target-lesion revascularisation (TLR; OR: 1.72; 95% CI: 0.95–3.12, p=0.07), and target-vessel revascularisation (TVR; OR: 1.59, 95% CI 0.94–2.69, p=0.07) between the simple and complex approaches.[27] However, there was a significantly lower incidence of myocardial infarction (MI) at follow-up (OR: 0.6; 95% CI: 0.43–0.86, p=0.005) after simple strategy surgery.[27] However, the DK-CRUSH-II trial showed that rates of MI were similar between the DK crush and simple strategies (3.2% versus 2.2%, p=0.751).[17] This trial only included true bifurcation lesions and a SB of ≥2.5 mm, which may account for these differences.[17] Given these disparities, we need to be careful when concluding that complex approaches truly have a higher risk of MI.

The EBC consensus states that the provisional approach should be the preferred technique for most bifurcations.[7] However, if there is significant SB ostial disease or if the vessel is particularly large and supplies a large area of myocardium, then a complex strategy should be used.[7]

TWO-STENT TECHNIQUES: ARE THERE DIFFERENCES BETWEEN VARYING STRATEGIES?

On the whole, the majority of interventionists prefer the provisional approach; however, with 'true' bifurcation lesions (Medina 1,1,1; 1,0,1; 0,1,1) in large vessels a complex two-stent technique is sometimes necessary. In particular, if a provisional approach results in injury, recoil, or dissection in a large SB, one has to commit to two stents. Below we describe the current literature comparing the techniques described in Figure 2, including the clinical and angiographic outcomes.

The Culotte Technique Versus Crush Techniques

The first randomised study comparing culotte and crush techniques was from the NORDIC PCI group.[15] The majority of patients included had true bifurcation lesions with SB angulations <70°.[28] At 6 months the number of MACE was comparable between culotte and crush (3.7% versus 4.3%, p=0.87), but at the 8-month angiographic follow-up, culotte was associated with significantly less in-stent restenosis (4.5% versus 10.5%, p=0.046).[28]

Further studies over 36 months have confirmed these findings with similar MACE rates in both culotte and crush (16.7% versus 20.6%, p=0.32).[29] It should be noted, however, that the majority of the increased MACE is due to SB TVR, and whether this is of clinical relevance or just an angiographic anomaly related to the procedure remains to be seen. There was a trend towards increased restenosis rates in the crush group, but this did not translate into increased TLR[29] as cardiologists may have thought the restenosis did not need revascularisation, hence this may be related to the aggressiveness of the interventionists' treatment style. Studies focussing on ischaemic-driven TLR are therefore more clinically relevant. There were lower rates of FKBI in the crush group (crush 84.3% versus culotte 91.6%, p=0.02),[29] probably owing to the difficulty of crossing multiple stent layers; however, this did not translate into higher rates of stent thrombosis.

The Culotte Technique Versus the Double Kissing Crush Technique

The culotte and double kissing crush techniques were compared in a randomised trial involving unprotected distal left main bifurcation lesions. The culotte technique had significantly higher 1-year MACE rates compared to DK crush (16.3% versus 6.2%, p<0.05).[30] This was mainly driven by the need for TVR. These improved MACE rates were also apparent in lesions with a bifurcation angle ≥70°. This would suggest that refinement of a full-crush technique into either a mini-crush or DK crush has more favourable outcomes and it is currently the preferred approach.

Culotte Stenting Versus T Stenting and T and Protrusion Stenting

A retrospective study compared culotte with T stenting, and showed improved MACE rates at 9 months with the former technique (13.3% versus 27.3%, p=0.051).[31] Indeed, there was significantly lower residual stenosis at the SB ostium with culotte compared with T stenting (3.44±7.39% versus 12.55±11.47%, p<0.0001).[31]

Complex techniques were compared in a study investigating strut apposition and stent coverage of the bifurcation lesion. It is recognised that stent malapposition leads to an increased risk of late stent thrombosis.[32] This small study compared culotte, crush, and T/TAP techniques using micro-computed tomography.[32] They found higher rates of malapposition within the bifurcation with crush compared to culotte or T/TAP techniques (41.5±8.2%, 31.4±5.2%, and 36.7±8.0%, respectively).[32] The percentage of residual stenosis at the SB ostium was similar with all techniques (32.7%, 29.2%, and 25.9%, respectively).[32] However, there was a significantly higher rate of strut malapposition in the proximal vessel with the crush and culotte techniques compared with T/TAP (39.1±10.7%, 26.1±7.7%, and 4.2±7.2%, respectively, p<0.01).[32] The study highlighted that even after FKBI, strut apposition remained poor in all complex techniques.

Crush Versus T Stenting

A retrospective study compared crush to T stenting of bifurcation lesions. At 1-year follow-up culotte, as opposed to T stenting, had lower rates of TLR (14% versus 31.1%, p=0.01) and TVR (16.5% versus 32.8%, p=0.02).[33] Indeed, there was significantly less restenosis of the SB with culotte compared with T stenting when FKBI was used (8.6% versus 26.5%, p=0.04).[33]

Bioresorbable Vascular Scaffold in Bifurcations

The future use of bioresorbable vascular scaffolds (BVS) is of interest as it is possible that struts across the SB in large vessels will eventually dissipate, and so as long as patients remain on prolonged dual antiplatelet therapy, no adverse outcome can ensue. This hypothesis may also hold for patients with complex layers of scaffold. Some case reports with reasonable outcomes have been described so far; however, randomised trials are still required and the current recommendation is against the use of BVS for bifurcation lesions.[34,35]

DEDICATED BIFURCATION DEVICES

Dedicated bifurcation devices have been used in an attempt to overcome the problems associated with complex strategies by enabling both vessels to be more easily stented using a single delivery device. They are broadly divided into three categories:[36]

Devices that are deployed in the main vessel and facilitate side branch stenting by maintaining access to it, usually via side-ports

These devices facilitate provisional T or V stent techniques, with examples including:

- **Antares®** (Trireme Medical, USA): This BMS has an opening aperture in the middle of its shaft to facilitate T stenting. No adverse events were reported at 30 days in a small first-in-man (FIM) study.[37]
- **BioSS Expert stent®** (Balton, Poland): This DES is advanced into the MV until a marker is positioned at the carina, which identifies a zone with reduced struts to facilitate SB stenting using the T technique. It had an 11.1% TLR rate at 1 year.[38]
- **Drug-Eluting Balloons** (DEBs):[39] There is evidence in small studies that support the use of DEB for the treatment of in-stent restenosis. There has been some use of DEB in the SB of a provisional T approach and it has also been utilised before or after the use of dedicated BMS bifurcation devices such as Tryton™ (see following). In patients that cannot have dual antiplatelet therapy or are frail, and in whom plain old balloon angioplasty is considered for the bifurcation lesion alone, FKBI DEB can be used. However, the precise role of DEB in bifurcation lesions requires further investigation.
- **Invatec Twin-Rail** (Invatec S.R.L, Italy): This BMS is pre-mounted on double balloons and the stent is deployed by simultaneous kissing inflation using a single indeflator. It aids a provisional T approach and had a 14.3% MACE rate at 7 months in a small FIM study.[37]
- **Multi-Link Frontier™** (Abbott Vascular Devices, USA): This BMS is pre-mounted on double balloons, which are joined by a mandrel. The mandrel is retracted when the device is at the carina, releasing the SB balloon to enable T stenting.[40] It has now been discontinued.
- **Nile Croco®** (Minvasys, France): A BMS is crimped on two balloons pre-mounted onto two catheters. The MV balloon has a marker on it indicating the position of the SB orifice,

thus when the stent is deployed, the SB balloon can be advanced into the SB. It had a 14% MACE rate at 6 months.[41]

- **Petal™** (Boston Scientific, USA): This device contains an aperture in the mid section of the DES, with deployable struts to cover the ostium of the SB. It had a 7% TLR rate at 1 year in a FIM study.[42]
- **SLK-view™** (Advanced Stent Technologies, USA): This BMS contains side apertures which enable SB access with a provisional T technique, although it is no longer available.[37]
- **Stentys®** (Stentys, USA): This is not a true dedicated bifurcation stent but the links of the DES can be removed by balloon angioplasty. It had a 3.7% MACE rate at 1 year.[43]
- **Xience SBA** (Abbott vascular devices, USA): This had an opening port in the body of the DES for SB access[44] but it never came to market.
- **Y-Med Side-Kick™** (Y-Med, USA): This device contains exit ports that enable the SB to be wired when the BMS is in the MV. It facilitates the T approach and had a 5.8% MACE rate at 3 months.[37]

Devices that are used to treat the side branch first with subsequent main vessel stenting

Examples include:

- **Sideguard®** (ArraVasc, Ireland): This is a self-expanding BMS, mounted on a balloon delivery system enabling its precise delivery to the SB. Further MV stenting is carried out using the crush or T techniques.[45] It is no longer available.
- **Biguard™** (Lepu Medical Ltd., China): This device uses a DES to stent the SB with facilitated access to the MV through its wider struts to enable a provisional T, culotte, or DK crush approach. It had a 10.6% MACE at 12 months.[46]
- **Tryton™** (Tryton, USA): This is similar to the culotte approach due to the use of a BMS made of three zones divided into a SB, MV, and transitional zones. The stent is deployed in the SB with the transition zone facilitating MV stenting.[47]

Conical stents that cover the whole bifurcation

One example of a conical stent is the Axxess stent™ (Devax, USA). This self-expanding device is advanced along the wire that has the steepest bend to the proximal MV, until markers on the DES are in the distal vessel. The sheath is gently retracted enabling markers to flare into the opposite vessel. The device is gently advanced whilst the sheath is fully retracted to allow full deployment.[48]

A characteristic of many of these new devices is the high rate of procedural success. The Axxess and Tryton stents will be discussed further given their common use in clinical practice and larger study populations. The DIVERGE study investigated clinical outcomes with the Axxess stent with a follow-up of 3 years.[48] Further treatment with a CYPHER® stent was advised if there was residual stenosis in any vessel of >30% or if there was evidence of dissection.[48] The cumulative MACE rate was 9.3% at 1 year and 16.1% at 3 years.[48] These outcomes were comparable to other studies investigating complex approaches. In CACTUS, the 6-month MACE rate was similar to the 3-year rates found in DIVERGE.[19] 3-year MACE rates after PCI in bifurcation lesions in patients with multivessel disease were similar to those seen in DIVERGE.[49] Although the initial results are promising, further randomised trials are needed.

The efficacy of the Tryton device was analysed in the TRYTON study, which compared it to SB balloon angioplasty.[47] At 9 months, the primary endpoint of TVF occurred in 17.4% of the bifurcation stent group, but also in 12.8% of the provisional group (p=0.11), meaning it did not meet the non-inferiority endpoint.[47] However, there was reduced stenosis in the SB with the Tryton device, although this did not relate to differences in binary restenosis rates.[47] Only 41% of the SB diameter inclusion criteria of ≥2.25 mm was met, which may have adversely affected these results.

TIPS AND TRICKS

With a provisional approach, we suggest leaving a jailed wire in the SB to KIO and help facilitate location of the vessel if SB stenting is required at a later point. It is often useful to wire the more difficult branch first to ensure the wire does not twist around an already placed wire as a result of excessive manipulation.

Difficulty with Side Branch Access

Initially try different wire tip curves or guidewires. A longer and wider curve can improve access to an occluded SB.[50] A hydrophilic guidewire allows easier recrossing into the SB but carries a risk of dissection, whereas a stiffer wire enables better precision using torque but involves difficulties with manipulation.[50] Alternatively, the 'reverse wire technique' can be used which involves advancing

the curved wire into the distal MV and slowly retracting it towards the SB until it is engaged.[7] It can then be advanced into the SB. If these techniques fail, then MV balloon predilation can help to change the angle with the SB but this does pose a risk of plaque rupture into the SB.[50] Additionally, rotational atherectomy can debulk ostial SB lesions that have a high plaque burden.[50] Finally, if these measures fail than placing a microcatheter at the level of the carina and exchanging various stiffer or steerable wires through it can help entry into the SB; the Pilot family of wires are particularly useful in this regard.

Difficulty Re-wiring the Side Branch Through the Stented Main Vessel Struts

If the aforementioned tips fail, then try the proximal optimisation technique. This involves using a short, oversized, non-compliant balloon to expand the proximal stent to just before the carina such that the angle between the MV and SB are changed to facilitate SB re-wiring.[7] Another technique involves using the SB jailed wire to inflate a small balloon at the SB ostium to help SB re-wiring.[50] Once access has been achieved, the MV stent will require balloon dilation and FKBI. Finally, the placement of a proximal guide extension device such as a guideliner or a mother-in-child technique will facilitate the crossing of balloons and stents into the SB. In general, noncompliant balloons are recommended.

Final Kissing Balloon Inflation and Two-Step Kissing Balloon Inflation

It is important to use noncompliant balloons to enable high pressure inflations and more predictable expansion. This is evidenced from intravascular ultrasound studies and bench testing.[51] FKBI is recommended for all complex strategies and can be useful in provisional stenting if a significant SB stenosis remains after MV stenting.[7] The COBIS registry showed that routine use of FKBI after simple stenting can be harmful due to increased rates of TLR.[52] Lastly, a refinement to KBI has recently been demonstrated to be more effective at reducing SB ostial stenosis; by performing a two-step KBI, which involves placing a noncompliant balloon in the SB and performing a prolonged inflation at high pressures (>20 atm), ostium can be opened before FKBI.[53]

CONCLUSION

Coronary intervention has evolved through the years to produce more complex PCI. Although several studies support the 'less is more' notion for bifurcation lesions, there are circumstances when a complex approach is needed. The introduction of dedicated devices has simplified this strategy but it remains to be determined if they improve outcomes. The use of FFR and intracoronary imaging (optical coherence tomography or intravascular ultrasound) also facilitates choice of strategy and reduces unnecessary lesion treatment, ensuring adequate final stent optimisation in both the MV and the SB. With further device and procedural refinement, we envisage that dedicated devices will eventually play a central role in the treatment of true bifurcation lesions.

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EVOLUTION OF DRUG-ELUTING STENT DRUG ELUTION PROFILE: IS A CRYSTALLINE DRUG FORM THE IDEAL SOLUTION?

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ABSTRACT

Since its introduction into clinical practice, coronary angioplasty has seen game-changing advances incomparable to any other medical technology. In particular, the progression from balloon angioplasty to stent technology has not only seen significant advances in technology but, more importantly, improved patient outcomes.

The introduction of the drug-eluting stent (DES) has further pushed the technology to a new standard of care. However, even in the current day, top performing DESs still have several limitations. Their safety has been limited by suboptimal polymer biocompatibility, delayed stent re-endothelialisation, and local drug toxicity, leading to adverse clinical outcomes such as very late stent thrombosis, allergic reactions, and chronic inflammation. In addition, current DESs have a consistent yearly increase in late restenosis and revascularisations. Furthermore, durable polymer coatings used in first-generation DESs have been associated with mechanical complications and non-uniform coating, resulting in drug loss and poor distribution.

As a consequence, in recent years, the focus of research has been on the development of novel drug carrier systems including absorbable (or biodegradable) polymer coatings and non-polymeric stent surfaces. Additional improvements have included the development of more modern stent platforms. Optimised drug delivery requires a combination of refined stent designs and drug delivery technology. The combination of highly-refined bare-metal stent designs and polymer coating materials have been two areas of focus for the development and improvement of next-generation DESs. Despite all the changes in stent design and polymer materials, there has been little done in the past 15 years to improve drug elution profiles.

The need for new advancements in DES design to overcome late event occurrence, and possibly even improve on the clinical outcomes of current DESs, has led to interest in moving away from the standard drug elution profile to explore alternatives. A new manufacturing technique that may have overcome traditional limitations has led to the development of a novel stent platform. This review will explore the principles, device technology, and clinical data to date on a crystalline form of the anti-restenotic drug for stent implantation. This approach could truly be game changing due to an improved elution pharmacokinetic profile, as well as reduced local toxicity and improved long-term biologic arterial wall response.

Keywords: Drug-eluting stent (DES), crystalline sirolimus, coronary angioplasty, coronary artery disease (CAD), interventional cardiology.

INTRODUCTION

Coronary artery disease (CAD) is the most common type of heart disease and the first cause of mortality worldwide in people aged ≥60 years.[1] Complications include acute coronary syndromes (ACS) (unstable angina or myocardial infarction [MI]), congestive heart failure, cardiac arrhythmias, and sudden death.

Since its introduction into clinical practice, coronary angioplasty has witnessed a remarkable surge in innovation incomparable to any other medical technology. In particular, stent technology has been a source of remarkable improvement, reaching an outstanding rate of development which has nowadays increased in a similar fashion to that of Moore's Law (pertaining to computing hardware, the number of transistors in a dense integrated circuit doubles approximately every 2 years).

WIDESPREAD UTILISATION OF STENTS IN CORONARY ARTERY DISEASE

Bare-Metal Stenting

Wide acceptance of coronary stenting was based on the results of the BElgian NEtherlands STENT (BENESTENT)[2] and the STent REStenosis Study (STRESS)[3,4] trials, which showed the superiority of bare-metal stenting over plain old balloon angioplasty (POBA) (also called percutaneous transluminal coronary angioplasty) in terms of reduction of angiographic restenosis and need for repeated intervention in focal lesions and large coronary arteries.[2,5-7]

Since then, the growing use of stents in ever more complex lesions and patients[8,9] has stimulated the introduction of a rapidly increasing number of different stent design characteristics and catheter technology advances (rapid-exchange, flexible tips, increased retention, decreased dislodgement, etc.). Among the reasons why different stent characteristics and designs have been proposed is the concept of physiological mechanisms influencing outcomes; indeed, a primary concern of stent development is the need to reduce device profile and to increase flexibility to facilitate safer delivery and improve clinical performance.

In addition to the improvements in bare-metal stent (BMS) design, another clinical advance was the introduction of oral dual antiplatelet therapy (DAPT). Antiplatelet agents have almost eliminated the occurrence of acute and subacute stent thrombosis (ST), hours to weeks after stent deployment. ST can lead to significant clinical events (sudden cardiac death or acute MI).

Other important issues that have been improved upon with better stent designs are lesion coverage to minimise plaque prolapse; increasing radial support to prevent elastic recoil of the artery; and greater radiological visibility to precisely position stents. Furthermore, the possibility of easy access to side branches through the stent struts of a deployed stent in bifurcation lesions has become progressively more important.

First-generation stenting devices were made of stainless steel (BMS), and aimed to improve arterial restenosis over POBA. Still, 1-year post-procedure, these devices were associated with a residual risk of clinical restenosis as high as 20%, requiring target-lesion revascularisation (TLR).[2,6,10] The BMS design continued to advance with the use of alloy metals, allowing for thinner struts and greater flexibility while maintaining radial strength.

The Drug-Eluting Stent Revolution Starts

The high incidence of restenosis and the need for TLR, as well as further improving clinical benefit, were the stimuli for developing the drug-eluting stent (DES). The first DES had a polymer coating that served as the vehicle for delivery of an anti-restenotic drug, (e.g. the Cypher™ sirolimus-eluting stent [SES] and Taxus™ paclitaxel-eluting stent [PES] devices), which is slowly delivered over a few months following implantation. The first few generations of DES used a permanent or durable polymer coating that remained on the stent indefinitely, even though the entire drug was released from the polymer within a few months of stent deployment. The introduction of DESs further pushed the technology to a new level of patient care, through a combination of the increased understanding of the biology of restenosis, the selection of drugs that target one or more pathways in the restenotic process, controlled-release drug delivery strategies, and the use of the stent as a delivery platform.

Although first-generation DESs were demonstrated to be superior to BMSs with regards to the rates of recurrent MI, ST, and restenosis/TLR, their safety has been limited by suboptimal polymer biocompatibility, delayed stent re-endothelialisation contributing to late and very-late ST, initial spike or drug dumping, and local drug toxicity.[11-21]

Furthermore, durable polymer coatings used in first-generation DESs have been associated with mechanical complications (e.g. polymer delamination, weaved polymer surface leading to stent expansion) and non-uniform coating resulting in non-uniform drug distribution.[22]

Second-generation DESs including Xience™ (Abbott Vascular, IL, USA), an everolimus-releasing durable polymer cobalt-chromium (CoCr) DES which became the gold standard; Promus™ (Boston Scientific, Boston, MA, USA), an everolimus-eluting stent (EES); and Resolute™ (Medtronic Cardiovascular, Minneapolis, MN, USA), a zotarolimus-eluting stent (ZES) used a durable polymer coating that was more biocompatible, resulting in better re-endothelialisation and less inflammation but still carried the problem of an increasing rate of late and very-late restenosis and TLR.

Durable Polymer Coating Drug-Eluting Stents

As the stent is a foreign body not recognised by the blood, the most threatening acute complication of a stenting procedure is ST. This event has been reduced to <1–2% (compared to 5–7% in the first trials), due to the introduction of high-pressure deployment of the stent[23-25] and the use of DAPTs (aspirin and a thienopyridine), instead of aspirin and an oral anticoagulant.[24] It has been demonstrated that there are substantial differences in haemodynamic and wall rheological characteristics of implanted stents of different designs, and the 'hydrodynamic compatibility' of a stent is now recognised as an important feature of ideal stent design. In this setting, Gurbel et al.[26] recently demonstrated that stent design can also affect the degree of platelet activation; thus, ST may be higher with coil than tubular stents.

Moreover, after the initial vessel trauma with intimal and medial injury, permanent polymer coatings can generate focal chronic inflammation with cell infiltration and extracellular matrix remodelling, leading to neoatherosclerosis formation, a contributor to late (and very-late) post-procedure restenosis and/or ST, as demonstrated in animal and human pathological studies.[27-33] Therefore, the cardiology community has focussed its attention on safety, with the introduction of a stricter indication of DES use and prolonged DAPT (European Society of Cardiology [ESC]/European Association for Cardio-Thoracic Surgery [EACTS] guidelines recommend DAPT for 6–12 months with 162–325 mg acetylsalicylic acid plus a platelet $P2Y_{12}$ receptor inhibitor).[11,26,34-40]

The optimal duration of DAPT is, however, a controversial topic that has been debated in recent years.[41,42] Recently, Verdoia et al.[34] published a meta-analysis of 11 randomised trials, which suggested that 3–6 months of DAPT after second-generation DESs provided a reduction in mortality and major bleeding risk, but at the cost of a slightly increased risk of MI and ST; nevertheless, it was evaluated as the safest duration. Major concerns still remain with the observation of a higher incidence of very late ST (i.e. ST that occurs >12 months) in patients receiving a DES versus patients receiving a BMS.[27-33] Issues related to the increased incidence of very-late ST are late malapposition, incomplete strut coverage, and chronic inflammation. The mechanisms behind late ST seem to be multifactorial; factors including inappropriate stent deployment techniques and delayed or inadequate stent surface endothelialisation have been implicated.[43-46]

The challenge of ST could be addressed by applying an antiproliferative drug to the vascular smooth muscle cells activated by stenting and subsequent inflammation, rather than to the endothelial cells, which must proliferate. To that effect, the abluminal coating with sirolimus derivatives, which leaves the luminal side of the stent free from the drug and polymers, has been introduced in some of the latest DESs together with bioabsorbable polymers, e.g. poly(acid), as polymers could potentially cause chronic inflammation and subsequent endothelial dysfunction.[28,47,48]

The abluminal coating was designed to enhance re-endothelialisation, i.e. proliferation of endothelial cells, on the luminal surface of the stent, by preventing exposure of this surface to the antiproliferative drug. Accordingly, reduced late ST and better endothelial function of the DES-implanted artery employing the abluminal coating with sirolimus derivatives have been reported in both preclinical and clinical settings.[49-52] On the contrary, no significant differences in endothelialisation between the abluminal coating and the conventional full-surface coating of DESs have been reported.[53,54]

Recently, the results of the ODESSA trial confirmed this expectation. Among three different DESs; the

Cypher (SES), Taxus (PES), and Endeavor® (ZES); and the Liberté BMS, the ODESSA Trial observed the rate of uncovered struts and late malapposition after 6 months with optical coherence tomography (OCT). The results demonstrated a difference in the rate of uncovered struts and malapposed segments among different DESs and among DESs versus BMS (8.2%, 4.3%, 0.02%, and 0.9% for Cypher, Taxus, Endeavor, and BMS, respectively).[55]

Further Improved Safety: Thin Struts, Absorbable Polymers, Polymer Free, Bioresorbable Stents

In recent years, the focus of clinical research has not been limited to the composition, distribution, and thickness of the polymers. Improvement strategies have also focussed on the material, geometry, and thickness of the stent platforms, as well as the selection and dosage of antiproliferative agents. Stent platforms consisting of cobalt or CoCr instead of stainless steel allowed stent strut thickness to be reduced by more than half as compared with early-generation devices, all the while maintaining radial force and stent visibility. Thin-strutted BMSs have been associated with a reduced risk of restenosis.[56] Moreover, experimental data indicate a lower thrombogenicity, which may be related to more rapid endothelialisation compared with thick-strutted stent types.[57] Antiproliferative substances of the rapamycin family prevailed over paclitaxel in new-generation DESs and brought forth several limus analogues with comparable efficacy.[58]

Of note, the permanent polymers used in early-generation SES (polyethylene co-vinyl acetate/poly-n-butyl methacrylate) were modified with new-generation permanent polymer EESs (poly-n-butyl methacrylate/co-polymer of vinylidene fluoride and hexafluoropropylene). The combined effects of technological progress on different levels has translated into improved clinical outcomes, with elimination of previous concerns over very-late ST, while the anti-restenotic efficacy of early-generation DESs has been preserved: this constitutes the current standard of care. As a consequence, in recent years the focus of clinical research has been on the development of novel drug carrier systems, including thinner strut structures, absorbable (or biodegradable) polymer coatings and nonpolymeric stent surfaces.

The clinical need for bioresorbable or biodegradable DES devices was based on the fact that vessel scaffolding is only needed transiently.[59,60] The perspective of positive long-term outcomes for patients with no residual scaffold seemed appealing and led to the development of alternative fully bioresorbable devices such as the Absorb™ vascular scaffold (Absorb BVS, Abbott Vascular), a first-of-its-kind EES that is naturally resorbed and fully metabolised.[61-65] Additional improvements included the development of more modern platforms (e.g. better deliverability, radiopacity, flexibility, and radial strength) as well as the use of novel antiproliferative agents or reduced doses of currently approved antiproliferative drugs (Table 1).

The Drug-Eluting Stents Paradigm

Optimised drug delivery requires a combination of effective drug delivery technology and refined stent design. Stent-based drug delivery has been accomplished by three distinct mechanisms:

a) Bioabsorbable polymeric stents can be loaded with a drug that is eluted slowly over time
b) Metal stents can have a drug bound to their surface or embedded within macroscopic fenestrations or microscopic nanopores, thus providing more rapid drug delivery
c) Metal stents coated with an outer layer of polymer (bio-stable or bioabsorbable) can be drug-loaded; in turn, drug coating could be conformal (around the stent strut) or abluminal (only towards the arterial wall), thus providing more controlled and sustained drug delivery, which might allow more effective drug-tissue interactions

Moreover, the combination of highly refined stent designs and polymer coating materials has been the standard approach in several DES initiatives. In this regard, the novel combination of a biodegradable polymer with a thin-strut CoCr or platinum-chromium platform introduces a logical next step in the refinement of biodegradable polymer DES.

Limitations of Absorbable Polymer Coated Drug-Eluting Stents with Conventional (Amorphous) Drug Elution

The need for new DES advancements in percutaneous coronary interventions (PCI) to overcome late event occurrence, like late restenosis, stems from the fact that current drug elution profiles are a limitation of DES engineering characteristics.[64,66-68]

Table 1: Polymer type and stent strut thickness among different polymer coated drug-eluting stents (durable versus bioabsorbable) of second and third-generation.

	Brand name	Manufacturer	Material	Eluted drug	Polymer	Strut thickness (μm)	Distribution	Coat thickness
DURABLE	Xience	Abbott Vascular	CoCr	Everolimus	PVDF	81	Conformal	7–8 μm/side
	Promus	Boston Scientific	PtCr	Everolimus	PVDF	81	Conformal	7–8 μm/side
	Resolute	Medtronic Cardiovascular	CoNi	Zotarolimus	BioLINX	89	Conformal	6 μm/side
BIOABSORBABLE	Biomatrix	Biosensors International	316L	Biolimus A9	PLA	120	Abluminal	10 μm
	Nobori	Terumo	316L	Biolimus	PLA	125	Abluminal	20 μm
	Synergy	Boston Scientific	PtCr	Everolimus	PLGA	74	Abluminal	4 μm
	BioMime	Meril Life Sciences	CoCr	Sirolimus	PLLA+PLGA	65	Conformal	2 μm / 2 μm
	Ultimaster	Terumo	CoCr	Sirolimus	PLLA-CL	80	Abluminal	15 μm
	Orsiro	Biotronik	CoCr	Sirolimus	PLLA	61	Conformal	3.5 μm / 7.5 μm
	MiStent	Stentys	CoCr	Sirolimus	PLGA	64	Conformal	5 μm / 15 μm

316L: 316L stainless steel; BioLINX: C10, C19, and polyvinylpyrrolidone; CoCr: cobalt chromium; CoNi: cobalt nickel; PLA: poly-D/L-lactic acid; PLGA: polylactic-co-glycolic acid; PLLA: poly(L-lactide); PLLA-CL: poly(L-lactide-co-caprolactone); PVDF: poly(vinylidene fluoride); PtCr: platinum chromium.

The latest advances in DES technology have been mainly focussed on stent material, strut thickness, or polymer development because, until recently, technological limitations prevented the optimisation of the drug elution profile. Most manufacturing techniques for DES production involve the use of solutes to apply the drug to the polymer/stent, leaving the drug in an amorphous or aqueous form. This process limits the margin of control over the elution profile, which is mainly dependent on diffusion of the drug along a concentration gradient. As a consequence, the distribution profile of the drug consists of an uncontrolled initial burst, which in turn may contribute to delayed healing and possibly late adverse events.[69-71]

This rapid drug burst quickly overwhelms smooth muscle cell receptors, followed by a rapid clearing of the drug due to systemic loss. Therefore, there is a limited therapeutic benefit for the amount of drug released in this initial burst. Because the polymer is the vehicle for the drug release, the polymer is required to elute the remainder of the drug. At a certain point the tissue drug level will drop beneath the therapeutic level and have no effect. However, the polymer will continue to reside for an extended period of time, which leaves the vessel vulnerable to its negative effects.

Moreover, the drug elution profile of conventional DES decays with a logarithmic-type pattern, and is relatively short. Lengthening the elution period would require an increase in the total drug load, with a significant increase of the initial burst of the drug. This may reach toxic levels,[69-72] which may in turn promote delayed strut coverage, consequently increasing late and very-late ST with necessity of extended DAPT.

ABSORBABLE POLYMER IN LATEST GENERATION DRUG-ELUTING STENTS: IS THERE ROOM TO IMPROVE CLINICAL OUTCOMES?

Crystalline Drug Form Breaks the Relationship Between Polymer Presence and Drug Elution

A new manufacturing technique seems to have overcome this limitation and led to the development of a novel system. The MiStent SES Sirolimus Eluting Absorbable Polymer Coronary Stent System (Stentys/Micell Technologies, Durham, NC, USA) is a balloon-expandable stent that received Conformité-Européenne (CE)-marking in 2010 for the treatment of CAD. MiStent SES is a CoCr alloy stent platform with very thin 64 μm struts (one of the thinner struts currently present

in the European market), based on the Eurocor (CE-marked) Genius MAGIC® CoCr Coronary Stent System. The main innovation of MiStent SES is that this device includes a coating made of polylactide-co-glycolic acid (PLGA; a fully bioabsorbable polymer) delivering sirolimus in a crystalline form. A patented, supercritical fluid technology allows a rigorously controlled drug and polymer coating to be applied to this BMS.

Possible Advantages of MiStent Sirolimus-Eluting Stents in Terms of Efficacy and Safety Outcomes

Optimising the Drug Elution Profile: Fast Polymer Absorption with Sustained Slow Drug Release

The innovative coating technology allows for encapsulation of sirolimus as tiny crystals. This crystalline form is responsible for a precise and consistent drug elution profile: as the polymer softens and disperses from the stent struts into the adjacent tissue, the crystals are slowly released and deposited in the tissue surrounding the stent (Figure 1). The rate of elution is independent of the polymer coating. Rather, it is dependent on the dissolution of the crystal and then diffusion along a gradient, eliminating the initial uncontrolled burst of the drug observed in other DESs.

The drug elution profile is gradual, near linear, and much longer compared with other DESs. The controlled and sustained release of therapeutic concentrations of the drug provides a continued local antiproliferative and anti-inflammatory effect for several months, thus reducing vessel over-scarring and inflammation. In this respect, data from the DESSOLVE II Study demonstrate that vessel healing is similar to that obtained with other contemporary DESs, with no paradoxical vasoconstriction effect after acetylcholine injection.[73] Moreover, in this study, the OCT control subgroup reported an almost complete percentage of strut coverage as early as 4 months after MiStent implantation, thus suggesting an optimal re-endothelialisation rate and absence of toxicity due to the presence of a high initial burst dose of drug, as seen with earlier generation DESs.

According to preclinical studies, the PLGA/sirolimus coating is cleared from the stent in 45–60 days, and absorbed into the tissue within 90 days, leaving a BMS.[74] PLGA is completely absorbed into the surrounding tissue within 3 months of implantation to promote fast vessel healing, long-term patency, and compatibility with the artery, while allowing for drug elution to continue beyond its absorption. In addition, the fast polymer absorption characteristic limits polymer exposure duration, thereby reducing some safety risks associated with currently available DES technologies.

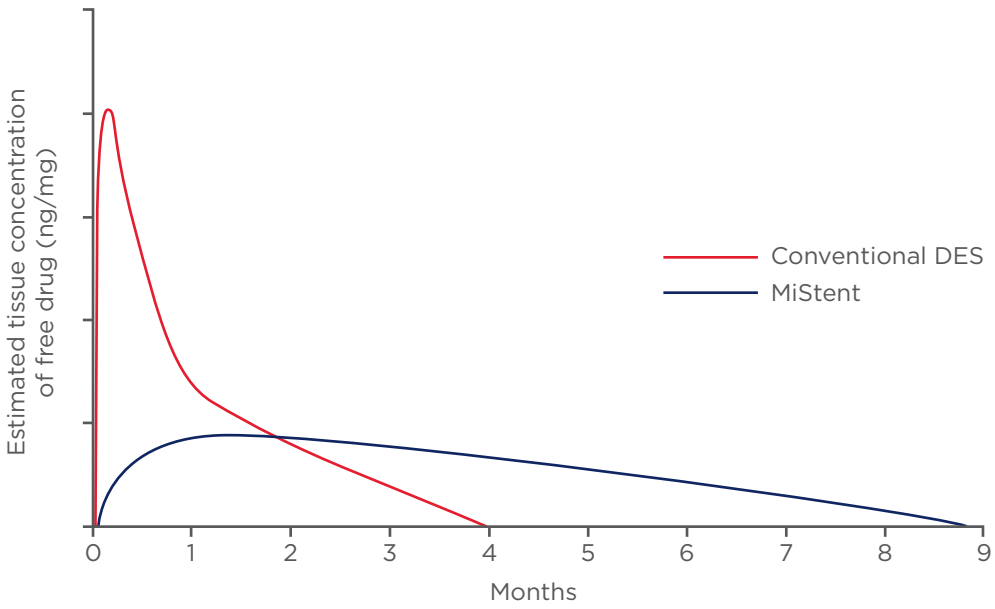

Figure 1: Crystalline sirolimus allows for a gradual, linear, and long-term elution profile targeted to minimise the long-term hyperplastic response of the vessel.
Stentys, data on file.
DES: drug-eluting stent.

Crystalline sirolimus remains in the tissue and continues to elute and maintain therapeutic levels of the drug into the surrounding tissue for up to 9 months. This long-term delivery of the drug is a unique feature which inhibits vessel restenosis.[74,75] Preclinical and early clinical data seem to suggest that this controlled elution profile may be beneficial over the long-term and translate into clinical benefits by slowing the progression of late lumen loss (LLL) and preventing the TLR catch-up phenomena.[74,75]

Safety

The MiStent SES may also offer a safety benefit, as the polymer absorption occurs within 3 months thereby limiting the duration of polymer exposure, and therapeutic levels of sirolimus persist beyond the presence of polymer, further limiting inflammation. This characteristic is not currently available in other DESs and should increase the safety profile of such stents even with short DAPT. However, this hypothesis should be proven in powered randomised clinical trials.

CLINICAL EXPERIENCE ON MISTENT SIROLIMUS-ELUTING STENTS

DESSOLVE I and DESSOLVE II Clinical Trials

In the DESSOLVE I and II Trials, patients with discrete *de novo* lesions in native coronary arteries were enrolled and followed for clinical events at predefined intervals. The 4-year clinical follow-up from these two studies were recently presented and demonstrate the long-term efficacy and safety of this device. All available patients are currently undergoing long-term follow-up.

DESSOLVE I

The DESSOLVE I Trial was the first clinical evaluation of the safety and efficacy of the MiStent SES, and was conducted in 30 patients with lesions ranging from 2.5–3.5 mm in diameter and amenable to treatment with a ≤23 mm long stent. Subjects were enrolled across five study centres in New Zealand, Australia, and Belgium.[76] Three independent subgroups of 10 patients were each evaluated using angiography, intravascular ultrasound (IVUS), and OCT at three time points post-treatment: 4, 6, and 8 months with all available patients returning at 18 months. The primary efficacy endpoint was in-stent LLL. Safety was assessed by incidence of major adverse cardiovascular events (MACE) and presence of strut coverage with tissue within the treated artery at each time point.

At 4, 6, 8, and 18 months of follow-up, the MiStent SES was associated with a low and stable in-stent LLL (4 months, median 0.03 mm, range: -0.22–0.21 mm; 6 months, median 0.10 mm, range: -0.03–1.20 mm; 8 months, median 0.08 mm, range: -0.01–0.28 mm; 18 months, median 0.08 mm, range: -0.30–0.46 mm). In all 30 patients, the small mean±SD in-stent LLL up to 8 months of 0.1±0.2 mm (95% confidence interval: 0.04–0.5 mm), demonstrated stent efficacy.

At OCT examination, the proportion of uncovered stent struts decreased from a median of 7.3% (range: 0.4–46.3%) at 4 months to 0% (range: 0.0–3.4%) at 18 months. The percentage of neointimal volume obstruction as evaluated by IVUS increased from a median of 5.3% to 9.1% between 4 and 6 months and remained nearly unchanged thereafter through to 18 months. An evaluation of the safety outcomes at 3 years was published for DESSOLVE I. At this time point, there were no target-vessel MACE for MiStent SESs. Two non-target-vessel non-Q-wave MIs were reported. In addition, there was no evidence of ST or TLR.[77,78]

At the 27th Annual Transcatheter Cardiovascular Therapeutics (TCT) Conference held in San Francisco in October 2015, 4-year safety outcomes were consistent with previous clinical findings, with no target-lesion failure (TLF), no target-vessel MACE, and no ST. Two non-target-vessel non-Q-wave MIs were reported as before, along with one target-vessel revascularisation (TVR), non-TLR at 1,280 days.[79,80]

DESSOLVE II

The DESSOLVE II CE-mark Trial was a randomised (2:1), multicentre, superiority study conducted in 184 patients from 26 sites in Europe and New Zealand, with documented stable or unstable angina pectoris.[73] The primary endpoint was superiority of the MiStent SES in minimising in-stent LLL at 9 months, versus Medtronic's Endeavor Sprint DES (delivering zotarolimus). LLL was measured by an independent angiography core laboratory in *de novo* coronary lesions from vessels ranging from 2.5–3.5 mm in diameter and amenable to treatment with a ≤30 mm long stent.

DESSOLVE II met all study objectives, as the MiStent SES demonstrated a competitive in-stent

LLL, with a mean in-stent LLL of 0.27±0.46 mm in 103 MiStent SES patients versus 0.58±0.41 mm in 52 Endeavor patients (p<0.001, Figure 2). The MiStent SES achieved a strong safety signal, as the proportion of uncovered stent struts by OCT at 9 months was very low in both groups (MiStent, 0.3% versus Endeavor, 0.0%; Figure 3). The mean neointimal thickness of covered struts (p=0.002) and percent net volume obstruction (p≤0.003) were significantly lower in the MiStent SES group than in the Endeavor group. MACE and ST rates were low and comparable between groups.[73]

Safety outcomes at 2 years were subsequently published and further supported clinical implementation with low event rates, as evidenced by a 6.7% MACE rate for the MiStent SES versus 11.7% for Endeavor (p=0.129).[77,81] There was no definite or probable ST for the MiStent SES (versus 1.7% with Endeavor), while the TLR rate was identical with both devices (1.7%). At 3 years, rates of MACE for MiStent and Endeavor were 8.3% versus 15.3% (p=0.197), respectively; TLR and MI rates for the MiStent SES and Endeavor stent were 2.5% and 3.4% (p=0.665) and 3.3% and 5.1% (p=0.686), respectively.[82]

The updated 4-year results of DESSOLVE II presented by Dr Alexandra Lansky at TCT 2015 confirmed the safety profile of the MiStent SES with low event rates, as evidenced by a 13.3% MACE rate for MiStent SES (n=118) versus 20.3% for Endeavor (n=59), and this difference was mainly driven by TVR rates (4.3% versus 10.2% for MiStent SES and Endeavor, respectively). There was no definite/probable ST for the MiStent SES (1.7% with Endeavor).[80]

Retrospective Cross-Study Propensity Analysis

In a late-breaking clinical trial session presented at the 2015 European Association of Percutaneous Cardiovascular Interventions (EuroPCR) congress, Dr Lansky presented the results from a retrospective cross-study propensity analysis comparing the MiStent SES to Abbott's Xience V stent, the market leader.[83] The results were subsequently published in the American Journal of Cardiology in February 2016.[84] The objective of this study was to compare the clinical outcomes of both devices at 1 and 3 years post-implantation. A retrospective, patient level, propensity-matched analysis was conducted comparing data from the DESSOLVE I and II studies to the Xience V arm of the ISAR-TEST-4 study with pre-specified baseline and lesion characteristics. As all three studies used very similar event definitions, clinical and angiographic endpoints were compared between treatment groups in the matched cohort.

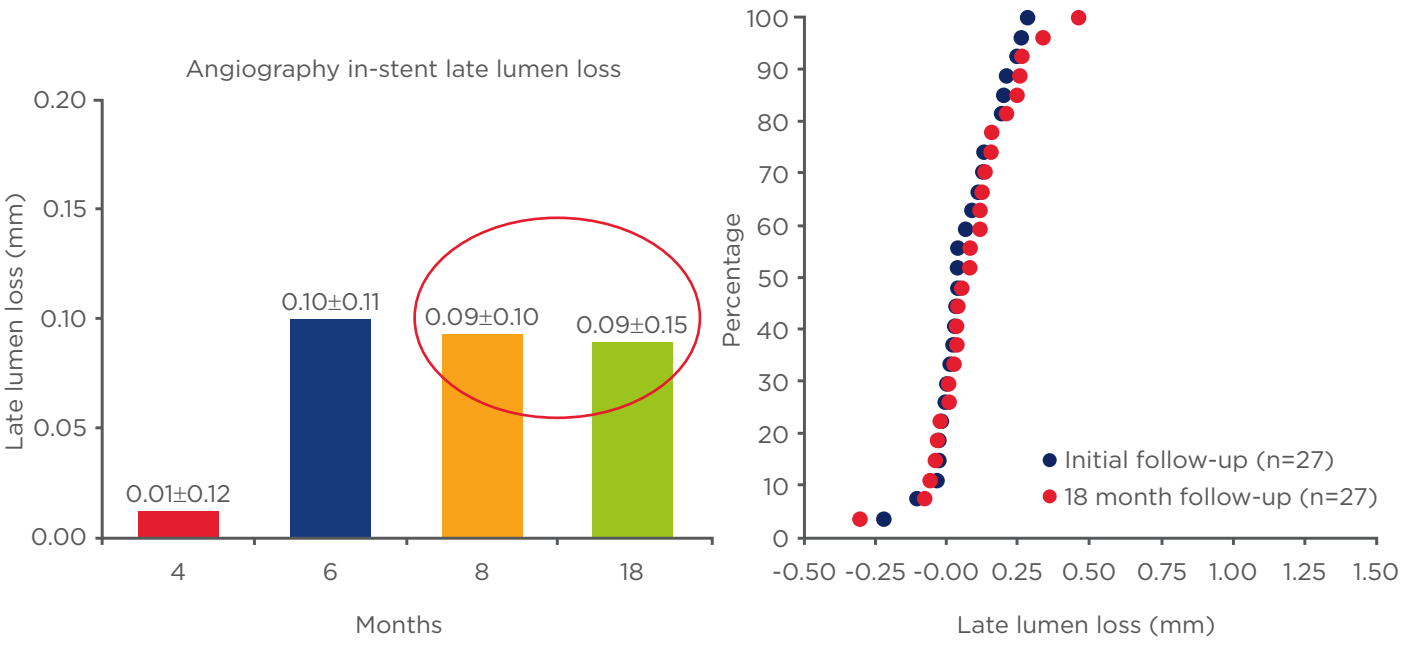

Figure 2: Cummulative distribution curves of the In-stent late lumen loss for MiStent between matched cases during study course.[88,89]

Data represents matched cases for each time point with serial 3D analysis.
4 months, n=9; 6 months, n=9; 8 months, n=9; 18 months, n=27.

Median	4-month group	6-month group	8-month group	18-month group
Strut coverage (%)	93	97	96	100

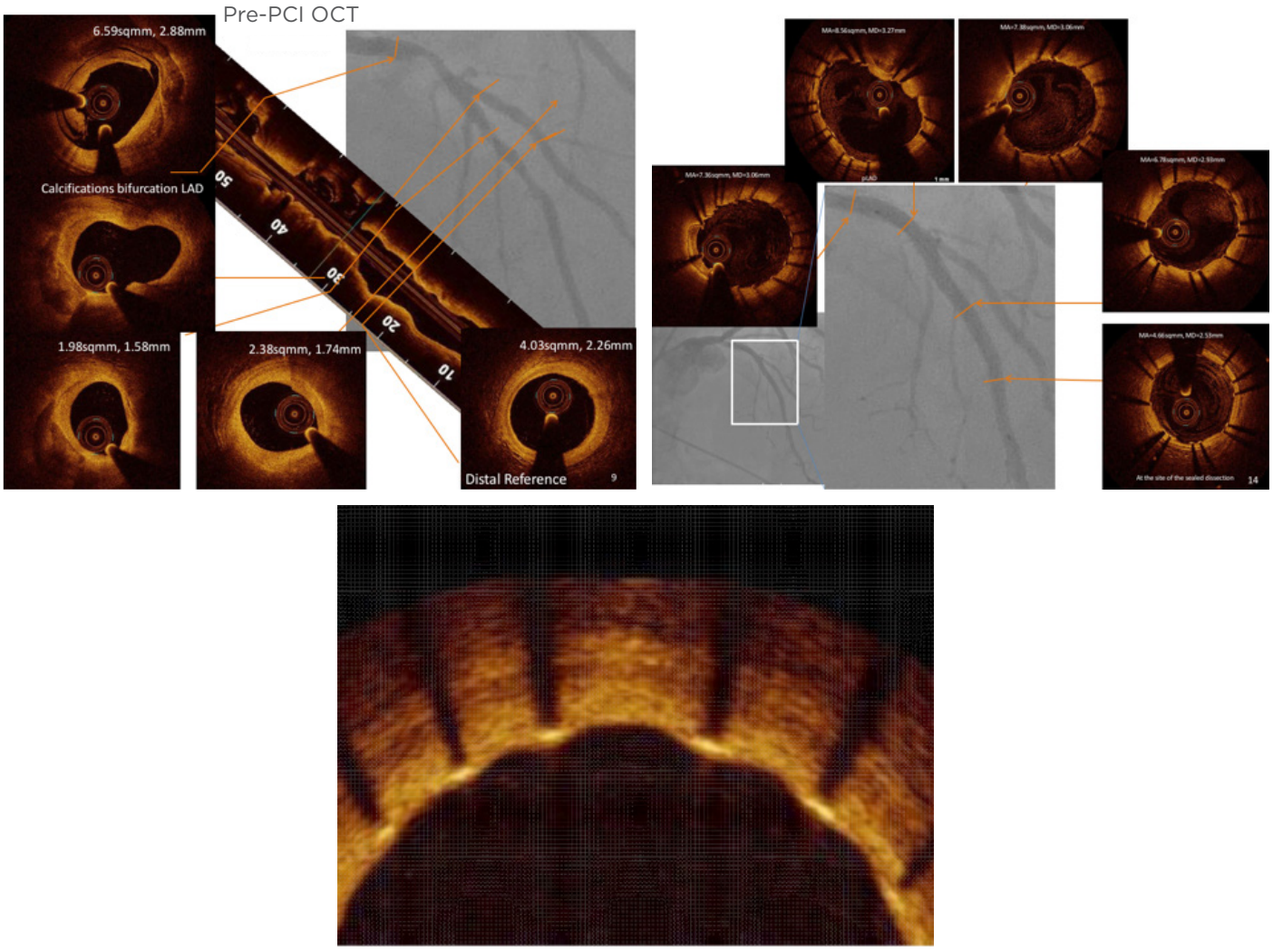

Figure 3: Case example from the DESSOLVE II study.[76,88]

Table indicates the median percentage of strut coverage during the study time intervals. Figure shows the OCT pre-PCI (left panel) with a complex plaque in the proximal and middle segment of the LAD, which was stented with two MiStents in overlapping (right panel). OCT result at 6 months is shown in the lower magnified insert.

LAD: left anterior descending artery; OCT: optical coherence tomography; PCI: percutaneous coronary intervention.

Table 2: Propensity-matched analysis between the MiStent sirolimus-eluting stent and the Xience V devices.[83,84]

	MiStent SES (%; n=102)	Xience V (%; n=102)	p-value
TLF: 1 Year	3.0	8.0	0.08
TLF: 3 Year	5.0	12.5	0.07
TLR: 1 Year	1.0	6.0	0.05
TLR: 3 Year	2.0	8.4	0.04

TLF: target-lesion failure; TLR: target-lesion revascularisation; SES: sirolimus eluting stent.

The primary endpoint was TLF at 1 and 3 years. More than 800 patients (MiStent, n=153 and Xience, n=652) were included, with propensity matching in 204 patients (MiStent and Xience, n=102 each). The analysis demonstrated statistically significant reduced TLR rates at 1 and 3 years for the MiStent SES, as compared with the Xience V DES (Table 2).

At 3 years, there was no significant difference in target-vessel MI (MiStent 2.0% versus Xience 3.1%, p=0.34), and there were no additional late or very-late ST in either group. These results suggest that the improved device design characteristics translated into clinical benefits in the targeted patient populations.

CURRENTLY ONGOING STUDIES

DESSOLVE III Post-Market Clinical Trial

As the DESSOLVE II Study was not powered to compare clinical outcomes between the MiStent SES and Endeavor, a larger study was initiated. DESSOLVE III is a landmark prospective, balanced, randomised, controlled, single-blind, multicentre clinical study comparing MiStent SES to Xience.[85] Patient enrolment (1,400 'real-world all-comers' patients from 20 hospitals throughout Europe) was completed in December 2015, with early results expected in the first half of 2017.[86] Patients in the trial suffered from symptomatic CAD, including those with chronic stable angina, silent ischaemia, or ACS, and qualified for PCI.

The primary endpoint is a non-inferiority comparison of a device-oriented composite endpoint or TLF of the MiStent SES group versus the Xience group at 12 months post-procedure. This trial will also include a sub-study on the OCT evaluation of 60 patients (30 assigned to each treatment group), in order to explore volume obstruction and frequency of neoatheroma formation over time (assessments at 6 and 24 months post-treatment).

DESSOLVE C Clinical Trial

DESSOLVE C is a prospective, randomised, controlled, single blind, multicentre clinical trial comparing the MiStent SES to the Tivoli™ stent. The study is currently enrolling in China at approximately 18 clinical sites. The enrolment is expected to include approximately 428 patients with symptomatic CAD, including those with chronic stable angina, silent ischaemia, and ACS who qualify for PCI.[87] Patients will be randomised to the MiStent SES or the Tivoli® device (a bioabsorbable polymer-based SES [Essen Technology Company, Beijing, China]). The primary endpoints will be the 9-month in-stent angiographic LLL along with 12-month clinical outcomes between both devices.

CONCLUSIONS

Numerous new and exciting trends are leading to a variety of improved DES platforms. The ideal DES has not been determined, but will most likely incorporate a number of new and improved materials and delivery mechanisms to further enhance safety, efficacy, and cost efficiency. Among those characteristics, the development of crystalline forms of anti-restenotic drugs combined with a thin strut BMS and fast absorbing polymer coating for stent implantation could truly be game changing due to improved elution pharmacokinetic profile, decreased local toxicity, and improved long-term biologic arterial wall response.

In this setting, the MiStent SES could be the driver for a new class of DES associated with meaningful clinical and safety outcomes, building on the successive revolutions and innovations in PCI over the last four decades.

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TWO-STENT STRATEGY? WHICH ONE TO CHOOSE? FIRST CASE EXAMPLE

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ABSTRACT

Optimal treatment of bifurcation lesions is still a major challenge for coronary intervention. A planned two-stent approach may be more appropriate when both the parent vessel and side branch (SB) are large, and when there is significant disease distal to the ostium of a SB that arises from the main vessel at a shallow angle.

A simple, provisional stenting approach that is associated with shorter fluoroscopy time, lower incidence of periprocedural myocardial infarction, and similar rates of target-vessel revascularisation compared with a routine two-stent strategy is needed. The combination of a biovascular scaffold and drug-eluting stent implantation as a two-stent technique using a 'mini-crush' technique is a safe, feasible, effective, and durable treatment option for patients with true bifurcation disease. Patient selection for complex stenting requires accurate lesion evaluation. Our current institutional recommendations are to use provisional stenting in the majority of cases, but if a planned two-stent approach is required, we recommend the use of imaging methods, plaque modification before stent implantation, final kissing balloon, and proximal optimisation inflation technique to achieve good final results.

Keywords: Stent, coronary artery disease, angiography, bifurcation, two-stent technique.

INTRODUCTION

Optimal treatment of bifurcation lesions is still a major challenge for coronary intervention. Important factors such as anatomic variation, angulation between branches, downstream territory, and extent of plaque burden should be taken into consideration when addressing a bifurcation lesion, to choose the most appropriate approach and achieve the optimal result. A planned two-stent approach might be more appropriate when both the parent vessel and side branch (SB) are large. This mainly occurs when there is significant disease distal to the ostium of a SB, that arises from the main vessel, at a shallow angle.

Nevertheless, there is still a need to try simple, provisional stenting approaches that are associated with shorter fluoroscopy time, lower incidence of periprocedural myocardial infarction, and similar rates of target-vessel revascularisation compared with a routine two-stent strategy.[1] A meta-analysis of previous randomised studies demonstrated that a provisional one-stent approach was comparable to a two-stent approach in terms of mortality, repeat revascularisation, and quality of life.[2] The one-stent technique was superior to the two-stent technique in terms of risk of periprocedural myocardial infarction, however the two-stent technique is still a viable option in patients with complex true bifurcation lesions.[3] In randomised studies comparing one-stent techniques with two-stent techniques, the two-stent approach was used in between 4% and 31% of all cases.[1]

Before making a decision on whether to treat a bifurcation lesion with two-stent strategies several questions must be answered:

- How large is the SB? (Diameter, vessel length, and myocardial territory supplied)
- Is the SB ostium diseased? If yes, what is the severity and length of the lesion?

- Is there severe disease in the SB beyond the ostium?
- What is the angle of the SB take-off? Is it difficult to wire/rewire?
- What is the severity and distribution of the main branch (MB) lesion?
- What will happen to the SB after MB stenting (mild or significant compromise or occlusion)?
- What are the clinical consequences of SB occlusion? (dependent on the territory supplied)[4]

The European Bifurcation Club (EBC) consensus from the first 10 years of meetings regarding planned two-stent strategy recommends that the main vessel should be stented first in most cases. However, when the SB is particularly difficult to access, there is dissection after pre-dilatation in the SB, or downstream stenosis is stented, then the SB can be considered for stenting first. For the two-stent method, final kissing balloon (FKB) dilatation is mandatory, as well as using moderate pressure.[5] Drug-eluting stents are recommended for bifurcation treatment. The main vessel stent should be sized according to the distal main vessel reference diameter and should achieve adequate stent apposition in the proximal main vessel by the proximal optimisation technique (POT).[6] The bifurcation treatment technique classification, proposed by the EBC, was based on two principles: the final position of the stent(s) in the bifurcation and the implantation order. There are four strategies designated by the MADS (main, across, distal, side) classification system. 'M' begins with a stent in the proximal main segment. 'A' begins with a stent in the main vessel across the SB. 'D' defines a double stent implantation, whether simultaneous or not. In an aborted form, a stent and a balloon are at the ostium of the two distal branches, with a slight protrusion (V-stenting), or a long new carina. 'S' consists of a stent implantation beginning in the SB, with or without protrusion (short or long). After implantation of the first stent(s), further stents can be implanted using different techniques. No wire or balloon manoeuvres are described in MADS, such as SB protection by wire or balloon, or different ways to crush an SB stent (kissing, balloon crush, double kissing [DK] crush, etc.).[7] A variety of two-stent techniques can be performed and because of a lack of studies on the comparative outcomes of diverse two-stent techniques, selection of bifurcation treatment approach should be based on a patient's clinical condition, bifurcation morphology, the operator skills, and preferred choice.

From dedicated two-stent techniques we know that:

- T stenting techniques can be performed in many variations (modified T stenting, reverse T stenting, and T stenting and protrusion). The technique is appropriate for bifurcations near to 90°
- The culotte technique regained popularity in the drug-eluting stent (DES) era. The EBC recommends a 'mini-culotte' to reduce the proximity of a double layer of stent struts as much as possible. This technique could be used in almost all bifurcation lesions
- The main advantage of the crush technique is that the patency of both branches is ensured during procedure. This can be used in almost all bifurcation lesions. There are some modifications of the crush technique ('mini-crush' technique, step-crush technique, reverse-crush technique, DK crush technique). Rates of successful kissing balloon inflation in crush stenting are 75–90%, which is lower than for culotte stenting. In cases of technique change during procedure it is impossible to crossover from provisional stenting to crush stenting[8]
- Either the V-stenting or simultaneous kissing stenting technique can be used for bifurcations in the large proximal main vessel. These are not frequently used due to relatively unfavourable angiographic and clinical outcomes and are not recommended as a routine two-stent technique[9]

PATIENT CASE EXAMPLE

Our case report using the two-stent bifurcation treatment approach was based on our single-centre design to treat bifurcation lesions with a 'keep it simple, swift, and safe' (KISSS) principle. Where possible we look to incorporate a bioresorbable vascular scaffold (BVS) into our two-stent technique as subsequently this will be absorbed leaving just one stent *in situ.*

The patient was a 65-year-old man with persisting Grade II–III stable angina for a period of 6 months. His past medical history includes hypertension, active smoking, peripheral vascular disease with claudication, and well controlled dyslipidaemia. Angiographic images demonstrated a critical true bifurcation lesion in the left

circumflex (LCX) artery and first obtuse marginal (OM1) branch. LCX was the MB and OM1 was the SB. Medina classification was 1,1,1; this was confirmed by intravascular ultrasound (IVUS) (Figure 1). After careful lesion analysis using IVUS and optical coherence tomography (OCT) data for both branches, the bifurcation type was clear and it was possible to plan a treatment strategy according to the patient's vessel plaque morphology. In this case OM1 was suitable for stenting as the disease extended from the SB ostium >5 mm. We decided to treat this bifurcation lesion with the mini-crush two-stent technique using the newest generation DES in the MB (LCX), and a BVS in the SB (OM1).

Using the 7 Fr Launcher® coronary guide catheter (Medtronic, Minneapolis, MN), both branches were wired with soft-tip wires. IVUS and OCT pre-percutaneous coronary intervention images confirmed that mixed plaque was present, along with the presence of heavy calcification.

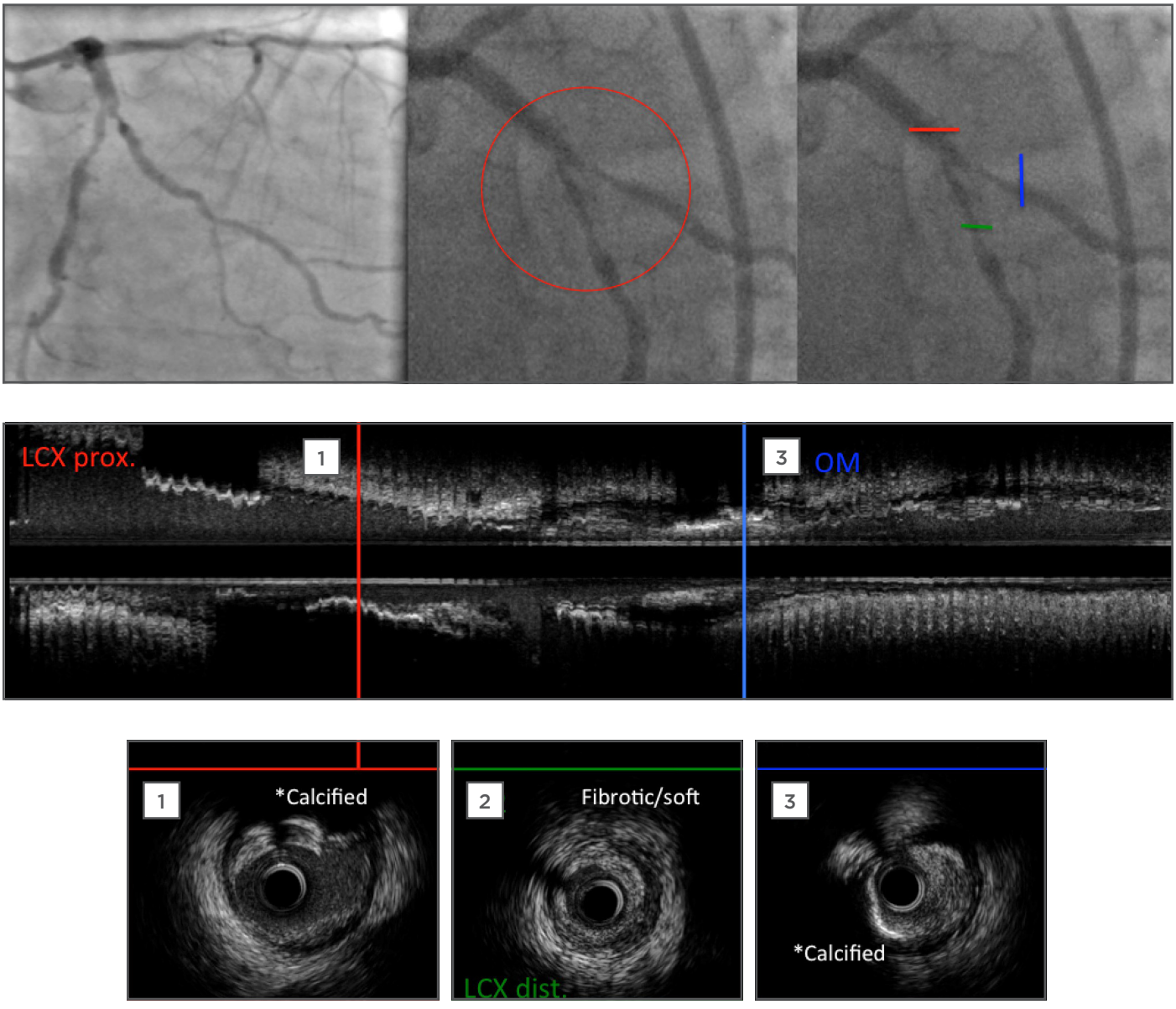

Figure 1: Pre-percutaneous coronary intervention angiographic images and intravascular ultrasound (IVUS) pullback.

Angiographic images show a diffuse coronary artery sclerosis with severe bifurcation stenosis in LCX/OM1. IVUS pullback confirmed a calcified plaque in proximal LCX (MB) and fibrotic/soft plaque in distal part. Proximal LCX mean lumen area is 4.98 mm^2. Distal LCX lumen area is 2.68 mm^2. OM1 branch (SB) is calcified too with lumen area 2.47 mm^2. SB ostial disease extended >5 mm length.
LCX: left circumflex artery; OM1: first obtuse marginal branch; MB: main branch; SB: side branch.

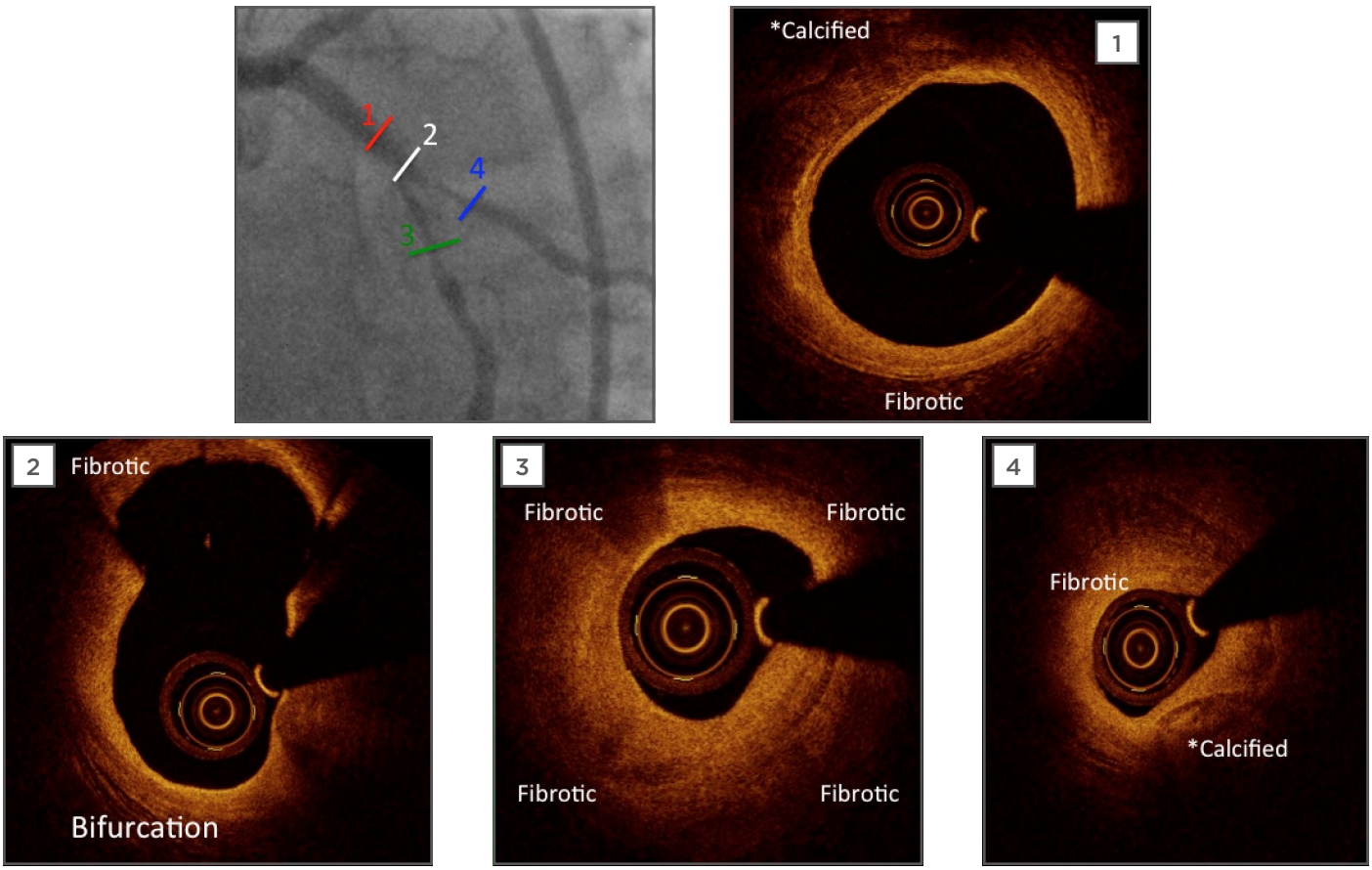

Figure 2: Pre-percutaneous coronary artery optimal coherence tomography imaging.
OCT confirmed calcified and fibrotic plaque composition in MB (1,2,3) and SB (4).
OCT: optimal coherence tomography; MB: main branch; SB: side branch.

We began with thorough lesion preparation because the treatment would involve a novel technique, using IVUS-guided cutting balloon plaque modification in both branches. The next step after pretreatment was BVS implantation in the SB (OM1), following DES implantation in the MB (LCX) using a mini-crush technique, and ending with kissing and POT. The percutaneous coronary intervention result was evaluated using IVUS and OCT.

Mini-Crush Stenting

First it is important that the lesion and affected vessels are suitable for this technique. Angulation between the vessels should be <60° and the diameter of the two branches should be similar. The guiding catheter should be suitable for the insertion of two stents. From the beginning, both branches need to be wired and pre-dilated if required. Pre-dilatation of the SB origin before MB stenting has the potential to maintain SB thrombolysis in myocardial infarction flow and access to the SB after MB stenting. After this, both stents need to be advanced. The MB stent should be positioned proximally and the SB stent should protrude only minimally into MB. The SB stent can then be deployed, following which, the result of the stent implantation should be checked. If optimal, the stent system balloon and the wire from SB can be removed; the MB stent can then be deployed, crushing the SB stent. After this you will need to rewire branches and conduct a high pressure post-dilatation in the SB and finally, a kissing dilatation for both branches. DK crush modification may aid rewiring of the SB after MB stenting.[5]

The standard crush and mini-crush techniques require use of a 7 or 8 Fr guiding catheter. Operators who prefer smaller diameter guiding catheters can choose modified crush techniques:

- Step-crush: This is suitable for use with a 6 Fr guiding catheter and can be modified by the balloon crush technique. The result of this technique is identical to that obtained with the standard crush technique, except that each stent is advanced and deployed separately[10]

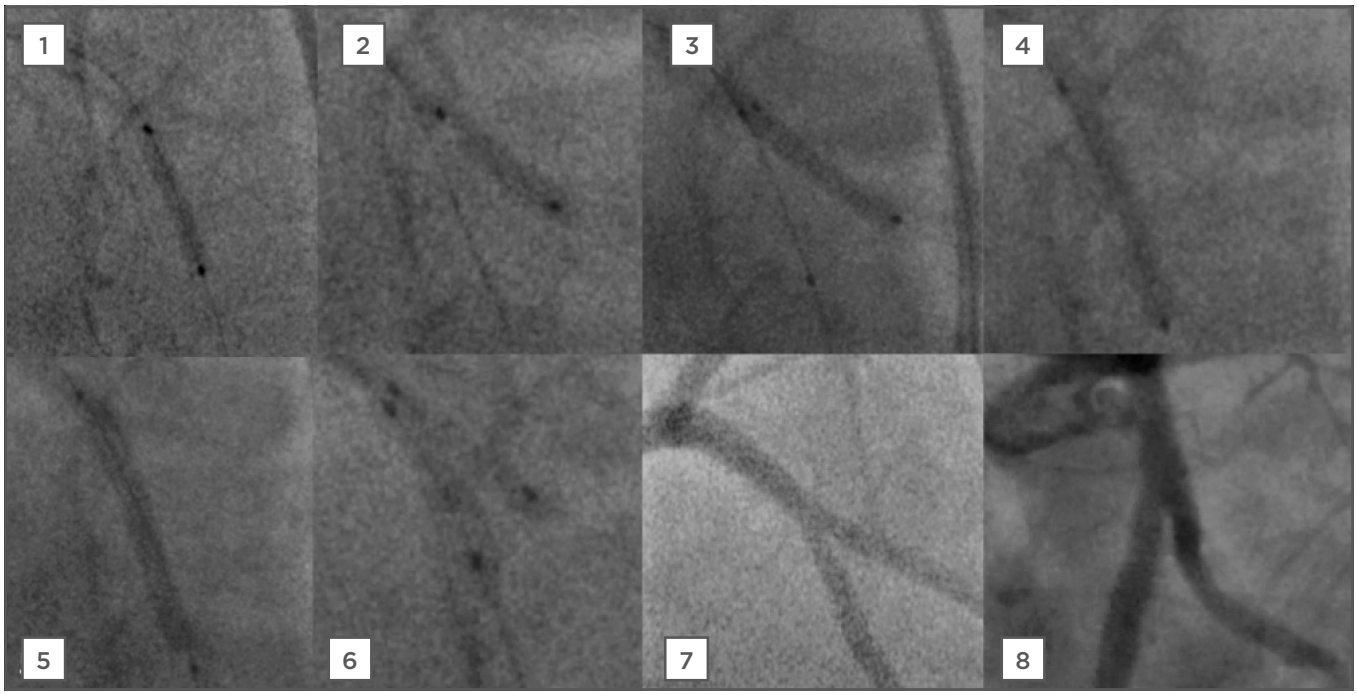

Figure 3: Percutaneous coronary intervention steps for elective mini-crush stenting with a drug-eluting stent and bioresorbable vascular scaffold.
1) LCX (MB) plaque modification with cutting balloon (3.25x15 mm, 4,5,6 bar).
2) OM1 (SB) plaque modification with cutting balloon (3.0x10 mm, 4,5,6 bar).
3) BVS implantation in SB (Absorb 3.0x18 mm, 11 bar) following by NC balloon post-dilatation 3.25x15 mm.
4) SC balloon dilatation in MB mini-crush (3.0x15 mm, 18 bar).
5) DES implantation in MB (Synergy 3.5x28 mm, 7 bar), following NC balloon post-dilatation 3.5x15 mm.
6) Final kissing with 2 SC balloons (3.0x12 mm, 8 bar).
7) and 8) Final images after PCI.
LCX: left circumflex artery; MB: main branch; OM1: first obtuse marginal branch; SB: side branch; DES: drug-eluting stent; NC: non-compliant; SC: semi-compliant; PCI: percutaneous coronary intervention.

- Reverse or internal crush: This is an option in the setting of provisional SB stenting and can be performed through a 6 Fr guide catheter, however this technique shares the same disadvantages as the standard crush technique but with more technical steps[11]
- DK crush technique: This is a modification of the step-crush procedure in which a balloon kissing inflation is performed twice, the first after a MB balloon crushes the SB stent, followed by the standard final kissing inflation at the end of the procedure. The DK crush technique therefore consists of five steps: SB stenting, balloon crush, first kissing, MB stenting and crushing, and final kissing. DK crush may result in less stent distortion, improved stent apposition, and facilitate final kissing inflation[12]

In our patient's case Figure 2 demonstrates the procedural steps of bifurcation angioplasty. The final result of bifurcation treatment in the mini-crush approach is seen in Figure 3, where OCT images show excellent SB ostial coverage and neocarina formation. Figure 4 demonstrates the 1-year angiographic follow-up without signs of angiographic stent restenosis.

The feasibility of using the BVS in bifurcation lesions is still under investigation but so far, the results seem promising. BVS technology has some technical limitations to its use in bifurcation lesions, such as the risk of strut fracture.[13] Dzavík and Colombo[14] published bench testing in a synthetic arterial bifurcation model with T stenting, crush, and culotte procedures using a BVS. In crush cases, they could easily recross the crushed BVS with the wire and balloon and achieve good results after deployment of the main vessel BVS and FKB inflation. They concluded that in narrower angle bifurcations, a mini-step crush or culotte technique should be considered, deploying a metal DES in the SB.

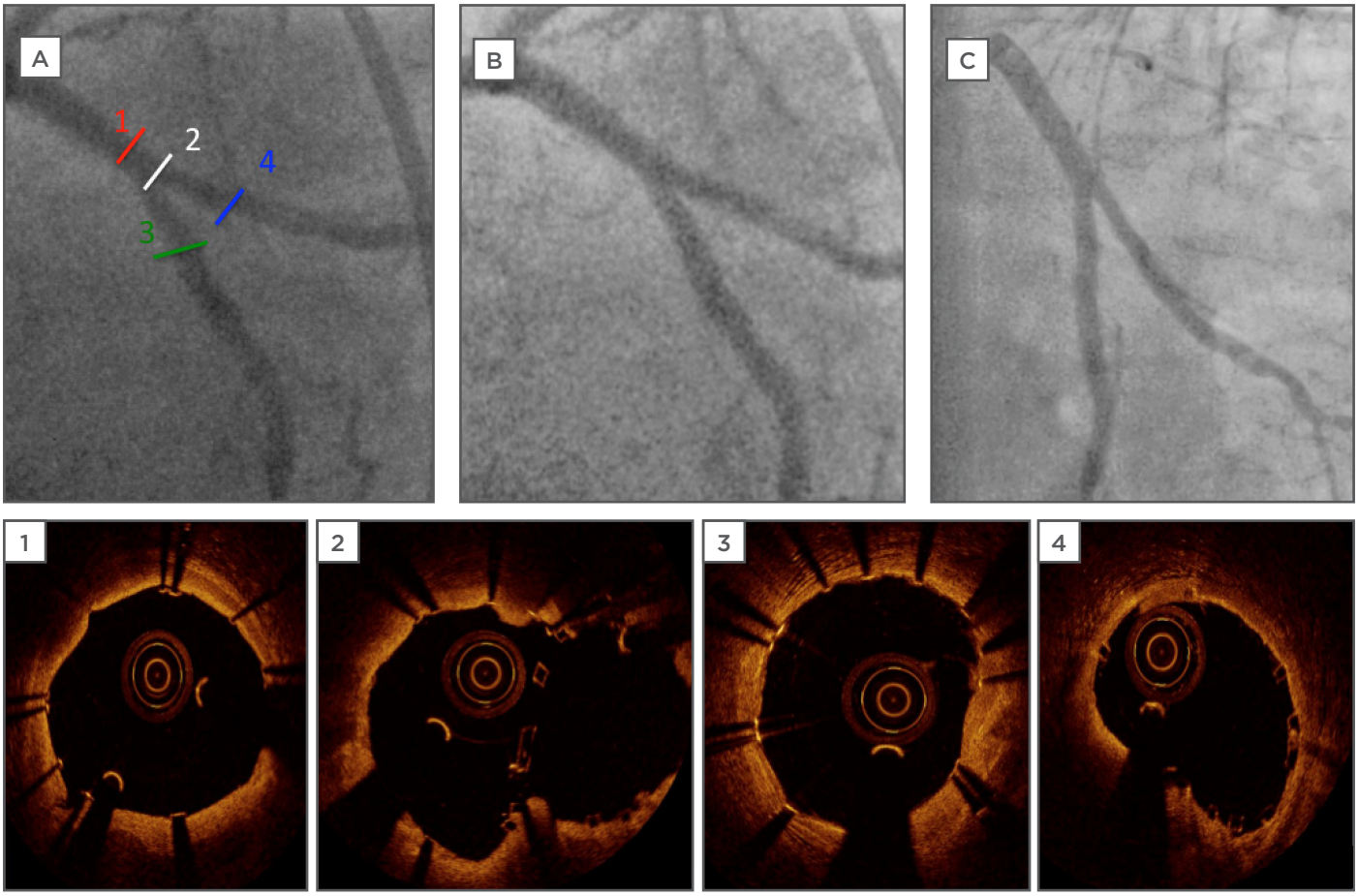

Figure 4: Final angiographic images and optical coherence tomography after percutaneous coronary artery and 1-year follow-up angiography control.

OCT measurement for 1) proximal MB mean vessel diameter after stenting is 3.73 mm; 3) distal MB mean vessel diameter is 3.4 mm; 4) SB mean vessel diameter after stenting is 3.2 mm. Bifurcation OCT (image 2) confirm an excellent result at the neocarina of the bifurcation and full coverage of the SB ostium without scaffold disruption. Angiographic images post-PCI A) segments for OCT; B) final image for bifurcation; C) 1-year follow-up angiography control for bifurcation.

OCT: optical coherence tomography; MB: main branch; SB: side branch; PCI: percutaneous coronary intervention.

Although using the BVS in both MB and SB appears feasible, their use requires careful evaluation in fractal models with different bifurcation angles and clinically should be limited to patients with large-calibre main vessels. As disrupted BVS struts cannotbe visualised by angiography, they recommend intravascular imaging, preferably with OCT, or alternatively with IVUS (of the MB in particular), whenever dilation of the BVS struts, POT, or FKB inflation has been performed, or two BVS have been deployed, to ensure the integrity of the final result.

CONCLUSION

In conclusion, combined BVS and DES implantation as a two-stent approach using the mini-crush technique is a safe, feasible, effective, and durable treatment option for patients with true bifurcation disease. Patient selection for complex stenting requires accurate lesion evaluation including assessment of distribution of disease (whether the disease involves both branches), size of branch, angle of branch, severity and length of the SB lesion, and presence of concomitant distal disease in the SB. Double stenting is more complex, time-consuming, and labour intensive, and requires specialist techniques, including IVUS/OCT guidance, plaque pretreatment, new-generation

DES and BVS usage; post-stenting optimisation is strongly recommended to avoid complications and ensure favourable long-term results. OCT is the best visualisation method for implanted BVS evaluation. Further investigation is needed to prove the long-term results. Our current recommendations are still to use provisional stenting in the majority of cases, but if there is a need to do a planned two-stent approach, we recommend the use of imaging methods, plaque modification before stent implantation, and FKB and POT inflation to achieve an effective final result. FKB inflation should be done with appropriately sized balloons during all two-stent techniques to achieve less proximal stent deformation. Additionally, the DK crush may be superior to the standard crush technique with respect to acute procedural results and clinical outcomes by facilitating successful final kissing inflation in all patients.

Our institution is conducting an ongoing pilot, prospective, consecutive, single-centre registry for unprotected left main intervention by IVUS-guided and OCT-optimised combined BVS (LCX) and DES (left main anterior descending coronary artery) stent implantation using either a two-stent, mini-crush, or T-stent strategy. At this time the registry has included >50 patients. Thirty-eight patients reached the 1-year follow-up whilst 16 patients so far have reached the 2-year follow-up. Data from these patients show good results for this bifurcation treatment strategy.

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THROMBUS ASPIRATION

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ABSTRACT

ST-segment elevation myocardial infarction results from acute occlusion of a coronary artery. Mortality is high in this acute coronary syndrome. Mechanical reperfusion by primary percutaneous coronary intervention (PCI) is the most effective method to restore coronary circulation. The ultimate goal of primary PCI is successful myocardial reperfusion. Thrombus aspiration (TA) using manual TA catheters has been reported to improve coronary and myocardial circulation. This, however, does not translate into long-term mortality benefit and may be associated with an increased risk of stroke. This article reviews the role of TA as an adjunct to mechanical reperfusion during PCI.

Keywords: Thrombus aspiration (TA), myocardial infarction, thrombectomy, myocardial reperfusion.

INTRODUCTION

Rupture of an atherosclerotic plaque with subsequent thrombus formation and vessel occlusion constitutes the principal mechanism of acute ST-segment elevation myocardial infarction (STEMI). Prompt recognition of symptoms and time-dependent return of the coronary blood flow is associated with greater myocardial salvage. Primary percutaneous coronary intervention (PCI) is the preferred method of revascularisation and is the standard of care in PCI-capable hospitals. Compared with thrombolytic therapy, patients undergoing primary PCI have faster resolution of symptoms and ST elevations, along with improved thrombolysis in myocardial infarction (TIMI) flow and myocardial blush grade (MBG). Better coronary artery patency, as well as lower re-infarction and re-occlusion rates are also seen with mechanical intervention. Thus, the most important therapeutic challenge, and the main objective of primary PCI is successful myocardial reperfusion.[1] This is dependent on restoration of flow in the epicardial vessel as well as in the microvascular circulation.[2,3]

Mechanical intervention in STEMI patients results in disintegration and distal embolisation of thrombus and plaque fragments. This cellular debris contains platelets, erythrocytes, fibrin, inflammatory cells, and tissue factors. Downstream, these cellular elements trigger a local inflammatory and vasoconstrictor response causing microvascular plugging. Other postulated theories of microvascular plugging include interstitial and cellular oedema, calcium overload, myocardial necrosis, and reperfusion injury from oxygen free radicals. Irrespective of the aetiology, the resultant microvascular injury causes circulatory stasis at the capillary level, thus precluding nutritive flow to the affected areas of the myocardium. Fortunately, extensive microvascular injury is uncommon, and in most cases is angiographically evident. Rarely, however, microcirculatory occlusion persists despite a patent epicardial vessel. This results in 'slow or no re-flow' phenomena and a low MBG.[4] Slow or no-reflow is an independent predictor of adverse outcomes and is associated with larger infarct size, contractile dysfunction, heart failure, ventricular arrhythmias, and death.[5-11] Myocardial obstruction and reperfusion can be measured by various angiographic, non-invasive, and clinical criteria. These include TIMI flow and MBG,[4] ST-segment resolution on echocardiogram, late gadolinium enhancement on cardiac magnetic resonance T1 imaging, and reduction in infarct size and survival free from heart failure.[12]

ANTI-EMBOLIC PROTECTION DEVICES

Myocardial salvage is dependent on reducing micro-embolisation. The presence of intracoronary thrombus at the culprit lesion site increases the risk of downstream embolisation. A large thrombus load at the time of PCI is associated with increased incidence of microvascular stasis and major adverse cardiac events (MACE).[13] In tackling this challenge, pharmacological agents such as systemic infusion of glycoprotein IIb/IIIa inhibitors, intracoronary infusion of vasodilators, and antithrombotic/thrombolytic agents have been ineffective in most cases. Mechanical devices including mechanical thrombectomy and distal protection devices seem attractive but have failed to show any superiority compared to conventional PCI in meta-analysis and randomised controlled trials.[14]

Manual aspiration catheters were developed with the intent to aspirate the clot and reduce the intracoronary thrombus burden. These devices have a simple design, are easy to use, and are an inexpensive adjunct to PCI. The catheters are soft tipped for ease of use, and front and side holes are made for maximal aspiration. They require a 6 Fr guiding catheter. A head-to-head comparison of catheters with different internal lumens did not show any difference in angiographic or electrocardiographic outcomes.[15] Thrombus aspiration (TA) can be performed readily and as expected, the retrieved material shows clot and plaque debris.[16] During PCI, extracting a part of the thrombus out of the vessel, visualising the clot, and establishing TIMI 3 flow is appealing to the interventional cardiologist. Due to the above mentioned advantages there has been a rapidly growing interest in TA, and its use has gained acceptance in everyday clinical practice.

TRIALS AND META-ANALYSIS

Initial studies showed that the use of TA improved the coronary blood flow and helped resolve the ST elevation.[17-19] The EXPIRA trial[20] further reinforced these findings and validated a reduction in 24-month MACE. Favourable results with regards to MACE and mortality benefit compared to conventional PCI alone were also reported.[14,21,22] A meta-analysis revealed that manual aspiration thrombectomy resulted in lower all-cause mortality and fewer MACE in patients who received aspiration thrombectomy compared to conventional PCI. This meta-analysis, however, was limited by the inclusion of data from non-peer-reviewed trials.[23] Another meta-analysis of randomised controlled trials looking at adjunctive manual TA during STEMI concluded that the use of manual TA devices could improve post-procedure myocardial reperfusion, but had no effect on long-term clinical outcomes.[24]

In certain selected STEMI patients, TA alone without balloon angioplasty and stenting was found to be safe and effective. These were, however, small and non-randomised studies. Additionally, STEMI in these patients was not due to plaque rupture but likely due to embolism, plaque erosion, hypercoagulable states, and endothelial dysfunction.[25,26] A recent analysis from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) suggests that TA may be beneficial in reducing the risk of stent thrombosis. This benefit may come without an increased risk of stroke. At 30 days, there was a 2.9% reduction ($p<0.001$) in the relative risk of stent thrombosis; however, the absolute difference was small. The rates of thrombosis were 0.4% in the aspiration group versus 0.6% in the PCI-only group, while the stroke rates and mortality were similar in both groups.[27] Although these findings are encouraging, they need to be interpreted with caution.

The TAPAS trial, a landmark study of 1,071 patients, was performed to assess whether manual aspiration was superior to conventional treatment during primary PCI. Angiographic and electrocardiographic signs of myocardial reperfusion, as well as clinical outcomes were assessed. An MBG of 0 or 1, defined as absent or minimal myocardial reperfusion, occurred in 17.1% of patients in the TA group versus 26.3% in the conventional PCI group. The authors concluded that manual thrombectomy results in better reperfusion and clinical outcomes than conventional PCI. This was irrespective of the baseline clinical and angiographic characteristics of the enrolled patients.[18] One-year follow-up of the TAPAS trial showed that TA was beneficial with respect to mortality even with a longer follow-up period.[28] The TAPAS trial was a major breakthrough and changed the practice paradigm; aspiration thrombectomy was adopted as a routine adjunct to primary PCI. Thus between 2011 and 2013 various STEMI guidelines endorsed manual TA as reasonable for patients undergoing primary PCI, placing it in Class IIa with level of evidence B

indication in STEMI patients; this included the guidelines from the following organisations: In 2011, the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography Interventions (ACCF/AHA/SCAI) for PCI; in 2012 the European Society of Cardiology (ESC) for STEMI; and in the 2013 the ACCF/AHA for STEMI.[29]

The debate regarding the routine use of aspiration prior to PCI was initiated by the results of the TASTE trail.[30] This well designed, multicentre, prospective, randomised, open-label controlled trial evaluated 7,244 patients with STEMI who were randomised to either manual TA followed by PCI or to PCI only. The primary endpoint was all-cause mortality at 30 days. Death occurred in 2.8% of the TA group compared with 3.0% in the PCI only group. There was no significant difference in the rates of stent thrombosis target-lesion revascularisation, rate of stroke, heart failure, or left ventricular dysfunction at the time of discharge. A neutral outcome was seen in all subgroups, irrespective of baseline clinical or angiographic characteristics. The authors concluded that manual TA before PCI did not reduce 30-day mortality among patients with STEMI. One-year follow-up of the TASTE trial showed comparable all-cause mortality of 5.3% in patients belonging to the TA group compared with 5.6% in the PCI only group.[31] The TASTE trial results were somewhat limited by the fact that angiograms were not reviewed in a blinded fashion. The findings with respect to myocardial salvage, microvascular obstruction, and biochemical variables were not recorded in the registry. Any reasons for deviation from the randomly assigned treatments were not documented. Additionally, the angiographic variables were entered into the registry by the treating physicians and as they were already aware of which group each patient was assigned to, these variables were susceptible to bias.

This set the stage for TOTAL, a large, international, investigator initiated, multicentre, prospective, randomised trial comparing primary PCI with or without upfront routine manual thrombectomy.[32] A total of 10,732 patients with STEMI, referred for primary PCI within 12 hours of symptom onset, participated in the trial. These patients were randomly assigned to routine upfront manual thrombectomy with PCI versus PCI alone. Thrombectomy was performed by Export AP® Aspiration Catheter (Medtronic) with a standard specified technique. PCI was performed either after or without thrombectomy according to the operator's usual technique. Baseline characteristics were well balanced between the two groups, however there were fewer smokers and a longer average time interval from symptom onset to hospital arrival in the thrombectomy group compared with the PCI alone group. There were low crossover rates: 4.6% from thrombectomy to PCI alone group, and 1.4% from PCI alone to thrombectomy group. Bailout thrombectomy was permissible in case of failure in the initial PCI alone strategy.

The primary outcome of composite death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association (NYHA) Class IV heart failure within 180 days was similar in both groups (6.9% in the thrombectomy group versus 7.0% in the PCI alone group). The incidence of stroke, however, was higher in the thrombectomy group at 0.7% versus 0.3% in the PCI alone group. The authors concluded that for patients undergoing primary PCI for STEMI, the strategy of routine manual thrombectomy did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA Class IV heart failure within 180 days, but was associated with increased rate of stroke within 30 days.

Limited data exist regarding TA in patients receiving bioresorbable vascular scaffolds (BVS). As the use of BVS is expanding, the interest in routine TA is dwindling down. A recent meta-analysis of six randomised controlled trials comparing everolimus-eluting BVS versus everolimus-eluting metallic stents showed an increased incidence of subacute stent thrombosis with the BVS group.[33] Nonetheless, there are not enough data available to properly assess the role of TA in this subset of patients as only a few STEMI patients given BVS were studied.

In the largest registry study of TA so far, 10,929 patients from the British Cardiac Intervention Society (BCIS) dataset had primary PCI performed at UK hospitals. Seven thousand three hundred and fifty-seven (67.3%) patients had conventional PCI while 3,572 (32.7%) underwent TA as an adjunct therapy. TA was performed at the operator's discretion. TA was more often performed in sicker patients who had TIMI 0 flow, were younger, and had poor left

ventricular function. There were fewer in-hospital MACE in the TA group (4.4% versus 5.5%), however there was no difference in the incidence of MACE at 3-year follow-up. This signifies that even in selected patients TA is not advantageous.[34]

In a recent meta-analysis of 17 trials, which included 20,969 patients, aspiration thrombectomy failed to show improved clinical outcomes compared to conventional PCI. There was no significant reduction in the risk of mortality, re-infarction, or stent thrombosis. Aspiration thrombectomy was, however, associated with a non-significant increase in risk of stroke.[35] TA may not be as benign as initially comprehended; complications such as systemic embolisation and a trend towards an increased risk of stroke were also reported with the use of TA devices in other studies.[36,37] Data reported from Sweden found higher mortality among patients who had TA before PCI compared to PCI alone.[38]

THE ROLE OF THROMBUS ASPIRATION IN SUBACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION AND NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION PATIENTS

Similarly, in contrast to earlier reports, a recent randomised trial evaluated thrombectomy in subacute STEMI patients. These patients presented between 12 and 48 hours after symptom onset. They underwent cardiac magnetic resonance imaging for assessment of reperfusion success. The study concluded that the routine use of TA in such patients does not have any benefit in angiographic and clinical endpoints.[39]

TA is ineffective and infrequently used in Non-STEMI (NSTEMI) patients. This may be due to a smaller thrombotic burden and delayed time to PCI compared with STEMI patients. Additionally, NSTEMI patients have a more organised and fibrin-based thrombus.[40] Subgroup analysis of the ACUITY trial showed a 2% use of TA in NSTEMI patients.[41] In the TATORT-NSTEMI trial, 440 patients with thrombus-containing lesions presenting with NSTEMI were randomised to PCI with aspiration thrombectomy or PCI alone. Adjuvant TA did not improve the TIMI flow or MBG, nor did it reduce the amount of late microvascular obstruction or infarct size. At 6 months there was no significant difference in mortality, target-vessel revascularisation, or new congestive heart failure benefits between the two groups.[42]

The most recent focussed update document by the ACCF/AHA/SCAI downgraded routine aspiration thrombectomy to Class III, level of evidence A (no benefit) as a result of the large randomised clinical trials TASTE and TOTAL.[43] Thrombectomy was demoted in the ESC/European Association for Cardio-Thoracic Surgery (EACTS) revascularisation guidelines from Class IIa level of evidence B recommendation to Class IIb level of evidence A recommendation.[44]

Different trials have shown varying results and many reasons account for this discrepancy. It is clear that not all STEMI patients are alike and not all vessels behave in the same fashion. STEMI resulting from atherosclerotic plaque rupture may behave differently from that of plaque erosion. TA in a calcified lesion will not respond in a similar way to a non-calcified vessel. Ectatic and aneurysmal arteries are prone to reduced TIMI flow, stasis, and large thrombus burden in acute coronary syndromes; TA in this group of patients is not well studied. Clinically, the time from symptom onset to reperfusion, the degree of thrombus burden, and concomitant pharmacotherapy use all impact the final results and success of PCI and TA. Additionally, trial design, patient selection biases, and other limitations of different trials will affect the outcomes of different trials.

The TAPAS trial had several limitations. It was a single-centre experience, randomisation was performed before PCI, and as a consequence some patients did not undergo PCI or receive alternate therapy. This selection bias may have diluted the positive effects of TA. The effect of pre-dilation of a lesion was not evaluated, while the findings of both TASTE and TOTAL apparently leave little or no role for manual TA as a routine adjunct to PCI in STEMI patients. These trials were also not without limitations. Patients with low thrombus burden, who would be less responsive to thrombectomy, were included in the trials. The treating interventionists were aware of the study group assignments and this could have led to management biases, e.g. concomitant use of different types and doses of antiplatelet and anticoagulant agents. Angiograms were not read in a blinded fashion. TA was reserved as bailout in the PCI alone group and so selective use of thrombectomy versus no thrombectomy was not compared. The reason for

deviation from randomly assigned treatment was not documented, and neither trial excluded the possibility of benefit in high-risk patients. On the contrary, the incidence of stroke associated with TA, one of the more important findings of the TOTAL trial, was noted between 30 and 180 days post-procedure. Certainly this cannot be explained by a periprocedural event, raising the possibility of it occurring by chance. Analysis from the SCAAR suggests that similar stroke rates occur in both groups.

Keeping these aspects in consideration, the door to TA may not be closed to all subsets of patients. STEMI patients that might benefit from this easy adjunct to PCI include those with large thrombus burden, especially in ectatic arteries. STEMI resulting from an embolic aetiology should be considered for TA. Additionally, young patients without much atherosclerotic disease and patients with STEMI resulting from plaque erosion may also have a favourable response. TA may also be valuable in retrieving a large, distally-embolised thrombus distal to the plaque rupture site.

CONCLUSION

Primary PCI, when available, is the most effective method of reperfusing an occluded artery. Distal embolisation of thrombus and plaque fragments during PCI triggers a local inflammatory and vasoconstrictor response causing microvascular obstruction. Failure to restore flow at the microvascular level results in expansion of the necrotic zone and is associated with adverse clinical outcomes. TA is an easy adjunct step to primary PCI, and initial studies demonstrate improved clinical outcomes. Nonetheless, large randomised clinical trials and recent meta-analysis have failed to show any clinical benefit. Thus, currently all major cardiac societies recommend against its routine use in STEMI revascularisation guidelines. Precisely which subgroups of patients may benefit from this technique, and the genuine concerns about its safety and increased risk of stroke, need to be investigated in future studies.

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ENDOVASCULAR TREATMENT OF SPONTANEOUS CAROTID ARTERY DISSECTION

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ABSTRACT

Spontaneous carotid artery dissection (SCAD) is a common cause of ischaemic stroke in young patients. Though SCAD is usually defined as carotid artery dissection without trauma, a minor traumatic event is often revealed by a detailed medical interview. An association with intrinsic vessel structure has been reported in connective tissue disease, pregnancy and the postpartum period, and in infectious and inflammatory disease. Mechanisms of SCAD vary and are still unclear, but a combination of fragile vessel walls and minor trauma can result in dissection. Headache, Horner's syndrome, transient ischaemic attack or ischaemic stroke are the most frequently seen clinical symptoms. Non-invasive diagnostic modalities including magnetic resonance imaging, computed tomography, and duplex ultrasonography have become an alternative to digital subtraction angiography, however this still remains the gold standard, with better detection of thrombus and collateral circulation. Antithrombotic therapy is the standard medical treatment for SCAD, achieving a good clinical course in most patients. Patients, including those on antithrombotic therapy, who are presenting with recurrent ischaemic symptoms, haemodynamic compromise, or expanding pseudoaneurysm should be considered for intervention therapy. As the main purpose of endovascular treatment is to avoid recurrence of ischaemic attack, performing the procedure under an embolic embolic protection device is preferable. To obtain sufficient blood flow and sealing of the thrombus, a stent is usually delivered, and coil embolisation can be performed for expanding pseudoaneurysm, if required. The most common regimen of post-procedural antiplatelet therapy is a double dose for 3 months followed by a single dose indefinitely, though a clear guideline does not exist. The clinical success rate and long-term results of endovascular treatment are acceptable. Endovascular treatment for carotid artery dissection is feasible, safe, and effective in a subgroup of patients, including those resistant to medical therapy.

Keywords: Spontaneous carotid artery dissection (SCAD), ischaemic stroke, carotid artery stenting, embolic protection device.

INTRODUCTION

Although uncommon in the general population, spontaneous carotid artery dissection (SCAD) is a common cause of ischaemic stroke in patients <50 years old, accounting for 14–20% of cases.[1] SCAD was first reported in 1959.[2] Carotid artery dissection can be divided into traumatic, spontaneous, and iatrogenic causes. When the patient does not have any obvious trauma the dissection is typically recognised as spontaneous, however certain minor events including rotation of the neck, coughing, and vomiting, precede dissection in 12–34% of cases.[3] Connective tissue diseases inducing intrinsic vessel structure abnormalities, such as Marfan's syndrome, Ehlers–Danlos syndrome,[4] cystic medial necrosis, polycystic kidney disease, osteogenesis imperfecta,[5] and fibromuscular dysplasia,[6,7] are also associated with spontaneous arterial dissection. In some case reports, SCAD was seen in pregnancy and the postpartum period.[8-13] Infectious and inflammatory disease may also be causative.[14,15] Although our understanding of the various mechanisms remains incomplete, it is clear that a combination of structural fragility in a carotid artery and minor trauma can induce SCAD.

Table 1: Treatment options for spontaneous carotid artery dissection and its indications.

Treatment		Indication
Medical treatment	Antiplatelet, anticoagulant, thrombolysis	Treatment with antithrombotic medicine including anticoagulant and/or antiplatelet is the first-line therapy and gold standard for patients with SCAD. Good clinical and anatomical outcomes over long-term follow-up are shown.
Endovascular treatment	Stent (bare-metal stent, flow-diverter stent, stent-graft), coil embolisation	This minimally invasive treatment should be considered when progression of symptoms is seen even with medical treatment. Coil embolisation will also be required in cases of an enlarging dissecting aneurysm.
Surgical treatment	Arteriotomy, intimal flaps removal, carotid ligation, bypass	Because of the high rates of stroke and cranial nerve injuries, surgery should be limited to the following cases; 1) progression of symptoms even with medical treatment, 2) unfavourable situation for endovascular treatment, 3) anatomically accessible lesions, 4) brainstem compression due to dissecting aneurysms, 5) intracranial arterial dissection causing subarachnoid haemorrhage.

SCAD: spontaneous carotid artery dissection.

CAROTID ARTERY DISSECTION

Pathophysiology

When a tear develops at the intima or media of an artery, dissection occurs resulting in the flow of blood into the dissected lumen. Ischaemic events are often seen in patients with SCAD. They are caused by thrombi formed as a result of intimal damage and turbulent flow, or by enlargement of the dissected lumen, which leads to stenosis or occlusion of the true lumen. In some cases, a pseudoaneurysm can be seen depending on the depth of the tear. SCAD commonly occurs about 3 cm distal to the origin of the internal carotid artery (ICA)[16,17] and intracranial dissection of the ICA is seen in 20% of cases.

Clinical Features

SCAD can cause a variety of symptoms, however headache, Horner's syndrome, and ischaemic stroke are the most common. Headache occurs in ~70% of SCAD cases[18] and neck pain is also seen in 26% cases.[19] Horner's syndrome is induced by damage to the sympathetic pathway distal to the superior cervical ganglion and is seen in 28–58% of cases.[20-22] Transient ischaemic attack or ischaemic stroke are seen in 67% of patients with SCAD as a consequence of artery-to-artery thromboembolism from the site of dissection.[23]

Diagnosis

Digital subtraction angiography (DSA) remains the gold standard modality for the radiographic diagnosis of SCAD, however alternative non-invasive modalities including magnetic resonance imaging (MRI), computed tomography, and duplex ultrasonography are available. DSA allows better evaluation of the thrombus and collateral circulation in haemodynamically-compromised situations. Obvious disadvantages are the time and expense of the procedure and the risks and discomfort to the patient. MRI and magnetic resonance angiography (MRA) can be viable alternatives to DSA and give information regarding ischaemic damage to the brain. MRI, however, has a limited sensitivity to identify an intraluminal thrombus and intramural haematoma, often overestimating the degree of stenosis. The sensitivity and specificity of computed tomography angiography (CTA) in detecting the dissections are similar to DSA and superior to MRA. The ease and speed of use are the primary advantages of CTA, however the problems with this modality are the exposure to contrast and radiation, and the lack of information about brain damage. Duplex ultrasonography is a less invasive imaging modality, but the quality of images is highly dependent on operator experience. Although there is a limited ability to evaluate lesions located more caudally and a tendency to mistake subtotal stenosis for occlusion, duplex ultrasonography remains a relatively suitable modality for follow-up investigations.

Treatment

Medical treatment with antithrombotic therapy is the standard because most ischaemic events are

induced by thrombus. In many cases, the patients with SCAD usually have an acceptable clinical course with medical therapy alone. It remains unclear whether anticoagulant or antiplatelet agents provide better antithrombotic effects in this context.[6,24,25] The European Cervical Artery Dissections and Ischemic Stroke Patient trial recommends treatment with antiplatelet drugs, except in situations favouring anticoagulation, when recurrent events while on antiplatelet drugs occur, or in the presence of a thrombus.[26] Although first reported in 1977, and despite numerous case reports and series, endovascular treatment for SCAD remains controversial due to benign outcomes with medical therapy.[27-30] There are no clear guidelines regarding endovascular treatment, however in the following situations endovascular treatment must be considered as an option: 1) patients with recurrent symptoms despite medical therapy; 2) patients with haemodynamic hypoperfusion; 3) patients with an expanding or symptomatic pseudoaneurysm; 4) contraindication to anticoagulation because of intracranial or systemic haemorrhage.[31] The indication of surgical treatment is limited to the situations described in Table 1, due to the high rates of stroke and cranial nerve injuries. Recurrence of SCAD is rare, with yearly rates reported at ~1%.[32-34] Recurrent dissections tend to occur in a different vessel to the previously dissected vessel.[35,36]

ENDOVASCULAR TREATMENT

Endovascular treatment for carotid artery dissection is uniquely challenging. The aims are to restore an adequate antegrade flow to prevent flow-limiting dissection, and to provide an adequate sealing of thrombus avoiding further dislodgment. The technical success rate of endovascular treatment has been reported as 99.1–100% with an overall rate of adverse events of 4–11% and no mortality. Intimal hyperplasia, in-stent restenosis, or occlusion of a treated vessel is seen in 3.3–8% of follow-up cases.[37,38]

Embolic Protection

To be effective, endovascular treatment of carotid artery dissection needs an adequate technique to protect the brain during the procedure, preventing thrombi dislodgement and embolisation, and an adequate technique to exclude the risk of pseudolumen or pseudoaneurysm. The former could be achieved by neuroprotection devices such as distal filters, or proximal protection with flow-blockage or inversion. Proximal protection allows complete protection during all phases of carotid artery stenting, as well as during lesion crossing with the wire. It has shown higher efficacy than distal filters in reducing silent cerebral embolisation and it should be the first choice in treating symptomatic patients.[39]

How to Ensure Correct Location of a Guide Wire

There are some difficult aspects to treating a dissected carotid artery. In particular, it is often challenging to advance the guide wire into the true lumen whilst avoiding the dissected lumen. To confirm that the guide wire is inside the true lumen, the the following techniques are recommended: 1) compare the angiography carefully; 2) use intravascular ultrasound; 3) tip injection by microcatheter.[40]

Stenting and Coil Embolisation

With regard to the type of stent, several techniques have been used to treat the dissected carotid artery and dissecting aneurysm:

- Bare-metal stent: A small diameter, balloon-expandable stent such as a coronary stent is often used for the distal and petrous portions because of the small diameter of the vessel. A self-expandable stent is usually used for the proximal and ostial portions of the ICA due to the continuous radial force toward the vessel wall. Two or more overlapping carotid stents can be used to increase the mesh density, preventing clot migration and leading to secondary occlusion of the pseudolumen and peusdoaneurysm[29]
- Stent-assisted coil embolisation: Coils are deployed under the stent struts, using the stent as a scaffold that prevents coil migration and dispersion; incomplete occlusion with recanalisation has been reported in up to 20% of cases[41]
- Flow-diverter stent: Aneurysm obliteration can be achieved using a flexible, self-expanding nitinol stent with platinum microfilaments specifically designed to produce a haemodynamic flow diversion and to reconstruct laminar flow in the parent artery[42]
- Stent-grafts: Commonly used to repair vascular lacerations, a covered stent deployed across the neck of the pseudoaneurysm could easilyfix this problem.[43,44] Navigation of the stent-grafts through the vascular loops can be challenging

due to the rigidity of the system, particularly through tortuous, small vessels, or the distal internal carotid artery near the carotid siphon. This may lead to vasospasm, propagation of the existing dissection or or new dissection at the ends of the stent, and even vessel rupture. Newly available self-expandable stent-grafts are more flexible and have a lower profile to overcome delivery problems. Stent-grafts may have a higher rate of thrombosis and restenosis compared to bare-metal stents

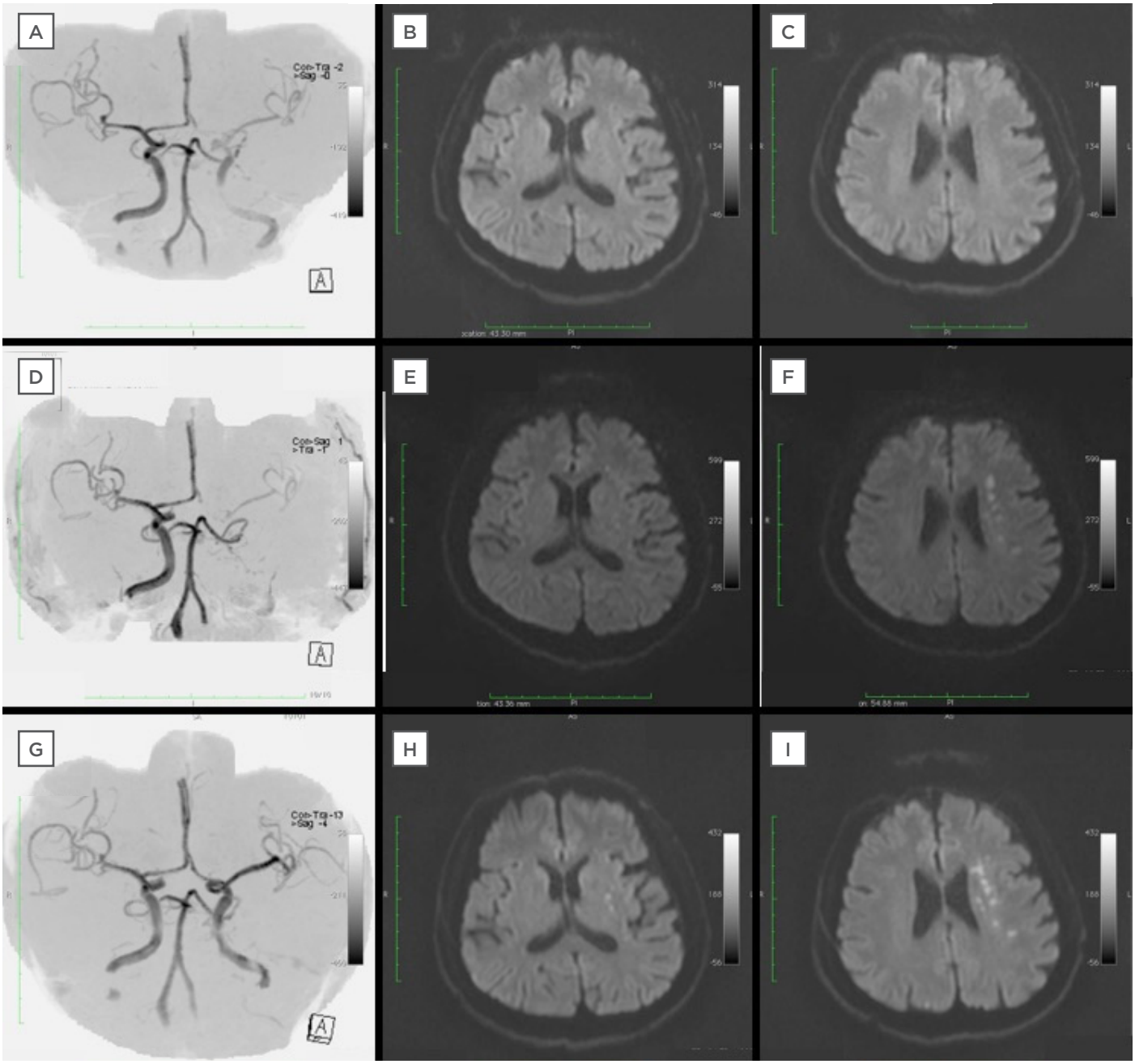

Figure 1: Magnetic resonance imaging of a 63-year-old man admitted with a National Institutes of Health Stroke Scale Score of 7.

A–C: On admission, MRA indicated insufficient flow of left ICA but no HIS in DW-MRI.

D–F: Decreased blood flow of left ICA was seen in MRA and HIS inside the territory of a middle cerebral artery in DW-MRI when the symptom was worsening.

G–I: MRA and DW-MRI performed after endovascular treatment revealed adequate flow of left ICA and no enlargement of HIS.

MRA: magnetic resonance angiography; ICA: internal carotid artery; HIS: high intensity spots; DW-MRI: diffusion weighted magnetic resonance imaging.

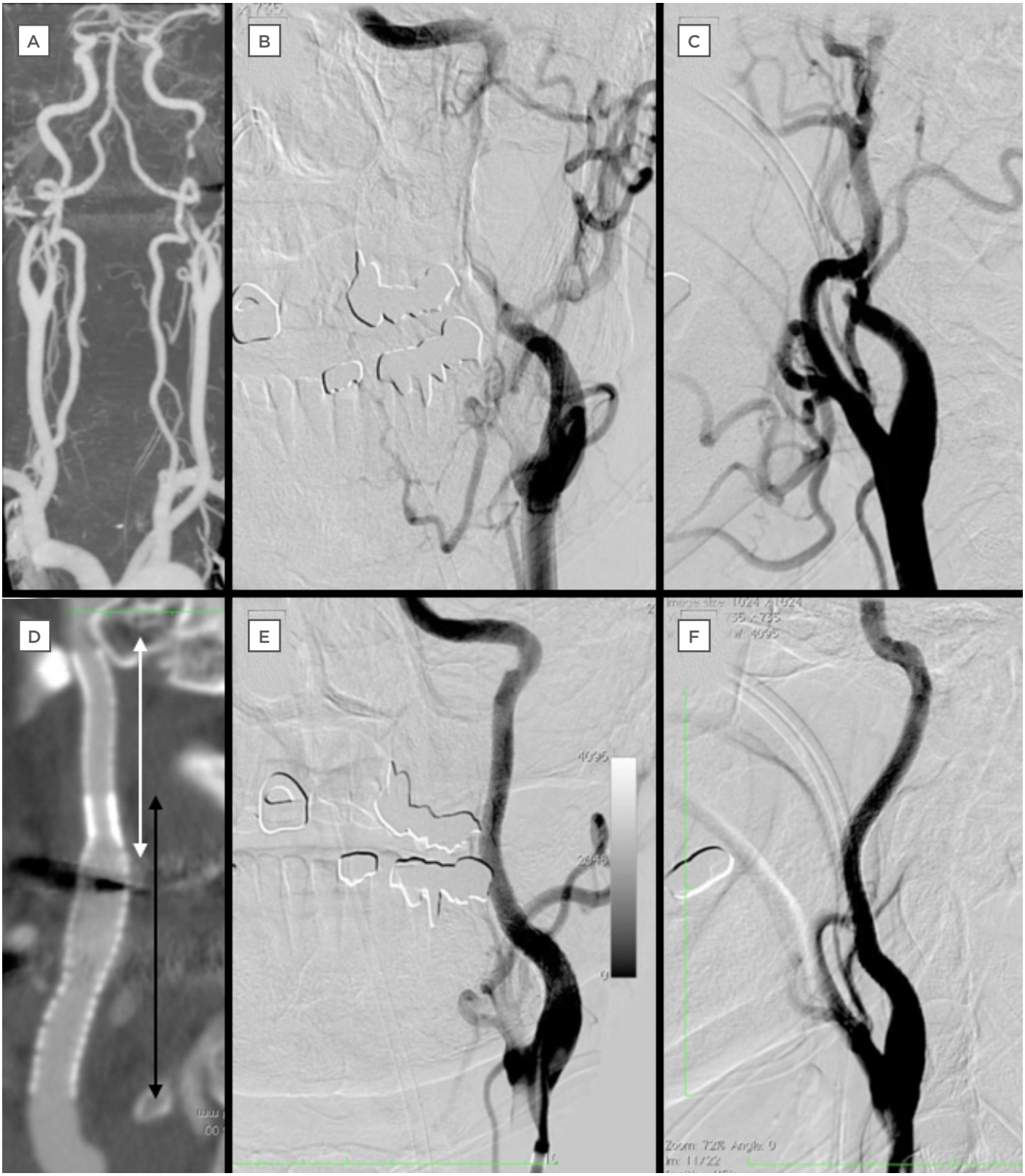

Figure 2: Computed tomography and digital subtraction angiography of a 63-year-old man admitted with a National Institutes of Health Stroke Scale Score of 7.

A–C: CTA and DSA on admission indicate artery dissection of left ICA.

D: CTA after the procedure shows the implanted stents (white double-headed arrow is Driver® stent 4.0 mm/30.0 mm, black double-headed arrow is Precise® stent 6.0 mm/40.0 mm).

E–F: DSA after stenting show complete reconstruction of left ICA.

CTA: computed tomography angiography; DSA: digital subtraction angiography; ICA: internal carotid artery.

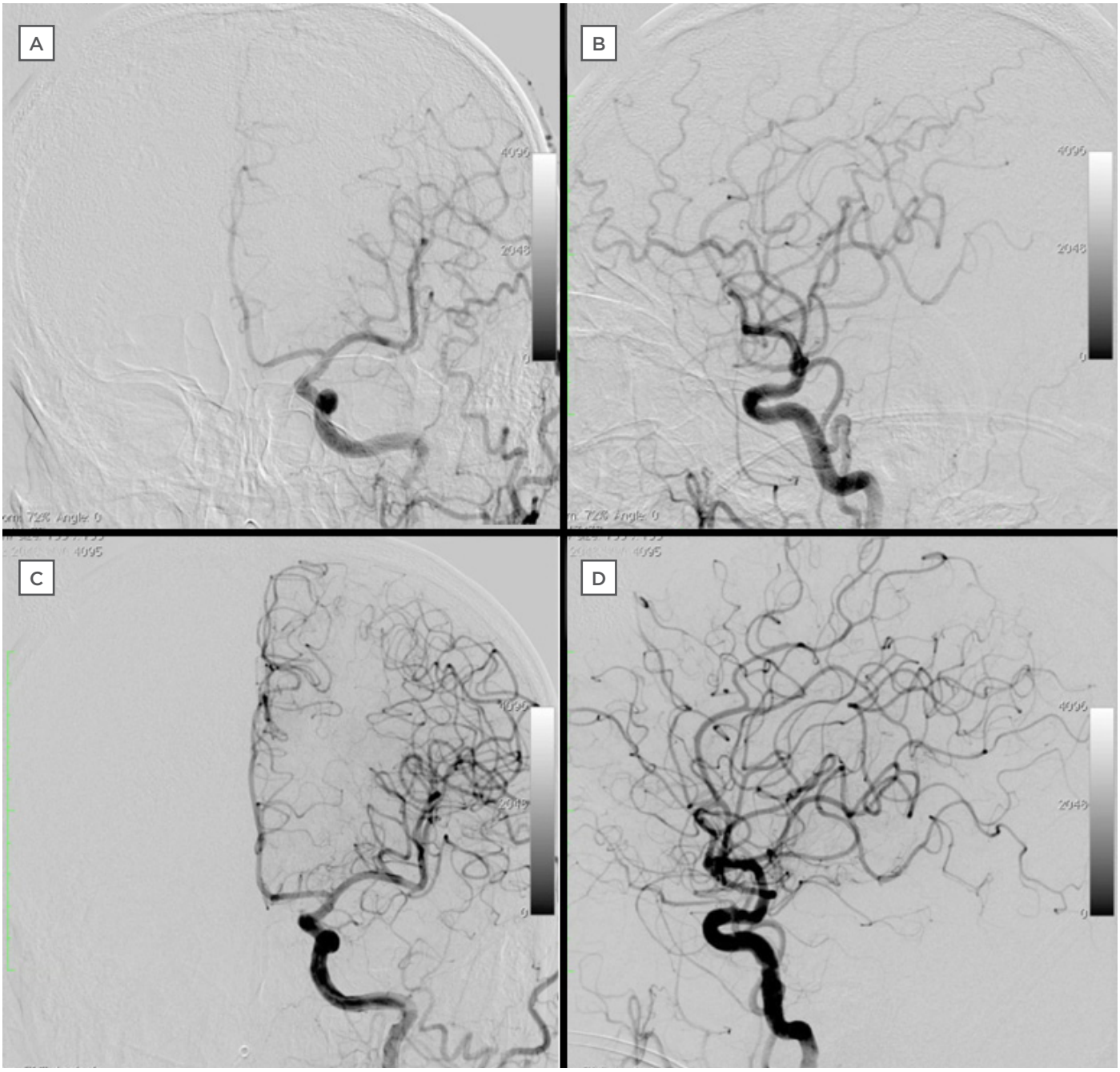

Figure 3: Comparison of intracranial vessel before and after procedure.
A–B: Intracranial DSA on admission.
C–D: Intracranial DSA after the procedure.
DSA: digital subtraction angiography.

Antiplatelet Therapy after the Procedure

The optimal regimen of post-procedural antiplatelet therapy is yet to be defined. Double antiplatelet therapy is typically used but the duration varies between centres from 1–6 months. Most commonly double antiplatelet therapy is completed for 3 months and single antiplatelet therapy was continued indefinitely.

REPRESENTATIVE CASE

A 63-year-old male was referred to the emergency department complaining of right hemiparesis and aphasia (National Institutes of Health Stroke Scale [NIHSS] score of 7). Diffusion weighted MRI (DW-MRI) showed no high intensity spots, but MRA indicated insufficient flow of the left ICA (Figure 1). CTA revealed a left carotid artery dissection (Figure 2).

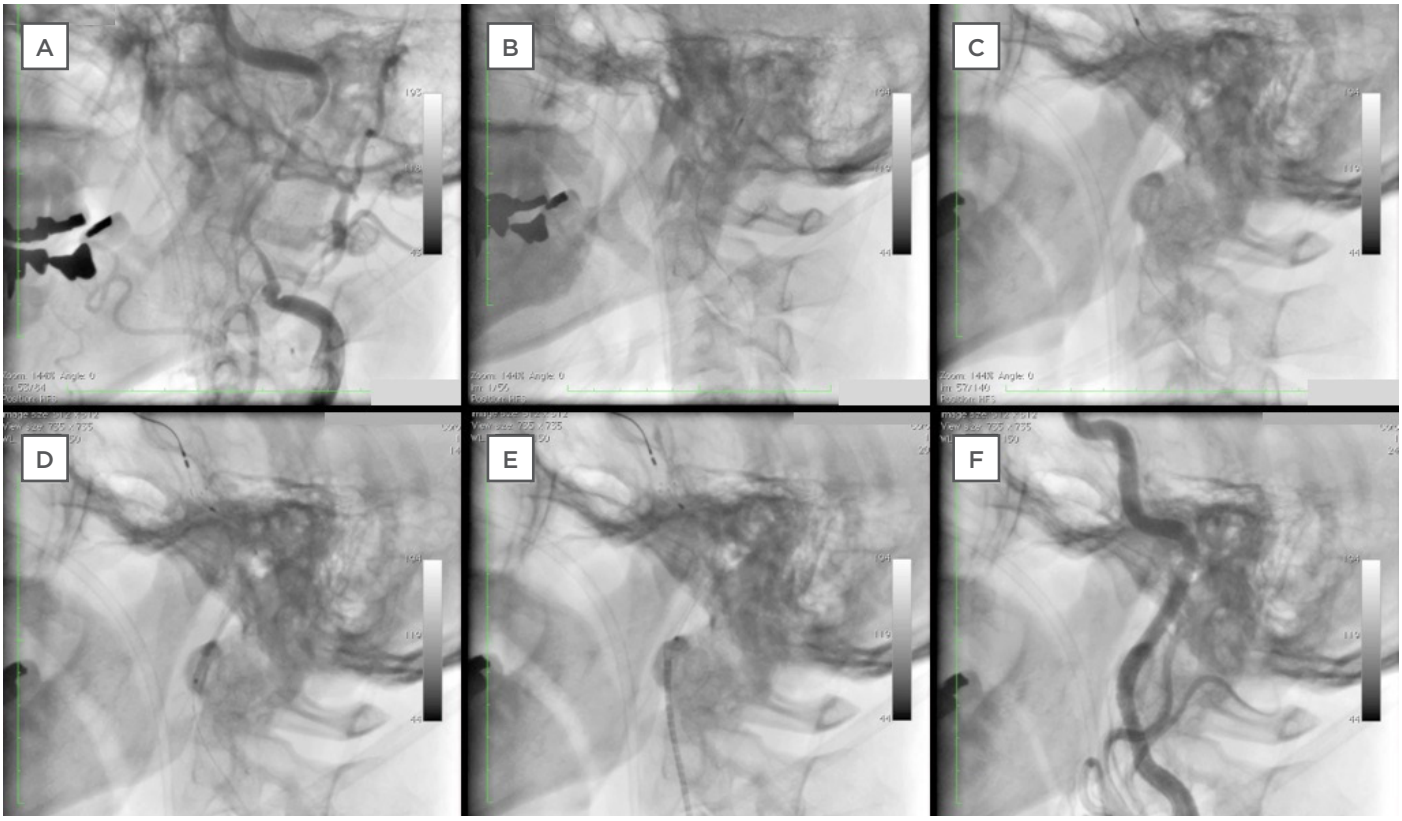

Figure 4: Progression of stent delivery from baseline to complete endovascular treatment.
A: Baseline angiogram.
B: Performing IVUS after advancing the guide wire in order to confirm the guide wire is inside true lumen.
C: Filter placed at the distal end of the left ICA.
D: Delivery of Driver® stent.
E: Delivery of Precise® stent.
F: Final angiogram.
IVUS: intravascular ultrasound; ICA: internal carotid artery.

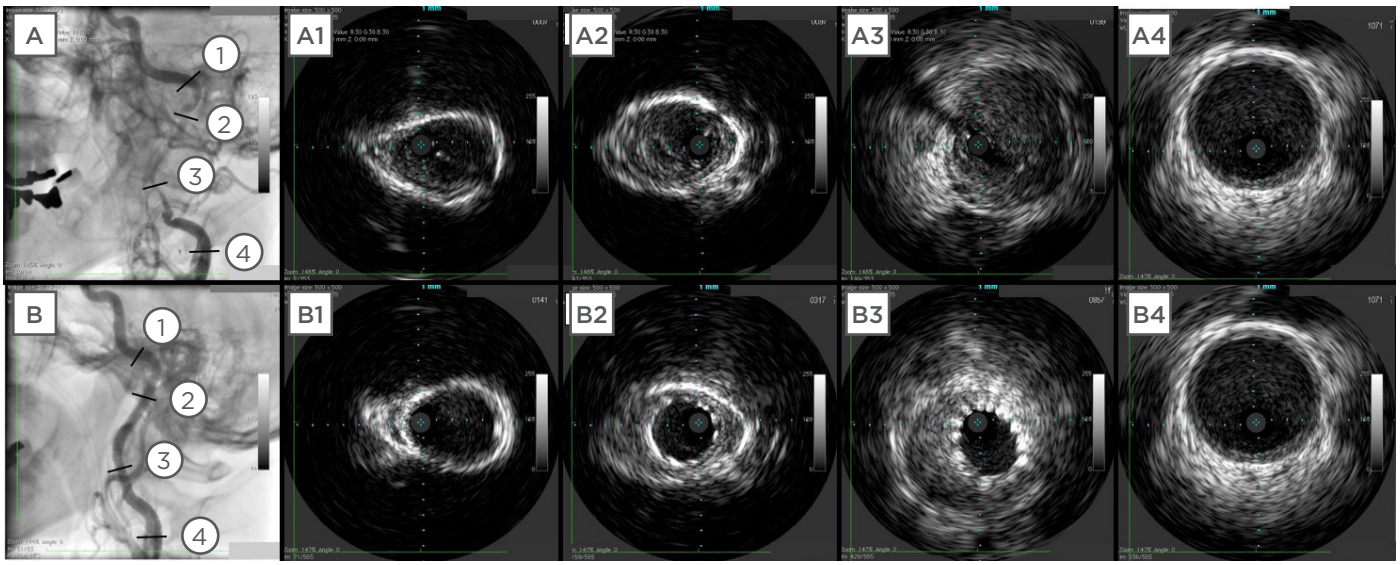

Figure 5: Comparison of intravascular ultrasound images before and after procedure.
A1–A4: Intravascular ultrasound images of the left internal carotid artery before the procedure.
B1–B4: Intravascular ultrasound images following stenting.

Just after these examinations, his symptoms markedly improved (NIHSS score of 0). The patient started to receive conservative therapy with antithrombotic drugs. The next day, DW-MRI and MRA were performed because of a deterioration in symptoms (NIHSS score of 8), and revealed high intensity spots inside the territory of the middle cerebral artery and decreased blood flow of the left ICA (Figure 1). The patient thus underwent endovascular treatment. Baseline DSA revealed dissection of the left ICA (Figure 2) and intracranial angiography showed insufficient flow to the brain (Figure 3). We advanced a 0.014 inch guide wire into the left ICA distal, confirming that the guide wire was inside the true lumen with intravascular ultrasound. Under an embolic protection device (Angioguard™ XP, Cordis Corp., FL, USA), a Driver® stent 4.0 mm/30.0 mm (Medtronic, MN, USA) was delivered from the distal lesion in order to completely cover the dissected lumen. After that, the Precise® stent 6.0 mm/40.0 mm (Cordis) was delivered for the proximal lesion in an overlap manner (Figures 4 and 5). The final angiogram showed complete reconstruction of the left ICA (Figure 2) and the intracranial DSA showed sufficient flow to the brain (Figure 3). The symptoms were improved immediately after the procedure without any complications.

CONCLUSION

SCAD is the most common cause of ischaemic stroke in younger patients. Preceding minor trauma and intrinsic vessel structure abnormalities are often seen in patients with SCAD. With regard to diagnostic modality, DSA is still the gold standard due to its advantage of detecting intraluminal thrombus. Alternative imaging modalities include MRI, computed tomography and duplex ultrasound, but each of these has its own advantages and drawbacks. Antithrombotic therapy with an anticoagulant or an antiplatelet is essential and most cases are successfully treated with low recurrence rates. For some patients however, such as those resistant to medical therapy, endovascular treatment is a viable option. According to a number of review articles and case reports, endovascular treatment for carotid artery dissection is feasible, safe, and effective in this group of patients.

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We attest to the fact that all authors listed on this article have contributed significantly to the work, have read the manuscript, and agree to its submission to the European Medical Journal.

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UPDATE ON TRANSCATHETER AORTIC VALVE IMPLANTATION

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ABSTRACT

Aortic valve replacement is the mainstay of treatment for symptomatic severe aortic stenosis. In this setting, the rapidly evolving field of transcatheter aortic valve implantation (TAVI) is currently considered a safe alternative to surgical aortic valve replacement in patients with severe aortic stenosis who are considered inoperable or at high surgical risk. This review will focus on recent changes in the field of TAVI, describing patient selection, valve types, procedural approaches, short and long-term outcomes, and complications. The rapid evolution of TAVI procedures supported by solid evidence will, in the near future, probably extend the indications to a wider portion of patients with aortic stenosis.

Keywords: Aortic valve stenosis (AS), transcatheter aortic valve implantation (TAVI), transcatheter aortic valve replacement (TAVR).

AORTIC VALVE STENOSIS: SCOPE OF THE PROBLEM

Aortic valve stenosis (AS) is the most frequent degenerative heart valve disease in the Western world; it affects up to 2% of the population >65 years of age and its prevalence increases proportionally with age.[1] The pathophysiology of AS includes processes similar to those of atherosclerosis, including lipid accumulation, inflammation, and calcification.[2] Causes of AS are degenerative calcification (senile AS), congenital valve defects such as bicuspid valve, and rheumatic disease.[3] While the development of symptoms (angina, syncope, or dyspnoea) demarks an inflection point in the survival of the patients with AS, the correlation between severity of the AS and onset of symptoms is poor and depends largely on the hypertrophic response of the left ventricle to the pressure overload.[4,5] However, following the onset of symptoms, patients without aortic valve replacement have a poor prognosis with a median survival of around 2 years.[4] Severe AS constitutes a growing and major health problem in developed countries, as it is the most prevalent cardiovascular condition after hypertension and coronary artery disease (CAD).[5]

TREATMENT STRATEGIES FOR AORTIC STENOSIS

In symptomatic patients with severe AS, the gold standard treatment was once a promptly performed surgical aortic valve replacement (SAVR). SAVR reduces symptoms and improves survival with low operative mortality in patients who are not at high surgical risk.[6-9] However, one-third of patients with severe symptomatic AS would not undergo surgery due to advanced age, left ventricular dysfunction, or the presence of multiple co-existing conditions (pulmonary hypertension, porcelain aorta, etc.).[4,10-12] Balloon aortic valve valvuloplasty procedures were considered as an alternative to SAVR, however their popularity declined due to poor long-term results;[13] the transcatheter aortic valve implantation (TAVI) was subsequently developed in the 2000s.

In asymptomatic patients with AS, the management and clinical decision making are challenging. Symptomatic status can be difficult to establish,

especially in elderly patients, who may ignore their symptoms or may reduce their level of physical activity to avoid or minimise symptoms. Exercise testing, such as exercise stress echocardiography, could thus be useful to unmask symptoms in patients with severe AS who claim to be asymptomatic or who have equivocal symptoms. Exercise testing is strongly advocated in the European Society of Cardiology (ESC) guidelines,[5] whereas it is a Class IIb recommendation in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.[21]

WHAT IS TRANSCATHETER AORTIC VALVE IMPLANTATION?

Alain Cribier performed the first TAVI[14] in humans in 2002 and since then there has been an incredible growth of this technique, supported by a substantial amount of research.[15,16] Following the Placement of Aortic Transcatheter Valves (PARTNER),[17,18] CoreValve Pivotal,[19,20] and NOTION[21] trials, TAVI was included in the ESC/European Association for Cardio-Thoracic Surgery (EACTS) and the ACC/AHA Task Force on Practice Guidelines in 2012 and 2014.[22,23] Current indications include inoperable and high-risk patients. In the latter group, the decision of TAVI versus SAVR should be made by multidisciplinary consensus within the Heart Team on a case-by-case basis. Expanded indications for TAVI (~10% of current procedures) include valve-in-valve procedures for degenerated bioprosthesis, AS due to bicuspid aortic valve, and pure aortic regurgitation, and the promising field of transcatheter intervention for pulmonary, tricuspid, or mitral valve disease.[24] Mitral valve-in-valve and valve-in-ring implantations have been shown to be effective at treating failed mitral annuloplasty or bioprosthesis, and are associated with low rates of complications.[25,26]

DIFFERENT TRANSCATHETER AORTIC VALVE IMPLANTATION DEVICES

A complete description of every device is beyond the scope of this paper, but the market is still dominated by the Edwards SAPIEN (Edwards Lifesciences, Inc., Irvine, CA) and Medtronic CoreValve® (Medtronic, Minneapolis, MN) valves, with increasing use of DirectFlow, Boston Lotus, and St Jude Portico devices. The latest valve iterations are the SAPIEN 3, a balloon-expandable frame housing a pericardial tissue valve[27,28] with a new outer polyethylene terephthalate cuff (to enhance paravalvular sealing) with the Commander transfemoral delivery sheaths of 14 Fr and 16 Fr; and the CoreValve Evolut™ R, resheathable, and repositionable self-expanding valve with a new 14 Fr delivery sheath.[29] Important data derived from one randomised controlled trial and five observational studies compared these different devices and demonstrated, at 30-day follow-up, that rates of death did not differ between self-expanding and balloon-expandable valves, and rates of all-cause death did not differ at 1-year follow-up.[30] In the 1-year results of the CHOICE trial comparing both valves, no differences in 1-year mortality rates were observed, despite the higher device success and lower paravalvular regurgitation (PVR) rate (which remained stable during follow-up) achieved with the Edwards valve.[31]

PATIENT SELECTION

Correct patient selection is crucial in order to achieve optimal results. Important points that should be considered include careful echocardiographic evaluation of left ventricular function, valve anatomy, other concomitant valve diseases, and confirmation of the severity of the AS. In patients with low-flow low-gradient AS, it is recommended to perform a stress echocardiograph, with exercise or dobutamine infusion. A cardiac computed tomography (CT) scan is now the most important imaging tool to study the aortic root and decide on the size of device to use. Issues with prognostic and functional significance are the load of valve calcification, size of aortic annulus and left ventricular outflow tract, morphology and calcification of aortic root, and location of coronary ostia.[32]

Surgical risk scores fail to accurately predict mortality after TAVI,[33] however risk can be estimated using the Society of Thoracic Surgeons' (STS) score (moderate risk 4–8; high risk ≥8–10 of predicted mortality), the Euroscore II, and the Logistic Euroscore. Current practice guidelines propose a careful evaluation of other risk factors not well reflected in those scoring systems, including frailty, poor mobility, obesity, end-stage liver disease, previous chest wall radiation, or cognitive impairment.[34] Potential poor functional outcome in spite of a successful TAVI procedure should also be taken into account.[35] The concept of medical futility has arisen in the TAVI scenario, and no invasive treatment should be considered if life expectancy with successful operation is

<1 year; chance of death or major morbidity (all-cause) is high; or other major organ systems (≥2) are compromised with improvement not expected after operation.[23,34]

Once superiority of TAVI over medical treatment in inoperable patients and the equipoise to SAVR in high-risk patients was widely accepted, the research focussed on intermediate-risk patients. Early results from registries and the all-comers randomised NOTION trial are promising. In this trial, TAVI was safe and effective, and comparable to SAVR in regards to the composite rate of death from any cause, stroke, or myocardial infarction after 2 years.[36] Recent data from the PARTNER 2 trial, which included patients at intermediate risk (mainly STS score ≥4) showed non-inferiority of TAVI compared to the SAVR in the primary outcome of death from any cause or disabling stroke at 2 years (19.3% TAVI versus 21.1% SAVR; p=0.25). Moreover, the TAVI group showed lower valve gradients and lower risk of bleeding events, acute kidney injury, and new-onset atrial fibrillation, as well as more rapid early recovery that resulted in shorter durations of stay in the intensive care unit and hospital.[37]

PROCEDURAL APPROACH

The current standard approach is the retrograde transfemoral, even though the first TAVI procedures were performed anterogradely through the atrial septum.[14,38] Other approaches (transapical, subclavian, or transaortic) are indicated for patients with inadequate lower limb arterial tree (roughly one-third of TAVI patients).[39-41] Selection of the best TAVI approach should be made on a case-by-case basis, focussing on the patient's anatomy and local experience. Transfemoral access is generally associated with better outcomes and should be used, if feasible.[42] Vascular access closure is key to avoiding bleeding and is usually obtained with percutaneous closure devices. The two most commonly used closure devices (Prostar and Proglide) were recently compared in an observational study that showed higher rates of major vascular complications in the Prostar group that contributed to a higher incidence of bleeding events and peri-procedural acute kidney injury, with no difference in mortality.[43]

CAD is a common comorbidity in the TAVI population, present or detected during pre-procedural coronary catheterisation in approximately 60% of TAVI candidates.[44] Even if there is no established strategy of how and when to treat CAD, European guidelines for myocardial revascularisation provide an IIa–c recommendation for percutaneous intervention of stenosis >70% in proximal coronary segments in patients undergoing TAVI.[45] Nevertheless, conflicting results exist concerning the influence of CAD on outcomes, and controversy persists regarding the extent and timing of revascularisation prior to a TAVI procedure.[46]

Another interesting field of investigation is the conventional versus minimalist approach. General anaesthesia and transoesophageal echocardiography guidance is being challenged by conscious sedation and local anaesthesia. The 3M TAVI study evaluated the efficacy, feasibility, and safety of next day hospital discharge in TAVI utilising the Multidisciplinary, Multimodality, but Minimalist (3M) approach compared with standard TAVI management (usually a 3–5 day stay after procedure). Preliminary data showed a feasibility of next day discharge in 97% of enrolled patients with only 3% re-admissions within 30 days.[47] The minimalist approach could also reduce the cost of the procedure. In a study that compared in-hospital cost between TAVI and SAVR, TAVI was demonstrated as an economically satisfactory alternative to SAVR, with a ~2-day shorter length of stay.[48] However, the most promising prospect regarding cost of the procedure is the expected reduction in valve device prices.[49]

PROCEDURAL OUTCOMES

The efficacy of TAVI in the treatment of patients with AS has been demonstrated in robust registries and large-scale studies.[17-20,21] The short-term outcomes from recent registries are summarised in Table 1. Indeed, a large meta-analysis of patients undergoing TAVI identified high pro-b-type natriuretic peptide levels and post-procedural acute kidney injury as the strongest independent predictors of 30-day and 1-year mortality.[50] In patients with mitral regurgitation (MR), a recent meta-analysis associated a concomitant moderate-severe MR with an increase in early and late mortality following TAVI. Half of the patients had a significant improvement in MR severity (greater in those who had received a balloon expandable valve).[51] There has been a gradual improvement in outcomes (increased success and reduced complication rates), probably due to the technological advances and the increased experience of the operators.

A few studies have follow-up data available for up to 4–5 years, all of them with a high mortality rate (>50%) at 5 years. It is important to emphasise that these studies included a very old population with significant comorbidities (high or extreme risk), some of them could probably be excluded from a TAVI procedure nowadays due to excessive risk (futility). The 5-year follow-up of the PARTNER trials published equivalent outcomes for high-risk patients who underwent SAVR or TAVI: there were no significant differences in all-cause mortality, cardiovascular mortality, stroke, or need for re-admission to the hospital. In addition, the functional outcomes were similar, and no differences were demonstrated between surgical or transcatheter valve performance. Other observational studies confirm similar results with 5-year mortality rates of 61–68% (Table 2).

COMPLICATIONS

With some disparity in the initial TAVR reports, the Valve Academic Research Consortium (VARC) one[52] and two[34] criteria helped to standardise reporting of postoperative complications. An outline of the most frequent complications or novel findings will be addressed in this section, although many other complications may occur during or after a TAVI procedure.

Bleeding

More than two-thirds of patients are now undergoing TAVI through the transfemoral route with a percutaneous arterial closure device.[53] The transfemoral approach is associated with higher vascular complications compared to the transapical TAVI,[54] however these have been significantly reduced by the introduction of the current reduced sized sheaths.[55] Hitherto, bleeding was one of the most relevant complications of transfemoral TAVI. Although VARC consensus documents recommend the Bleeding Academic Research Consortium (BARC) criteria, peri-procedural and long-term bleeding is inconsistently reported. There are also difficulties in quantifying procedural blood loss and in the reporting of the precise reasons for peri-procedural transfusion.

In the first TAVI devices 30-day bleeding could be as high as 41% (15.6% life-threatening), and the rate of transfusions reached 43%.[56] However, data from the PARTNER trial shows that TAVI considerably reduces bleeding and transfusions compared to SAVR.[57] Improvements in delivery catheters and experience cut current procedural bleeding in half (down to 6.3% life-threatening).[58] Patients who require a blood transfusion following TAVI exhibit an increased risk of major stroke and kidney dysfunction, as well as increased mortality at 1 year.[59] Risk factors for life-threatening bleeding following TAVI include female gender, using a larger size delivery system (>19 Fr), peripheral arterial disease, valve retrieval, and percutaneous access.[60] Late (>30 days) bleeding complications are low (5.9%), occur mainly (64.1%) in the first 6 months post-TAVI, and are associated with 1-year mortality, especially in atrial fibrillation patients.[61] Current guidelines recommend double antiplatelet therapy after TAVI to prevent thromboembolic events, which could be associated with a higher rate of major bleeding. The POPular TAVI trial is the first large, randomised, controlled trial to test if monotherapy with aspirin or oral anticoagulation versus additional clopidogrel after TAVI reduces bleeding (enrolment ends in August 2016).[62]

Conduction Disturbances

The incidence of new onset left bundle branch block (BBB) varies with valve system and time after TAVI (10–50%), but most of them are transient and may be resolved by discharge in 30–50%. A recent study described that conduction disturbances occurred primarily during hospitalisation (increase of PQ interval, QRS width, and first grade atrioventricular block) and subsequently stabilise during a 1-year follow-up. Post-procedural complete left BBB was more frequent in the CoreValve and transapical approach.[63]

Inconsistent data have been published on whether left BBB after TAVI increases the risk of mortality. Complete atrioventricular block requiring a permanent pacemaker implantation (PPI) varies widely among studies and devices, and may be 5–12% for SAPIEN and 24–33% for CoreValve.[64] This conduction disturbance is caused by damage to the atrioventricular bundle or node,[65] and is often peri-procedural but may be delayed up to 7 days after the procedure. The need for PPI is higher with CoreValve and Lotus implantation compared with the SAPIEN device. A pre-existing right BBB and deep valve implantation are the main predictors of subsequent PPI.[66,67] Although a new PPI could be associated to a decrease or lack of improvement in left ventricular function or increased rehospitalisation, it has not been linked to increased mortality.[68]

Stroke

The occurrence of cerebrovascular events is one of the most fearsome complications of TAVI. According to VARC definitions, procedural stroke (acute, <24 hours) has an incidence of 1.5% after TAVI. During the first month after TAVI (subacute) stroke has an incidence rate of 3–7%, reducing to 2.3% >1 year TAVI (late).[69,70] Imaging studies following TAVI showed new embolic events in 72.0%; however, only 6.6% of those patients presented with clinically significant neurological deficits.[71] The clinical relevance of this form of silent cerebral ischaemia remains to be resolved, though it has been speculated that it could be associated with a higher rate of cognitive decline in comparison with SAVR. The stroke rate has already declined with new-generation devices,[72,73] and a great effort is being made to assess the added value of embolic protection devices (filters or debris deflectors) during TAVI procedures.

Paravalvular Regurgitation

An inadequate sealing between the prosthesis and the annulus with the crushed native leaflets causes this complication. Severe and/or asymmetrical calcification of the annulus, the presence of a bicuspid aortic valve, and inadequate prosthesis sizing are risk factors for PVR after TAVI. An exhaustive preoperative CT assessment of valve calcification and anatomy of the aortic root complex should minimise the risk of PVR.[74] Approximately 70% of patients after TAVI have mild regurgitation,[75] and the incidence of moderate or severe PVR is 15–20%.[76] The quantification of the aortic regurgitation after TAVI can be done by angiography, by echocardiographic evaluation, or by invasive haemodynamic parameters.[77] However, the assessment and grading of PVR has become a challenge due to disagreement between techniques, methodologies, and even core laboratories.[78]

PVR has consistently been associated with increased long-term mortality, although some conflicting data persist on the true impact of PVR due to grading assessment, different study populations, and device differences (PVR could be higher at post-implantation but reduce over time with CoreValve).[31]

Potential treatments of this complication are post-dilatation, second valve implantation, or selective leak closure with a vascular plug. However, any post-implantation optimisation procedure might convey a risk of embolisation or root injury, so new iterations of the valve devices brought specific designs to prevent PVR, with promising initial results.[79] Some authors suggested prosthesis oversizing to improve adaptation to the aortic annulus, and thus minimise the leakage,[80] although some other reports show conflicting results.[81] In summary, the PVR is a multifactorial issue and warrants careful pre-operative evaluation, individualised implantation parameters (sizing, balloon volume), and expert management should the complication occur.

Valve Thrombosis

Probably the most commented on TAVI controversy in 2015 was the novel finding of subclinical leaflet thrombosis in bioprosthetic heart valves. Originally suggested in a CT evaluation at 30 days in the Portico IDE Study, and gathering the evidence from other studies, incidence varies from 7.4–43.2% across different devices (including surgical bioprostheses) and timepoints.[82] The finding was consistently missed by transthoracic echocardiography but could be detected by transoesophageal echocardiography, and was resolved in all cases following warfarin therapy. There are still insufficient data to link this finding to clinical events.

Likewise, a TAVI thrombosis registry gathered retrospective data on clinically relevant (dyspnoea or increased valve gradients over time) valve thrombosis, usually detected with echocardiography. Incidence of valve thrombosis was 0.61% (possibly underreported due to the retrospective design), appearing up to 2 years after TAVR, and resolved in most cases with warfarin.[83]

OPEN ISSUES AND FUTURE DIRECTIONS

Cumulative evidence has demonstrated the value of TAVI in the treatment of patients with severe symptomatic AS for inoperable or high-risk patients. Moreover, data from a recent randomised controlled trial suggest that TAVI might be superior to SAVR in this setting.[19] Expanded indications for intermediate-risk patients will follow should the upcoming PARTNER 2[72] and SURTAVI[84] trials show positive results. Furthermore, a trial on low-risk patients (STS score <4) has been recently approved (PARTNER 3) and will have started in spring 2016. Durability >5–10 years will become highly relevant if TAVI is to be offered to low-risk patients with higher life expectancy.

Table 1: Short and mid-term results of the main multicentre registries and controlled trials.

	N	Years	Valve type	Approach	Implatation success (%)	Major vascular complication (%)	Permanent pacemaker (%)	Stroke (%)	PVR ≥2 (%)	Surgical conversion (%)	30-day mortality (%)	1-year mortality (%)
GARY Registry[55]	15,964	2011–2013	8,390 ES/ 6,026 CoVa	11,292 TF/ 4,672 non TF	-	4.0	17.5	1.5	5.8	1.3	6.1[a]	21.3[a]
FRANCE 2 Registry[85]	4,267	2010–2012	2,858 ES/ 1,409 CoVa	3,141 TF/ 1,153 non TF	-	11.8	15.9	4.6	-	-	9.5[b]	23[b]
ADVANCE Registry[86]	1,015	2010–2011	CoVa	TF	97.5	10.9	26.3	3.0	13.5	0.1	4.5	17.6
SAPIEN 3 (Partner II)[79]	583	2013–2014	ES	490 TF/93 non TF	-	-	13.3	1.4	2.5	0.2	2.2	14.4[c]
TVT US Registry[87]	12,182	2011–2013	ES	6,871 TF/ 5,311 non TF	92	6.4	6.6	2.0	8.5	1.0	7.6	26.2

a) Follow-up data from 9,091 patients (2011–2012). 30-Day mortality was 5.4% (TF) and 8% (TA); 1-year mortality was 19.8% (TF) and 24.9% (TA) (TF-TAVI versus TA-TAVI: p<0.001), b) Follow-up data from 3,195 patients, c) 1-year survival: 85.6% overall, 87.3% high-risk patients, and 89.3% high-risk TF access.
ES: Edwards-SAPIEN; CoVa: CoreValve; TF: transfemoral; TA: transapical; TAVI: transcatheter aortic valve implantation; PVR: paravalvular regurgitation.

Table 2: Long-term mortality results after transcatheter aortic valve implantation. Procedures performed between 2007 and 2012.

	N	Valve type	1-year mortality (%)	2-year mortality (%)	3-year mortality (%)	4-year mortality (%)	5-year mortality (%)	6-year mortality (%)	Re-operation of transcatheter valve (%)
Ussia et al.[88]	181	CoVa	23.6	30.3	34.8	0	-	-	-
UK registry[89,90]	3,980	2036 ES/1897 CoVa	18.3	27.2	38.8	-	53.1	37.3	0.8
Rodés-Cabau et al.[91]	339	ES	24	33	49	57	-	-	0.6
Toggweiler et al.[92,a]	88	ES	17	26	47	58	65	-	1.1
Unbehaun et al.[93]	136	ES	18.4	33.1	42.8	51.8	61.4	-	3.0
Salinas et al.[94]	79	ES	20.3	29.1	41.1	50.5	68	-	0.8
El-Mawardy et al.[95]	61	CoVa	11.5	21.3	26.2	39.3	52.5	-	-
PARTNER A (TAVI arm)[48,96-98,b]	348	ES	24.2	33.7	44.2	-	67.8	-	0
PARTNER B (TAVI arm)[99,100]	179	ES	30.7	43	53.9	64.1	71.8	-	1.1

a) Selected population, excluding implantation failure or death before 30 days. Follow-up in 84 out of 88 patients, b) re-operation date reported at 2 years of follow-up.
ES: Edwards-SAPIEN; CoVa: CoreValve; TAVI: transcatheter aortic valve implantation.

New TAVI devices, most of them with self-expanding, recapturable, and repositionable technology, are being developed to further optimise results and reduce complications. Competition between devices will follow so implantation success, complications rates, long-term durability, price, and reimbursement systems will be important differentiating factors. Procedural simplification with a minimalist approach and advanced imaging modalities will increase TAVI application and its implementation in the treatment of other heart valve diseases. Off-label indications for valve-in-valve procedures similar to TAVI, implantation in different valvular heart diseases (aortic regurgitation, mitral, or tricuspid valve disease), or bicuspid aortic disease will expand; and more importantly, the technique will be thoroughly researched, hopefully with randomised, specific trials.[24]

Antithrombotic treatment after TAVI is one of the most important gaps in evidence at this moment, with a lack of support for specific regimes. A balance between recognised problems at both ends of the spectrum (late bleeding and subclinical valve thrombosis) must be found, and tailored treatments for specific populations given accordingly. The selective or widespread role of embolic protection devices for stroke prevention will be clarified with upcoming trials.

In spite of the increasing numbers of TAVI procedures, registries show no decline of SAVR, clearly demonstrating how senile AS is an undertreated disease. Should intermediate-risk trials have positive results for TAVI, it could become a standard of care, followed by a possible reduction in SAVR numbers. Beyond technical (device and procedure) details, keeping a multidisciplinary perspective on candidate selection will ensure continued improvements in survival and quality of life for AS patients, warranting a bright future for TAVI.

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PERCUTANEOUS CORONARY INTERVENTION AND BLEEDING COMPLICATIONS

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ABSTRACT

Percutaneous coronary intervention (PCI) is the most common form of revascularisation in patients with coronary artery disease in both the elective and acute coronary syndrome settings. Advances in pharmacotherapy have reduced ischaemic complications and improved outcomes in PCI, albeit at the expense of major bleeding. Major bleeding complications are amongst the most common to occur following PCI, with varying incident rates reported due to different definitions of what constitutes a 'major bleeding event following PCI', and the risk profile of the patients studied. Irrespective of the bleeding definition used, major bleeding events universally lead to a worse outcome. Major bleeds can occur at both the access site used for PCI and non-access site sources. Both access site and non-access site bleeding increase mortality following PCI. Patients who undergo PCI are at an increased risk of bleeding for several years following the procedure. Strategies to reduce the risk of bleeding should focus on pharmacotherapy, and importantly, use a radial rather than femoral approach to perform PCI.

Keywords: Percutaneous coronary intervention (PCI), complications, bleeding, haemorrhage, mortality.

INTRODUCTION

Cardiovascular disease causes >4 million deaths in Europe annually, and coronary artery disease is responsible for the majority of these.[1] Treatment of coronary artery disease with percutaneous coronary intervention (PCI) is increasing due to the presence of an ageing population and better access to specialist healthcare services.[2] PCI has become increasingly safe, with in-hospital mortality falling from up to 5% in the 1980s[3] to <1% in contemporary practice,[4] however bleeding following PCI remains a major cause of both morbidity and mortality.[5] This review article provides an overview of bleeding in the setting of PCI, exploring the definitions, frequency, sites, timing, and prognostic impact of bleeding in PCI patients, as well as strategies to minimise the risks of bleeding.

DEFINITION OF MAJOR BLEEDING

Reports of major bleeding in patients undergoing PCI procedures is variable, ranging from 1–10% in the literature.[6] This wide variability in reported incidence of bleeding is due to a variety of factors, including differences in patient populations, antithrombotic therapies, the nature of the intervention performed, and importantly, the definition of bleeding that is used. There is currently no universal definition of major bleeding, and there are >10 different definitions used in clinical trials and registries.[7] These definitions rely on different combinations of laboratory measures (a decrease in haemoglobin [Hb] or haematocrit) and clinical events (need for transfusion, haematoma, tamponade, need for surgery, etc.).

One of the most widely used definitions over the last three decades has been the Thrombolysis in Myocardial Infarction (TIMI) definition of bleeding.[8] This definition was initially developed to categorise bleeding into major and minor events within the context of patients undergoing thrombolytic therapy to treat ST-elevation myocardial infarction (STEMI), and relied largely on tested laboratory values of Hb and haematocrit. Criticism of the definition centred on both the values selected

for major bleeding (a decrease in Hb of >5 g/dL), and the lack of focus on clinical events. The original definition has been refined over time to reflect these observations with a broader range of bleeding categories. The Global Use of Strategies to Open Occluded Arteries (GUSTO) definition of bleeding has also been widely used.[9] Again this definition was originally developed in the context of thrombolysis in STEMI patients, but its grading of the severity of bleeding relied on an assessment of the clinical impact of the bleed. Importantly, it did not require changes in laboratory Hb levels, and did not quantify the size of any required blood transfusion. A comparison of outcomes in acute coronary syndrome (ACS) patients, using these distinct definitions, suggests that whilst both are good at predicting adverse outcomes in the acute setting, the risk of GUSTO-defined bleeding persists whilst that of TIMI does not.[10] Attempts have been made to combine the benefits of the TIMI and GUSTO definitions of bleeding to overcome their deficiencies.[11]

The Bleeding Academic Research Consortium (BARC) have also made efforts to create a universal bleeding definition.[7] The initiative developed a definition that captures the nature of bleeding complications, correlating this with prognosis to help guide diagnostic and treatment protocols. The BARC definition grades events from no bleeding (Type 0) up to fatal bleeding (Type 5). Early evidence suggests that this definition is a useful addition to clinical trials, demonstrating good correlation with clinical outcome. The definition of bleeding is vitally important as it can determine the outcome of a study. The landmark RIVAL study did not find a significant difference in major bleeding between the radial and femoral access sites.[12] This study however used its own definition of major bleeding (the need for transfusion of >2 units of blood, hypotension requiring inotropes, a drop in Hb of >50 g/dL, intracranial bleeding), which has limitations. Using a broader definition of bleeding (such as that used in the ACUITY trial)[13] would have resulted in radial access being associated with a significant reduction in major bleeding. Similarly, the MATRIX study used a BARC definition of bleeding and reported a significant reduction in major bleeding episodes associated with radial artery access.[14] Their analysis also reports that use of TIMI or GUSTO major bleeding definitions would have resulted in no significant difference in rates of major bleeding between the two groups.

Table 1: Different definitions of bleeding.

TIMI	GUSTO	BARC
Major bleeding: • Intracranial bleeding • Clinically overt haemorrhage with >5 g/dL decrease in Hb • Fatal bleeding (death within 7 days) Minor bleeding: • Clinically overt haemorrhage with <5 g/dL fall in Hb Requiring medical attention: (and does not meet criteria for major or minor bleeding) • Bleeding requiring intervention • Bleeding leading to prolonged hospitalisation • Bleeding prompting evaluation Minimal bleeding: • Any overt bleeding that does not meet any of the above criteria	Severe or life-threatening: • Intracranial bleeding • Bleeding leading to haemodynamic compromise requiring treatment Moderate: • Bleeding requiring blood transfusion but not leading to haemodynamic compromise Mild: • Bleeding that does not meet the above criteria	Type 0: • No bleeding Type 1: • Bleeding that is not actionable Type 2: • Clinically overt haemorrhage that does not meet criteria for Type 3, 4, or 5 Type 3 (a): • Overt bleeding + Hb drop between 3–5 g/dL Type 3 (b): • Overt bleeding + Hb drop >5 g/dL • Cardiac tamponade • Bleeding requiring surgical intervention • Bleeding requiring intravenous vasoactive drugs Type 3 (c): • Intracranial • Intraocular Type 4: • CABG related bleeding Type 5: • Fatal bleeding

TIMI: thrombolysis in myocardial infarction; GUSTO: Global Use of Strategies to Open Occluded Arteries; BARC: Bleeding Academic Research Consortium; CABG: coronary artery bypass graft; Hb: haemoglobin.

Table 2: Selected studies examining major bleeding and mortality outcome.

Study	Study design	Major bleeding definition	Outcome measure	Findings
Kinnaird et al.[5] (2003)	Retrospective analysis of 10,974 patients who underwent PCI (cohort)	TIMI	Major bleeding and relationship to mortality	Major bleeding independently associated with in-hospital death (HR: 3.5, CI: 1.9–6.7, p=0.0001)
Ndrepepa et al.[18] (2012)	Pooled analysis of 12,459 patients from six studies	BARC	Bleeding and relationship to mortality	BARC ≥2 bleeding independently associated with 1-year mortality (HR: 2.7, CI: 2.0–3.6, p<0.001)
Chhatriwalla et al.[16] (2013)	Retrospective analysis of 3,386,688 PCI procedures (matched cohort)	Required blood transfusion, prolonged hospital stay due to bleed, decrease in Hb >3.0 g/dL	Major bleeding and relationship to mortality	Major bleeding independently associated with in-hospital mortality (HR: 2.9, CI: 2.8–3.1, p<0.001)
Matic et al.[19] (2014)	Prospective cohort of 1,808 STEMI patients	BARC	Major bleeding and relationship to mortality	BARC 3a bleeding (HR: 2.0, CI: 1.2–3.4, p=0.012) and BARC 3b bleeding (HR: 3.2, CI: 1.7–6.2, p<0.0001) independently associated with mortality
Kwok et al.[17] (2014)	Meta-analysis of 42 studies with 533,333 patients	Variety	Major bleeding and relationship to mortality	Major bleeding independently associated with mortality (HR: 3.3, CI: 2.9–3.8)

Hb: haemoglobin; HR: hazard ratio; CI: confidence interval; BARC: Bleeding Academic Research Consortium; PCI: percutaneous coronary intervention; STEMI: ST-elevated myocardial infarction; TIMI: thrombolysis in myocardial infarction.

Table 1 summarises the differences in bleeding definition between TIMI, GUSTO, and BARC.

WHY IS BLEEDING IMPORTANT?

Regardless of the definition used, bleeding is associated with a significant increase in the risk of death, myocardial infarction (MI), and cerebrovascular accident (CVA).[5,15] Up to 12% of deaths following PCI may relate directly to bleeding complications.[16] Recently, strong evidence has emerged that bleeding is independently associated with a higher risk of death. A large meta-analysis by Kwok et al.[17] including 42 studies and >500,000 patients found that bleeding was an independent predictor of death. They found that in studies where adjustments were not made for confounding comorbidities, bleeding was associated with a 6-fold increase in risk of death. Studies in which these comorbidities had been factored in were still associated with a 3-fold increase in risk of death. Importantly, the definition of bleeding also had an impact, with a hazard ratio (HR) for death in the range of 1.5–6.7 depending on the definition used.

There are different mechanisms by which major peri-procedural bleeding has an outcome on long-term survival. A major bleed can lead to morbidity and mortality due to location (for example intracranial) or volume of blood loss leading to hypovolaemic shock. Different types of bleeding can have varying impact on outcomes. A pooled analysis by Ndrepepa et al.[18] of 12,459 patients undergoing PCI in six studies, found a close association between BARC-defined bleeding Class ≥2 and 1-year mortality. BARC Class ≥3 was even more strongly associated with 1-year mortality (HR: 3.2, confidence interval [CI]: 2.3–4.4, p<0.001) than BARC Class ≥2 (HR: 2.7, CI: 2.0–3.6). Another prospective cohort study by Matic et al.[19] also found a relationship between different BARC classes of bleeding and mortality. Of the 1,808 patients with a STEMI, 1-year mortality increased from 11.5% in BARC Class 0 and 1 to 43.5% in BARC Class 3b bleeding. Both BARC 3a bleeding (HR: 2.0, CI: 1.2–3.4, p=0.012) and BARC 3b bleeding (HR: 3.2, CI: 1.7–6.2, p<0.0001) were independently associated with death at 1 year. Some of the trials examining major bleeding and mortality are listed in Table 2.

Bleeding and anaemia can also lead to an increase in the production of erythropoietin, a substance that is known to have prothrombotic and platelet-activating effects.[20] Treatment with erythropoietin in patients following MI has been shown to be associated with an increased risk of further MI, CVA, and death.[21] This hypercoaguable state is a particular risk for patients who have had PCI and may have coronary stents. Bleeding (and the perceived increased risk of recurrent bleeding) may lead to alteration in antiplatelet regimes. Discontinuation of antiplatelets is strongly associated with stent thrombosis, MI, and death.[22] Bleeding may also lead to discontinuation of warfarin in patients with concurrent atrial fibrillation (AF) and this has been shown to be associated with significantly higher rates of death.[23]

PREDICTORS OF BLEEDING

Unsurprisingly, the risk of bleeding increases as patients become older, present with an ACS, or have renal or heart failure.[24] The risk of bleeding at 30 days following PCI increases from between 0.7% and 1% in elective patients[25] to 4.7% in non-STEMI patients[26] and 8.9% in STEMI patients.[6,27] The predictors of early bleeding are often procedure-related such as access site, sheath size, and antithrombotic regimen, in addition to comorbidities.[28] These are less likely to have an influence on late bleeding. Independent predictors of late bleeding include age, previous bleeding episode, chronic kidney disease, and triple therapy with dual antiplatelets and warfarin.[29]

WHERE DO PATIENTS BLEED?

Major bleeding following PCI can occur at different locations. Bleeding can occur at the radial or femoral artery access site (and spread to adjacent tissue), or at non-access sites such as the gastrointestinal (GI) tract, the pericardium, the pulmonary system, etc. A large meta-analysis by Kwok et al.[17] showed that non-access site bleeding is common and is responsible for between half and two-thirds of all TIMI classification bleeding events. Across seven studies, with a combined total of 301,404 patients, access site-related bleeding complications had a prevalence of 11.2%. Across six studies with 290,456 patients, non-access site bleeding had a prevalence of 10.2%. Although both access site and non-access site bleeding are associated with increased mortality, non-access site bleeding is more closely correlated with adverse outcomes, and is associated with a 4-fold increase in 1-year mortality.[30] The meta-analysis by Kwok et al.[17] corroborated these findings and showed that whilst access site bleeding significantly increased the risk of 30-day mortality (relative risk: 1.71, 95% CI: 1.37–2.13), the increase in risk following non-access site bleeding was much greater (relative risk: 4.06, 95% CI: 3.21–5.14). In patients who have non-access site bleeds, the anatomical location can also have an impact on outcome. The same meta-analysis of studies involving non-access site bleeding found a mortality of 13% in patients after a bleed into the GI tract, 6.8% after a retroperitoneal bleed, 56% following an intracranial bleed, and 8.6% following an intramyocardial or pericardial bleed. Haemorrhagic CVA is of particular concern as it is associated with very significant 30-day mortality (odds ratio: 13.87, 95% CI: 6.37–30.21).[31] A large meta-analysis found that the most frequent location of non-access site is the GI tract (20.4%), followed by genito-urinary tract (7.7%), with intra-cranial bleeding occurring in only 0.5% of the population.[32]

WHEN DO PATIENTS BLEED?

Patients undergoing PCI are at risk of peri-procedural bleeding but continue to be at excess risk for some time following this. In the CREDO trial, which followed patients who had undergone PCI, patients were randomised to receive clopidogrel and aspirin for either 1 month or 1 year, and the incidence of non-procedural major bleeding in the prolonged clopidogrel group was 1.2%.[33] In the PCI subgroup of the CURE study, major bleeding occurred in 1.1% of patients between 1 and 9 months in those randomised to aspirin and clopidogrel.[34] Real-world data suggests that in patients >65 years, major bleeding rates may be as high as 2.5% in the year following PCI in those treated with dual antiplatelets.[29] To place these rates of bleeding into context, patients with AF on warfarin have an incidence of major bleeding of 1.3% per year and 2.2% per year on warfarin plus aspirin.[35] Recent work from the ADAPT-DES trial reported on bleeding events related to PCI after hospital discharge and up to 2 years.[36] They found that the risk of bleeding accrues constantly with rates of first bleeding at 30 days, 1 year, and 2 years of 0.7%, 3.8%, and 8.8%, respectively.

This is an important message as it reiterates that patients who undergo PCI continue to be at significant risk following discharge from hospital. The same study found that a majority of bleeding events after hospital discharge are related to the GI tract (61.7%), and that following multivariate analysis, post-discharge bleeding was the strongest predictor of 2-year mortality.

The increased risk of death associated with bleeding may not be limited to the immediate hospital admission. Although bleeding following PCI is strongly associated with in-hospital and 30-day mortality, the evidence of an impact on longer-term outcomes is less clear. The TRITON-TIMI 38 analysis found that although major bleeding was strongly associated with mortality within the first month of PCI, the association was not significant beyond 40 days.[37] However, other groups have found that major bleeding is associated with increased mortality at 6 months,[38] 1 year,[29] and even 3 years following PCI.[39]

BLOOD TRANSFUSION

Anaemia is independently associated with an increased risk of MI and cardiac mortality in patients undergoing PCI.[40] The use of blood transfusion to correct anaemia and to treat bleeding remains controversial. Around 2% of all patients treated with PCI undergo a blood transfusion, either following an acute bleeding event or due to chronic anaemia.[41] In patients who present with an ACS who undergo PCI, the rates of blood transfusion may be as high as 10%.[42] Although there is great variation in practice regarding the use of blood transfusion, women, the elderly, patients with renal or heart failure, and those with a history of prior ischaemic heart disease are most likely to receive a blood transfusion.[43]

Regardless of whether a patient has a bleeding episode following PCI, the need for a blood transfusion is associated with up to a 3-fold increase in rates of MI or death in patients who present with an ACS.[43] A previous meta-analysis of >200,000 patients presenting with myocardial infarction that compared a liberal blood transfusion policy (defined as transfusion for Hb <9.0 g/dL) versus a more restrictive policy (transfusion for Hb <7.0 g/dL) suggested that a liberal blood transfusion policy was associated with increased all-cause mortality.[44] This study involved a majority of patients who were managed medically rather than following PCI so it is less relevant to contemporary practice. A more recent meta-analysis involving >2 million patients who had undergone PCI, examined the impact of blood transfusions on outcome.[45] It confirmed that blood transfusion following contemporary PCI is relatively common, with a prevalence of 2.3% (>54,000 patients received a transfusion). The study also found that blood transfusions were an independent predictor of major adverse cardiac events and death, increasing the risk by as much as 3-fold. Importantly, blood transfusions are associated with a worse outcome even in patients who do not have a bleeding event.[5] The absence of clear evidence from randomised controlled trials in the area of PCI and blood transfusion have led to a lack of clear guidelines as to when blood transfusion should be used in the setting of PCI and ACSs.[46]

BLEEDING RISK

As the importance of bleeding to outcome following PCI has become clear, models have been developed to help quantify the risk of bleeding. Mehta et al.[24] performed an initial analysis of 302,152 patients from the National Cardiovascular Data Registry (NCDR), and proposed an algorithm featuring age, sex, previous heart failure, renal impairment, peripheral vascular disease, previous PCI, heart failure class, presence of ST elevation, and cardiogenic shock to categorise patients into low, intermediate, or high-risk of bleeding. This was further improved after an analysis of 1,043,759 PCI procedures from the NCDR CathPCI registry by Rao et al.[47] The new NCDR model used 10 clinical variables to give a point score between 0 and 210 that predicted a bleeding risk of between 0.9% and 86% following PCI. An alternative model is the CRUSADE bleeding score developed by Subherwal et al.[48] and based on 71,277 non-STEMI patients who underwent PCI. This model uses clinical variables to give a score of between 1 and 100 points to grade risk of bleeding. This and other risk scoring systems are limited by the requirement for laboratory values, which may not always be available prior to emergency situations such as a primary PCI. Doubts have also been raised about the predictive value of scoring systems for bleeding in patients undergoing PCI.[49]

Table 3: Trials comparing radial and femoral access.

Trial	Patient population	Primary outcome measure	Findings
RIVAL[65] (2011)	7,021 patients with ACS (no STEMI patients)	Composite of death, MI, CVA, and major bleeding at 30 days	Primary outcome in 3.7% of radial group vs. 4.0% in femoral group (HR: 0.92, CI: 0.72–1.17, p=0.50)
RIFLE-STEACS[63] (2012)	1,001 STEMI patients	NACE composed of cardiac death, CVA, MI, target-vessel revascularisation, and bleeding	NACE 13.6% of radial group vs. 21.0% in femoral group (p=0.003)
STEMI-RADIAL[64] (2014)	707 STEMI patients	Co-primary endpoints of composite of bleeding and vascular access site complications, and NACE composed of death, MI, CVA, major bleeding/vascular complications	Composite of bleeding and vascular site complications occurred in 1.4% of the radial group vs. 7.2% of femoral group (p=0.0001). NACE of 4.6% in radial group vs. 11.0% in femoral group (p=0.0028)
MATRIX (2015)	8,404 patients with ACS (including STEMI patients)	Co-primary end points of MACE composed of death, MI, CVA, and NACE composed of death, MI, CVA and major bleeding)	MACE in 8.8% of radial group vs. 10.3% in femoral group (HR: 0.85, CI: 0.74–0.99. p=0.03), NACE in 9.8% of radial group vs. 11.7% of femoral group (HR: 0.83, CI: 0.73–0.96, p=0.0092)

RIVAL: Radial vs femoral access for coronary intervention; RIFLE-STEACS: the Radial Versus Femoral Randomized Investigation in ST-Segment Elevation Acute Coronary Syndrome; STEMI-RADIAL: ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicentre randomized clinical trial; MATRIX: Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX Program; MACE: major adverse cardiovascular events; MI: myocardial infarction; NACE: net adverse clinical events; ACS: acute coronary syndrome; HR: hazard ratio; CI: confidence interval; STEMI: ST-elevation myocardial infarction; CVA: cerebrovascular accident.

STRATEGIES TO REDUCE RISKS OF BLEEDING

Major bleeding complications are associated with significant immediate and long-term morbidity and mortality. Every effort should be made to minimise the risk of bleeding in patients undergoing PCI. The primary mechanisms available to achieve this are the adjustment of adjunctive pharmacotherapy, and a pragmatic choice of access site for PCI.

Pharmacology

Antiplatelet agents

The drive to reduce ischaemic complications during and following PCI has led to the development of increasingly potent antiplatelet agents. The benefit of clopidogrel (a thienopyridine) in addition to aspirin in patients undergoing PCI following an ACS was clearly established by the PCI-CURE study,[34] in which clopidogrel significantly reduced a composite endpoint of cardiovascular death, MI, and target-vessel revascularisation (HR: 0.70, CI: 0.50–0.97, p=0.03) with no significant increase in major bleeding. The loading dose of clopidogrel can also have an effect on outcome. It has been shown that a 600 mg loading dose of clopidogrel compared with 300 mg reduces mortality, reinfarction, and stent thrombosis with no increase in major bleeding in STEMI patients undergoing PCI.[50] The increased loading dose also reduced cardiovascular events without any increase in major bleeding in a group of ACS patients being treated with PCI.[51]

When compared with clopidogrel, the more potent agent prasugrel has been shown to significantly reduce cardiovascular death, MI, and CVA (HR: 0.81, CI: 0.73–0.90, p<0.001) in 13,608 patients with ACS being treated with PCI,[52] however these reductions came with a significant increase in major, life-threatening, and fatal bleeding. Net clinical benefit favoured prasugrel in most groups, but patients with a previous CVA

had net clinical harm from prasugrel, and patients aged >75 years and those with a weight of <60 kg obtained no net clinical benefit from prasugrel. Patients who did not have any of these risk factors did not have any additional bleeding with prasugrel compared with clopidogrel. Similarly, treatment with ticagrelor rather than clopidogrel in patients with ACS where an invasive strategy is planned was associated with a significantly lower rate of a composite of cardiovascular death, MI, and CVA (HR: 0.84, CI: 0.75–0.94, p=0.0025).[53] Within the GUSTO criteria, ticagrelor was not associated with any increase in severe bleeding compared with clopidogrel.

Oral anticoagulant therapy

If PCI is planned for a patient concurrently taking an oral anticoagulant for another indication (usually AF, mechanical heart valves, or history of thromboembolic disease), antiplatelet therapy with aspirin and a thienopyridine is indicated, but such triple therapies are associated with a significantly higher risk of non-fatal and fatal bleeding.[54] The WOEST study randomised 573 patients receiving vitamin k antagonists (VKA) and undergoing PCI to clopidogrel alone or clopidogrel and aspirin (triple therapy) for 1 year.[55] The clopidogrel alone group had significantly fewer bleeding events (HR: 0.36, CI: 0.26–0.50, p<0.0001) with no increase in thrombotic events (although the trial was not sufficiently powered to detect this). It should also be noted that femoral access was used in >70% of the patients in the trial. These findings were corroborated by a retrospective analysis where the authors investigated the risk for thrombotic events and bleeding according to multiple antithrombotic regimens after MI or PCI in AF patients.[56] At 1 year, there was no increased risk of recurrent coronary events for dual therapy (HR: 0.69, 95% CI: 0.48–1.00) relative to triple therapy, and bleeding risk was also not significantly lower for VKA plus clopidogrel (HR: 0.78, 95% CI: 0.55–1.12) versus triple therapy. The optimum length of triple treatment remains unclear. The risk of stent thrombosis is highest early after PCI and declines with time, whilst the risk of bleeding increases with length of treatment with triple therapy. The ISAR-TRIPLE trial investigated whether 6 weeks of clopidogrel therapy was superior to 6 months of clopidogrel therapy in patients receiving VKA and aspirin following PCI.[57] The study found that the primary endpoint (composite of death, MI, CVA, stent thrombosis, major bleeding) was not significantly different between the two groups.

Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitors (GPI) also have very strong antiplatelet effects with a subsequent reduction in ischaemic events at the cost of increased bleeding following PCI.[58] Comparison of heparin and GPI versus bivalirudin showed a net clinical benefit in the bivalirudin group, driven largely by bleeding events in the GPI group.[27] More recent work showed no benefit of bivalirudin versus heparin alone.[59] The use of low molecular weight heparins in the treatment of ACS is well established. There is evidence that the use of fondaparinux over enoxaparin leads to a similar reduction in ischaemic events with a reduction in major bleeding and subsequently mortality.

When considering treatment, there should be a balance between reducing ischaemic events such as stent thrombosis and myocardial infarction, and bleeding events following PCI. The selection of particular antiplatelet agents and adjunctive pharmacotherapy can be aided by using one of the described bleeding risk scoring systems to assess individual patient risk.

Access Site

Transfemoral PCI has historically been the default access site for many institutions across the world, although transradial PCI had been described as early as 1993. In recent years, the number of procedures carried out via the radial route has increased dramatically, particularly in Europe. Whilst pharmacotherapy has an impact on the rates of bleeding, there is a growing body of evidence that suggests that using a transradial rather than transfemoral approach has a much larger impact in relation to reducing bleeding events and subsequent adverse outcomes.

Analysis of UK data suggests that radial versus femoral PCI in STEMI patients causes significantly fewer access site-related bleeds, and is independently associated with a 30% reduction in 30-day mortality.[60] A meta-analysis comprising nearly 3,000 patients similarly found that radial PCI is associated with a significant reduction in mortality compared with femoral PCI, with the result being driven by a reduction in major bleeding events.[61] Other work has shown that the biggest reduction in mortality in patients treated

using radial PCI occurs in those who are at highest risk of bleeding.[62] A recently published large, randomised, multicentre trial comparing radial versus femoral access in ACS patients undergoing PCI also found a reduction in net clinical events including bleeding and mortality.[14] Similarly, the RIFLE-STEACS study observed a significant reduction in bleeding and cardiac mortality with radial compared with femoral access.[63] By contrast the STEMI-RADIAL trial showed a significant reduction in bleeding and access site complications with radial access but no mortality benefit.[64] Although the RIVAL study found no significant benefit in non-STEMI patients, the STEMI subgroup had a significant reduction in bleeding and mortality in the radial access group.[65] The findings of these important trials comparing radial versus femoral access are summarised in Table 3. The weight of evidence favouring radial over femoral PCI has led to the European Society of Cardiology (ESC) giving a 1A recommendation to radial over femoral access in patients presenting with an ACS.[46]

CONCLUSION

Bleeding following PCI is common and is associated with significant morbidity and mortality. Bleeding should be considered before, during, and after PCI procedures, with a focus on strategies to reduce risk for patients. Pharmacotherapy should be individually tailored to a patient's risk of ischaemic and bleeding events, and the use of bleeding risk scoring systems can be considered. Radial rather than femoral artery access should be utilised when possible. Blood transfusions should be used judiciously in patients who undergo PCI.

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