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INTERVENTIONAL CARDIOLOGY

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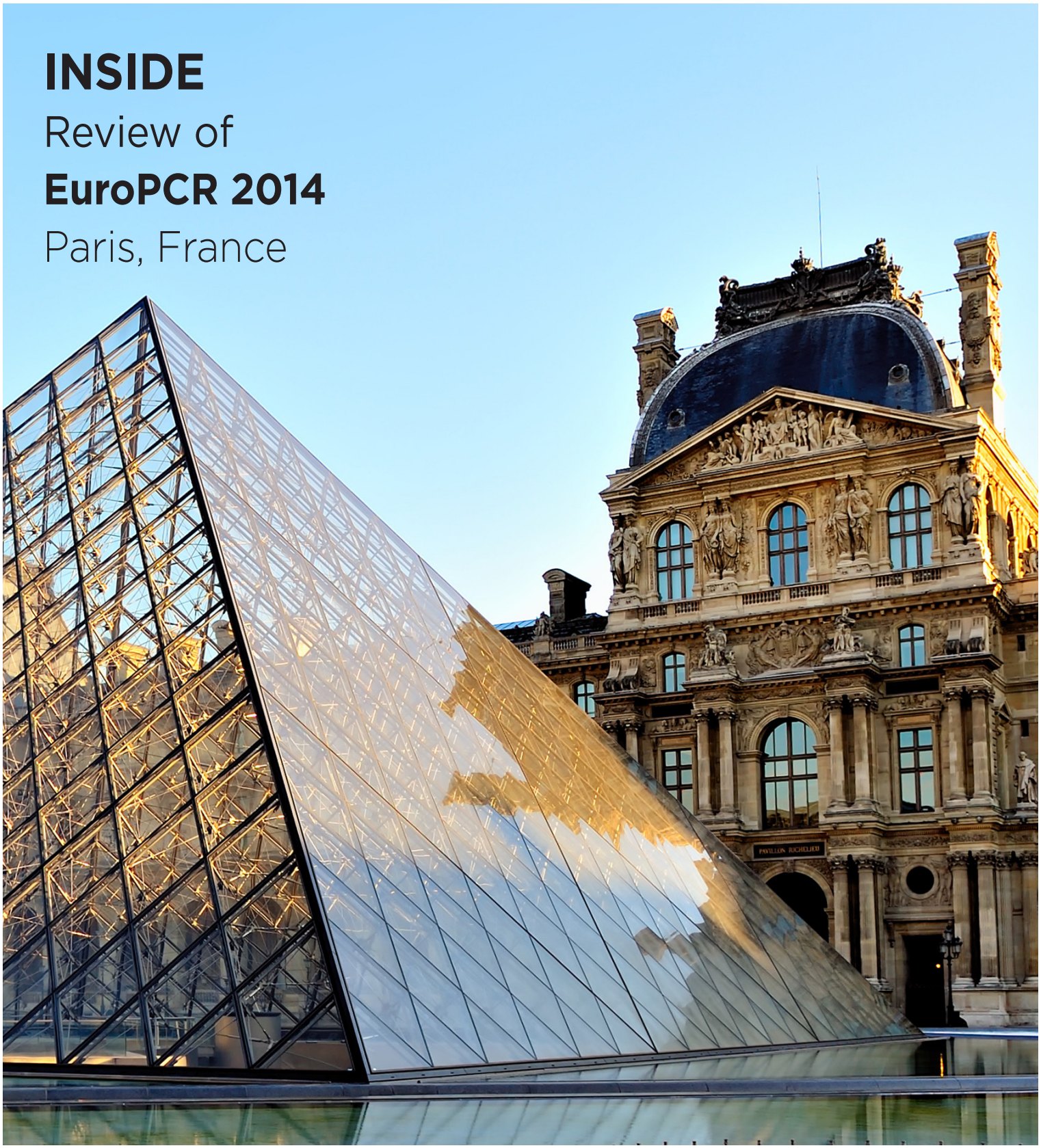
INSIDE

Review of

EuroPCR 2014

Paris, France



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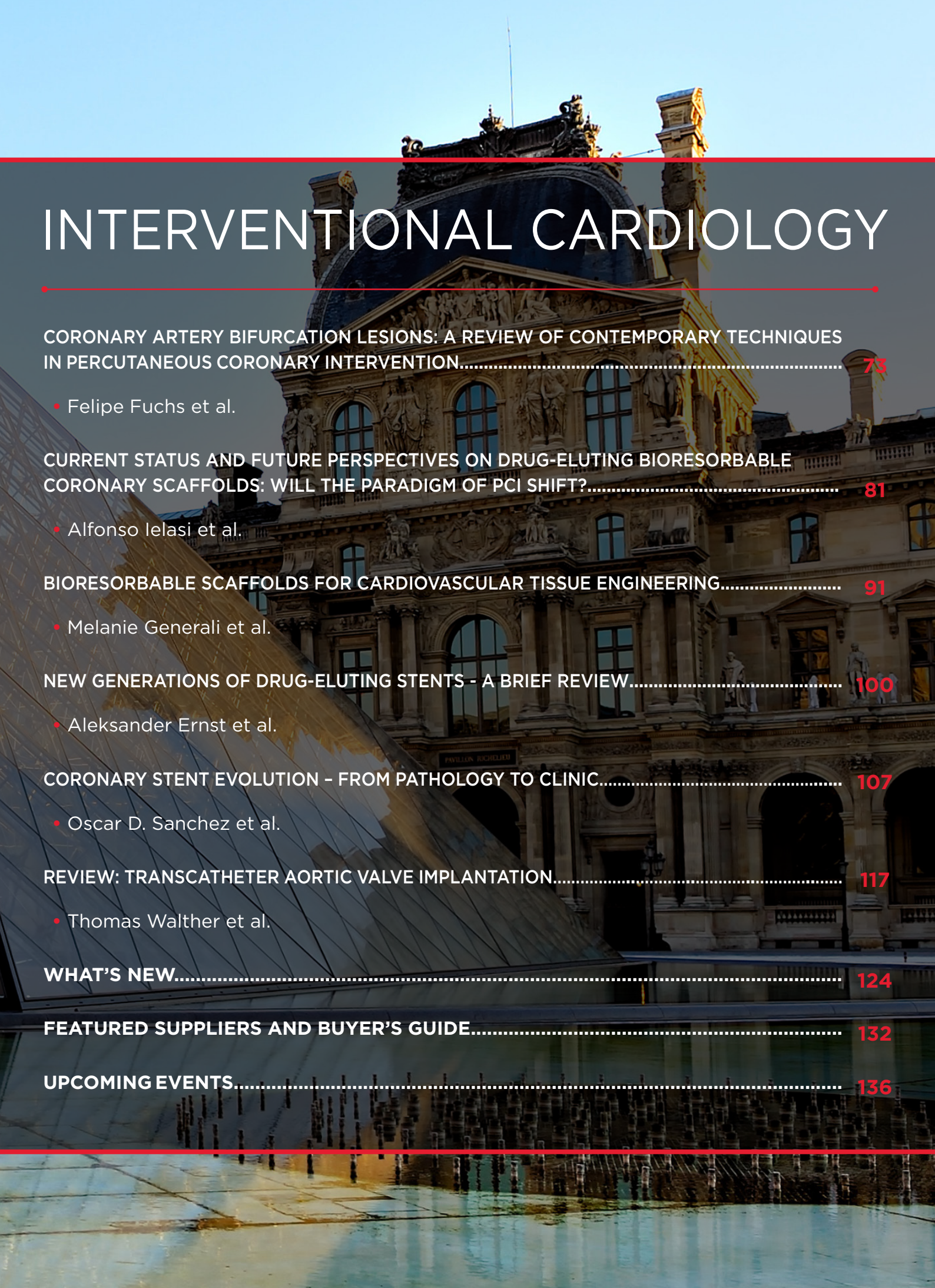

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Welcome

It is a pleasure to welcome you to the second edition of the *European Medical Journal – Interventional Cardiology*. This edition promises to deliver the most current, ground-breaking, and game-changing updates within this rapidly developing field.

Building upon the success of our publication last year, we have increased the size of this journal by increasing the number of peer reviewed articles and delivering to our readers more coverage of the 2014 EuroPCR Congress, 20th-23rd May, Paris, France, found in our 'Congress Review Section', ensuring that the latest developments are reported directly to you.

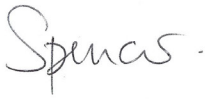
It is of paramount importance for all healthcare professionals to find the right blend between knowledge and evidence - which comes from studies - and science and practice. As Dr William Wijns, EuroPCR 2014 Course Director, said: "As doctors in interventional medicine, it is really at the heart of our practice that we need to be able to balance evidence and experience."

However, it can be a difficult task for clinicians to implement the findings of the clinically relevant trials into their daily practice. The aim of this journal is to undertake this difficult task ensuring that all doctors are provided with enough information to improve the treatment and also the lives of their patients.

Ms Valérie Collas and colleagues have written a very enlightening paper: *'Transcatheter aortic valve implantation: review and current state of the art'*, concerning the potential complications which can arise with the use of transcatheter aortic valve implantation. To overcome these complications, new valves have been designed and clinically evaluated; this paper discusses these new technologies, noting their uses, but also their downfalls.

Mitral regurgitation can be a very complex procedure, and while developments in this area have been made, it can now be corrected or replaced. Experience in treating this population is undoubtedly beneficial and, at times, can be mandatory. In his paper: *'Recent advances in surgical and percutaneous mitral valve therapies - implications of an integrated approach to mitral regurgitation*,' Dr Lenard Conradi and colleagues emphasise the need for an integrated, multidisciplinary heart team when treating these patients. An approach such as this will relieve under-treatment, and different treatment options can be suggested and explored. Dr Conradi also suggests that for high-risk patients, mitral valve therapies can represent an appropriate alternative to surgical therapies.

While it is difficult to teach experience, because it is something which can only be learned through time, it is our hope that this edition provides you with enough information to help you feel confident when treating patients.



Spencer Gore
Director, European Medical Journal

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EMJ GORELY NEW MEDIA

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Foreword

Prof Ran Kornowski

Professor of Cardiovascular Medicine,
Tel Aviv University, Israel.

Dear Colleagues,

Interventional cardiology is a generic term meant to embrace all forms of treatment involving minimally invasive approaches to diagnose and treat cardiovascular diseases. Over the last era, novel catheter-based techniques have been developed and studied as new adjunctive pharmacotherapies to treat most forms of cardiovascular disorders. Interventional cardiology builds on the seminal pioneer work of Andreas Gruentzig who first performed the successful coronary balloon angioplasty procedure on a conscious patient in 1977 in Zurich, Switzerland. Since then - and especially over the last decade - numerous exciting developments have emerged to achieve therapeutic benefits, especially in myocardial revascularisation and structural-valve interventions.

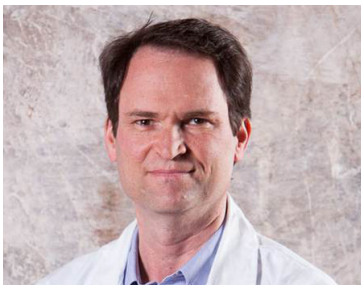
The *European Medical Journal-Interventional Cardiology* edition publishes high quality peer-reviewed articles using an 'open access' platform of medical publishing. All articles are freely accessible, without any charge to readers. This measure ensures the widest possible dissemination of valuable knowledge to a global readership. This journal calls for experimental and clinical experts to submit their work for publication, covering current therapeutic and diagnostic developments and novel techniques in all aspects of cardiovascular medicine. Clinical research, innovation topics, review articles, practice guides, and case reports will also be featured. To safeguard the quality of the published articles, EMJ has assembled an editorial board of recognised professional experts.

> "These are exciting times but also challenging ones for the field of interventional cardiology."

In addition, this journal reports on the most prominent interventional cardiology congress: EuroPCR. Breaking news of particular interest is also reported in the journal, and this feature is already integrated into social media platforms, providing immediately updated information to readers on their computers or mobile devices. Busy clinicians will thus be able to keep themselves informed with the latest developments in the field.

These are exciting times but also challenging ones for the field of interventional cardiology. The specialty is looking ahead to innovations in cardiac imaging technologies, bio-resorbable vascular scaffolds, catheter-based valve interventions, and additional ground-breaking diagnostic and therapeutic modalities. On behalf of the editorial board, I look forward to the development of *EMJ-Interventional Cardiology* into a productive forum for the propagation of cardiovascular knowledge to readers worldwide.

Best regards,



Ran Kornowski, MD

Ran Kornowski

Chairman, Department of Cardiology, Rabin Medical Center, Beilinson and Hasharon Hospitals, Petah Tikva; Professor of Cardiovascular Medicine, The 'Sackler' Faculty of Medicine, Tel Aviv University, Israel.

EUROPCR ANNUAL CONGRESS 2014

LE PALAIS DES CONGRÈS, PARIS, FRANCE

20TH - 23RD MAY 2014

Welcome to the *European Medical Journal* review of EuroPCR: The Official Annual Meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) 2014

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20TH - 23RD MAY 2014

Welcome to the *European Medical Journal* review of EuroPCR: The Official Annual Meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) 2014

A prominent jewel in Europe's colossal crown, Paris needs no introduction. People from all over the world come to eat, sightsee, and party in style at France's glittering capital. With the city's delicate beauty, countless hearts are captured year-upon-year. Paris also continues to lead the way not only in art and fashion, but also in science and discovery.

Eternal optimism springing from this cultural mecca makes Paris a great place for such a prestigious event, and here the 25th EuroPCR Course™, a registered branch of the European Society of Cardiology, did not disappoint.

Celebrating a landmark silver anniversary, the official annual meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), taking place from 20th-23rd May 2014 at the beautiful and iconic Palais des Congrès, saw the congregation of the world's leading experts in the field of interventional cardiology. Numerous technological advances were showcased in front of over 12,000 attending clinicians and scientists.

One word can be used to sum up the meeting in line with one of the course's novel features: illuminating.

Leading the way at the Congress were the substantial advances made in personalised medicine - a prominent feature throughout this section. In response to the needs of individual patients, revolutionary implants have been designed and trialled with the potential goal of delivering coronary intervention treatment to whomever may require it.

Notable examples demonstrated at the Congress include the Edward Lifesciences' FORTIS mitral transcatheter heart valve and Tiara™

"Each patient is unique. We meet here at EuroPCR to try to find the best solution for each individual patient, and that brings us to this concept of personalised medicine, personalised interventional care. I think that is, at the end of the day, what we are aiming at."

Dr William Wijns, EuroPCR 2014 Course Director

Transcatheter Mitral Valve for the treatment of mitral regurgitation, which offer hope to patients ineligible for surgical mitral intervention. Though still deep in the trial stage and noticeably raw, the technologies represent a breakthrough in mitral intervention, which could change the lives of many cardiac patients.

Dr William Wijns, EuroPCR 2014 Course Director, said: "Each patient is unique. We meet here at EuroPCR to try to find the best solution for each individual patient, and that brings us to this concept of personalised medicine, personalised interventional care. I think that is, at the end of the day, what we are aiming at."

A spearheading motivation at the Congress was the determination of the cardiovascular community to use their collective knowledge, expertise, and practice to find the best care for the individual patient.

One universally-known device which has helped to light the way for high-risk valve-in-valve procedures is also covered in this section. The smartphone/tablet app series designed by Mr Vinayak Bapat, Consultant Cardiothoracic Surgeon, Guys and St. Thomas' Hospital, London, UK, brings state-of-the-art information on crucial transcatheter heart valve procedures instantaneously to the doctor, adding a fresh angle to the burgeoning and much-discussed transcatheter aortic valve implantation industry.

This heartening overall technological progress has given the world of interventional cardiology a boost of encouragement, with the hope that these developments will soon be integrated into daily practice, thus delivering enhanced outcome and experience for patients and physicians, respectively.

Smartphone holds key for TAVI endeavours

> "Our goal is to have education that is free, easy to use, and is at doctors' fingertips."
>
> *Mr Vinayak Bapat, Guys and St. Thomas' Hospital, London, UK*

VALVE-IN-VALVE procedures have experienced renewed vigour with the introduction of a smartphone app aimed at making this type of operation much smoother.

The booming transcatheter aortic valve implantation (TAVI) industry has triggered a spill-over of new TAVI devices, including St Jude Medical's Portico™ and Jenavalve technology's Jenavalve™, into valve-in-valve operations such as the treatment of a degenerated bioprosthetic surgical heart valve.

Hopes of successful valve-in-valve procedures hang on correct identification of the surgical valve, selection of the correct size of TAVI valve, and ensuring its precise placement. A suboptimal result that manifests in short and long-term outcomes occurs from incorrect size and placement. Therefore, it is crucial that interventional cardiologists receive the best advice. Publications, however, take time to reach this target audience and, as a result, a more instant supply of knowledge is required.

"We felt that we should design a smartphone/tablet app to make information on valve-in-valve procedures available to interventional cardiologists anywhere in the world," said Mr Vinayak Bapat, developer of the smartphone app, Consultant Cardiothoracic Surgeon, Guys and St. Thomas' Hospital, London, UK.

Two apps are currently available: a valve-in-valve aortic app and a valve-in-valve mitral app, which provide information on various stented and TAVI valves, and valves and rings used in the mitral position, respectively.

Mr Bapat said: "The idea of the apps is to provide information specific for a clinical scenario, quickly and simply, and help reduce the need to trawl through vast amounts of literature to find information for planning and performing a valve-in-valve or valve-in-ring case. Our goal is to have education that is free, easy to use, and is at doctors' fingertips."

Mr Bapat added later: "We hope this will result in improved results and better outcomes for patients. This is a rapidly developing field and, as more transcatheter heart valves are used, the information will be updated and new apps added to this series to keep pace with newer developments."

Salute to advancing technology

TECHNOLOGICAL advances, including innovation in the field of cardiac pacing as seen in the area of leadless pacing and the latest generation of transcatheter heart valves, are generating renewed fervour in the interventional cardiology community.

State-of-the-art inventions, such as St Jude Medical's NanostimTM Leadless Pacemaker and Medtronic's MicraTM Transcatheter Pacing System - both single chamber leadless pacing systems - as well as the Edwards SapienTM 3 Transcatheter Heart Valve (Edwards Lifesciences) - the most advanced commercially available valve - are among the devices offering hope for the future of complex cardiovascular interventions.

A novel system providing reliable pacing and sensing is currently regarded as a necessity for leadless pacing, addressing the challenges of current pacing systems by minimising the risks of infection, pneumothorax, dislodgement, and long-term infection.

Prof Karl Heinz Kuck, Chief of Staff, St George Hospital, Hamburg, Germany, and President of the European Heart Rhythm Association (EHRA), commented on the status of the early clinical evidence in the field of leadless piercing: "The technical advancement with leadless pacemakers represents 'a big step forward'. These devices have the advantage of a reduced risk of infection and also a significantly lower risk of thromboembolic complications that may lead to pulmonary hypertension. The only uncertainties that we currently face are due to the fact that the experience with the device is still rather limited, and we are yet to identify the best position to have a safe implantation."

Prof Panos Vardas, University Hospital of Crete, Crete, Greece, added: "Leadless pacing is a very significant development, but to take it from the current VVIR [ventricular rate modulated pacing] configuration to the next stage of double-chamber pacing is going to be a challenge. Also, we need longer follow-up, and a better understanding of the thrombogenicity of the devices and possible complications, but I am optimistic that progress is underway."

"These devices have the advantage of a reduced risk of infection and also a significantly lower risk of thromboembolic complications that may lead to pulmonary hypertension."

Prof Karl Heinz Kuck, St George Hospital, Hamburg, Germany

Clash of two titans: PCI versus thrombolysis for STEMI patients

> "It is very reassuring for those of us who work in resource-scarce environments that thrombolysis, if given correctly, is shown to be equivalent to PCI."
>
> *Dr Sajidah Khan, University of KwaZulu-Natal, Durban, South Africa*

IMMEDIATE reperfusion therapies such as primary percutaneous coronary intervention (PCI) and thrombolysis for ST-segment elevation myocardial infarction (STEMI) are the two main lifesaving strategies which have been the main topic of thought-provoking debate.

Although both therapies have their advantages and disadvantages, when there is no option for one, the other can be used as a suitable replacement.

Dr Thomas Cuisset, University Hospital, Marseille, France, highlighted in his statement for the use of PCI that: "Within this, we sought to highlight that primary PCI has to be a personalised intervention. Within the 'STEMI box', we are dealing with many very different patients and so the choice of drugs, vascular access, and use (or not) of thromboaspiration, needs to be tailored to fit the patient."

Dr Sajidah Khan, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa, pointed out that although PCI remains the gold standard therapy to open the artery, in some areas where there is the lack of available resources, the alternative option of thrombolysis is a more realistically available therapy.

"It is very reassuring for those of us who work in resource-scarce environments that thrombolysis, if given correctly, is shown to be equivalent to PCI. However, we have to be cautious about the bleeding risk, particularly in the elderly. In those over 75, the benefit of primary PCI clearly outshines thrombolysis. In the developing world, we see that the age of the patient presenting with ST elevation is much younger and it is reassuring to know that the risk of bleeding from thrombolysis is lower in this population," Dr Khan commented.

Dr Khan also mentioned that death from coronary artery disease is becoming more prevalent in countries that face economic obstacles, with limited access to catheterisation laboratories.

Dr Khan suggested that there should be a fair comparison of PCI and thrombolysis in countries that have access to both resources. "This points to the fact that merely having the access to the cath lab does not necessarily translate to every patient reaching the lab and undergoing revascularisation within 3 hours," she added.

Transcatheter aortic heart valve generating beats of excitement

ADVANCED commercially available transcatheter aortic heart valve, Edwards SAPIEN 3 valve, has shown promising results in the replacement of dysfunctional valves which can be used to treat aortic stenosis.

The SAPIEN 3 Trial (prospective, multicentre, and non-randomised study) evaluated the outcomes of the first 150 high and intermediate-risk patients treated with the SAPIEN 3 valve for 11 months duration. The trial spanned 16 centres across Europe and Canada. Transfemoral (n=96) and transapical/transaortic (n=54) approaches were also evaluated, and it was reported that there was 5.3% all-cause mortality concerning the access points. Overall the outcomes after 1 month were deemed excellent.

"These data demonstrated that the improved valve and delivery system design allowed precise positioning of the SAPIEN 3 valve, and early outcomes from the trial clearly demonstrated outstanding safety. The results of this study indicate the SAPIEN 3 valve may enable treatment of intermediate-risk patients with aortic stenosis," said Dr John Webb, Director, Interventional Cardiology and Cardiac Catheterization Laboratories, St. Paul's Hospital, Vancouver, British Columbia, Canada.

The safety profile of the SAPIEN 3 valve via transfemoral implantation looks positive, with very low mortality and stroke rates of 2.1% and 1.0%, respectively, and very few complications at the access site. It was reported that 96.6% of patients had mild paravalvular leak but there were no cases of severe paravalvular leak.

"It is particularly encouraging that these early results showed that none of the patients were re-hospitalised during the follow-up period, which is a meaningful outcome for patients who had previously been very ill," said Mr Larry L. Wood, Corporate Vice President, Transcatheter Heart Valves, Edwards Lifesciences Corporation, Irvine, California, USA.

Improving upon past prototypes, the ergonomic model was designed to minimise paravalvular leakage (with its polyethylene terephthalate outer skirt), preserving radical strength (frame design plus cobalt chromium alloy material) and size variations according to the patient's anatomy. The valve can be delivered through a low-profile 14 French expandable sheath (eSheath).

The SAPIEN 3 valve is approved in Europe for the treatment of high-risk and non-operable patients with severe aortic stenosis but not for intermediate-risk patients, and it is currently being evaluated in the PARTNER II Trial in the USA.

"These data demonstrated that the improved valve and delivery system design allowed precise positioning of the SAPIEN 3 valve."

Dr John Webb, St. Paul's Hospital, Vancouver, Canada

First look at human mitral heart implants

> "The mitral valve and the mitral patient are complex. This journey is going to be difficult, but I believe that this therapy should be pursued and will lead to improved patient care."
>
> *Dr Martyn Thomas, St. Thomas' Hospital, London, UK*

RESULTS from the first-in-human experiences with Edwards' FORTIS mitral transcatheter heart valve for the treatment of mitral regurgitation, which were performed at centres in London, UK and Bern, Switzerland, have been preliminarily assessed.

The device is composed of bovine pericardial tissue and a cloth-covered, self-expanding frame with a distinct anchoring system, and uses the transapical approach.

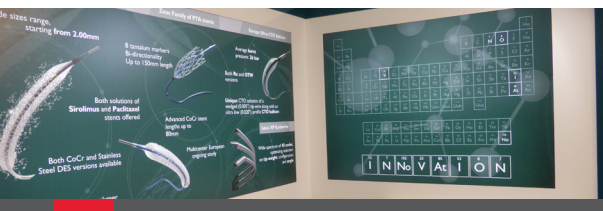
The general profile of the patients who received the mitral valve were not prime candidates for surgical mitral intervention due to a range of combined complications such as severe mitral regurgitation, marked breathlessness, and multiple comorbidities. It was under humanitarian/compassionate grounds that the patients were granted access to the device.

"Clinicians know there are many patients suffering from mitral valve disease who are too high-risk to benefit from traditional surgical options. Although these early patient outcomes have been disappointing, we demonstrated that this valve can be successfully implanted, and functions as intended," said Dr Martyn Thomas, Clinical Director, Cardiology and Cardiothoracic Services, St. Thomas' Hospital, London, UK.

Of the five patients, three died between 4–76 days after the procedure, the fourth patient continued to be followed-up at 76 days, while the fifth patient was treated recently and is currently recovering.

"The mitral valve and the mitral patient are complex. This journey is going to be difficult, but I believe that this therapy should be pursued and will lead to improved patient care," Dr Thomas continued.

"We are grateful for the Heart Teams that guided the first-in-human implants with compassion and deep clinical experience. Similar to the early days with transcatheter aortic valves, we know developing transformational therapies is challenging," said Mr Michael A. Mussallem, Chairman and Chief Executive Officer, Edwards Lifesciences Corp, Irvine, California, USA. "We are confident that our commitment to addressing the unmet needs of patients will lead to transcatheter mitral valve replacement becoming a meaningful therapy."




Angioplasty balloon reaches stratosphere

> "These encouraging, long-term findings suggest Stellarex may be uniquely effective compared with other paclitaxel-based DCBs."
>
> *Dr Mark A. Turco, Covidien, Dublin, Ireland*

STATE-OF-THE-ART drug-coated angioplasty balloon (DCB) has been given the green light for the treatment of peripheral artery disease (PAD).

Covidien's Stellarex™ DCB was found to be safe and efficient following the company's 24 month ILLUMENATE first-in-human (FIH) study. Stellarex adopts EnduraCoat™ technology: a durable, uniform balloon coating preventing drug loss during transit and catalysing controlled, effective drug delivery to the treatment site.

"ILLUMENATE's long-term results represent some of the best 24-month patency and freedom from target lesion revascularisation rates seen in FIH studies to date. These encouraging, long-term findings suggest Stellarex may be uniquely effective compared with other paclitaxel-based DCBs," said Dr Mark A. Turco, Chief Medical Officer, Vascular Therapies, Covidien, Dublin, Ireland.

In 2010, there were 40.5 million PAD cases reported in Europe; associated with heart attack, stroke, amputation, and death, PAD is one of the most prevalent vascular diseases. Intense pain, limited physical mobility, and non-healing leg ulcers can occur in PAD through the blockage of leg arteries.

58 superficial femoral and/or popliteal lesions in 50 subjects were pre-dilated using an uncoated angioplasty balloon, and subsequently treated with the Stellarex DCB.

In treating leg artery lesions, the Stellarex DCB is designed to open narrowed or occluded vessels to revive blood flow, while simultaneously delivering paclitaxel – the drug used in the balloon coating – to the vessel wall.

Excellent results were obtained at 24 months; primary patency was 82.3%, freedom from clinically-driven target lesion revascularisation was 87.9%, and no amputations or cardiovascular death were recorded.

Dr Hendrik Schröder, principal investigator and Radiologist, Vascular Center-Jewish Hospital, Berlin, Germany, said: "Good patency after 2 years, which translated into the absence of new clinically-driven target lesion revascularisations after 1 year and through the second year patient follow-up, demonstrates the durability of the Stellarex drug-coated angioplasty balloon."

Covidien is currently holding additional large clinical trials to reinforce the FIH study conclusions.

Vessel healing stent system showing strong performance

COMPARISON of safety and performance between the SYNERGY™ Everolimus-Eluting Platinum Chromium Coronary Stent System (SYNERGY Stent System) and the PROMUS Element™ Stent System for the treatment of atherosclerotic lesions has been reported in 3-year follow-up EVOLVE clinical trial.

"The SYNERGY Stent 3-year results from the EVOLVE trial continue to show promise with respect to safety and efficacy," said Prof Ian Meredith, Director, MonashHeart, Monash Medical Centre, Melbourne, Australia. "Target lesion revascularisation remains very low, at a rate of 1.1%, while there is no stent thrombosis in the SYNERGY full-dose arm at 3 years. The EVOLVE clinical data support the hypothesis that this novel bioabsorbable polymer stent technology could allow for improved healing over durable polymer drug-eluting stents."

With its ultrathin abluminal bioabsorbable drug/polymer coating technology, the SYNERGY Stent System aims to reduce the risk associated with long-term polymer exposure. This stent system can also offer reduction in restenosis, faster vessel healing after stent implantation, and can possibly even reduce the duration need for post-procedure dual antiplatelet therapy.

"The SYNERGY Stent System underscores our ongoing commitment to delivering meaningful innovation to the interventional cardiology community and is expected to reinforce our position as a global leader in medical devices," said Mr Kevin Ballinger, Interventional Cardiology, Boston Scientific,

"The EVOLVE clinical data support the hypothesis that this novel bioabsorbable polymer stent technology could allow for improved healing over durable polymer drug-eluting stents."

Prof Ian Meredith, Monash Medical Centre, Melbourne, Australia

Stent System is uniquely designed to provide exceptional outcomes in complex cases by promoting early healing and eliminating long-term polymer exposure."

The SYNERGY Stent System is currently undergoing extensive research for FDA and Japanese Ministry of Health, Labour and Welfare approval. The follow-up to the EVOLVE trial is the EVOLVE II clinical trial which is a multicentre, randomised, controlled, pivotal trail which includes 1,684 participants from 125 global sites (including USA, Canada, Europe, Australia, New Zealand, Japan, and Singapore).

The comparison of stent systems will be further investigated to evaluate the same concentration of everolimus contained in a polymer coating (PROMUS Element Plus) against a bioabsorbable polymer coating (SYNERGY). The reduction of dual antiplatelet therapy will be further investigated among other additional clinical criteria.

One big step for mitral valve technology

> "From this early evidence it appears feasible that the Tiara device can be safely implanted in a short, catheter-based procedure that can be well tolerated by these high-risk surgical patients."
>
> *Mr Alexei Marko, Neovasc Inc., Richmond, Canada*

PROSTHETIC mitral heart valve implanted using the Tiara™ Transcatheter Mitral Valve (Neovasc Inc., Richmond, Canada) device has received promising results for the treatment of mitral regurgitation (MR) – an abnormal heart condition where the mitral valve does not close properly.

Dr Anson Cheung, Professor of Surgery and Director of Cardiac Transplant, St. Paul's Hospital, Vancouver, British Columbia, Canada, discussed the two transcatheter Tiara implantations.

The first implantation was placed in a 73-year-old patient who was deemed extremely high-risk for surgery due to severe MR and other severe comorbidities. The time taken to implant the device was approximately 20 minutes and there were no complications experienced. There was complete elimination of MR and paravalvular leak (PVL), and other positive favourable prognostic factors such as an increase in stroke volume and decrease in pulmonary pressure were also experienced by the patient. The follow-up appointments continued to show optimistic progress, excellent prosthetic valve function and haemodynamics with no PVL or residual MR, but unfortunately the patient died from his comorbid conditions which were not caused by the Tiara valve.

The second implantation occurred in a 60-year-old patient with severe MR, also categorised as high-risk for surgery. The implant took approximately 12 minutes and there was immediate cessation of MR without PVL, increase in stroke volume, and decrease in pulmonary pressure. There was excellent prosthetic valve function and haemodynamics with no PVL or residual MR in the follow-up appointments. This patient continues to have a significantly improved quality of life due to the implant. So far there have been no adverse events attributable to the implant.

"From this early evidence it appears feasible that the Tiara device can be safely implanted in a short, catheter-based procedure that can be well tolerated by these high-risk surgical patients. Our focus is now shifting to the design and initiation of a rigorous multicentre, multinational clinical study for Tiara, which we hope will provide further evidence to support the safety and feasibility of the Tiara device and procedure. We are continuing to build our clinical team and capabilities as we prepare to move Tiara into this next phase of development," said Mr Alexei Marko, Chief Executive Officer and Director, Neovasc Inc., Richmond, British Columbia, Canada.

New leader emerges on the stent scene

DRUG coated stents with 1-month dual anti-platelet therapy (DAPT) have successfully combined the effectiveness of drug-eluting stents (DES) and safety of bare metal stents (BMS) to take the lead in the active stent scene.

The study enrolled 2,466 patients from Europe, Asia, Canada, and Australia, who were identified as having a high risk of bleeding during this procedure.

BioFreedom represents the latest development in Biosensors' stent technology, featuring a micro-structured abluminal surface that permits the controlled release of Biolimus (BA9) without the use of a polymer or other carrier. BA9 is a highly lipophilic anti-restenotic drug, which has been developed by Biosensors (Hillegom, the Netherlands) specifically for use with stents.

Biosensors hopes to confirm, through this trial, that their potentially revolutionary drug-coated stent (DCS) will be as safe as a BMS, while also delivering the anti-restenotic benefits of a DES.

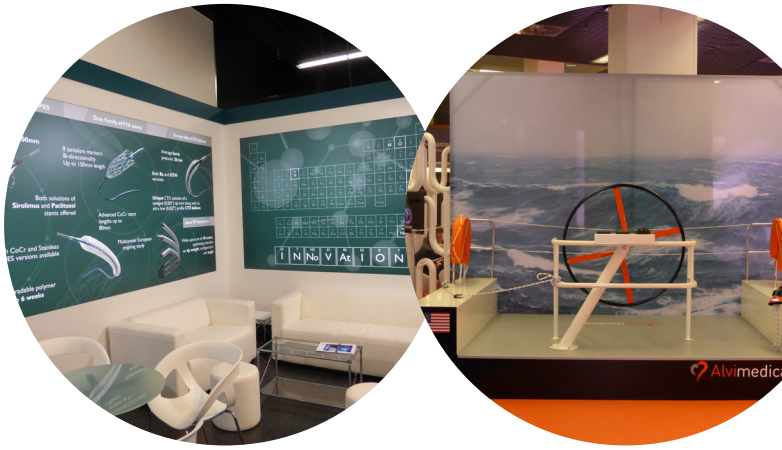
"The results of this study will be particularly important as we hope that they will show, for the first time, that a DCS can be more effective than a BMS, yet just as safe, in a subgroup of patients not previously studied," said Dr Philip Urban, Division of Cardiology, Hôpital de la Tour, Geneva, Switzerland.

> "This study could potentially change clinical practice by permitting the use of a DCS in conjunction with only 1 month of DAPT."
>
> *Dr Philip Urban, Hôpital de la Tour, Geneva, Switzerland*

Thus far, results have been promising for this contemporary stent. In its first in man study, treatment with BioFreedom demonstrated excellent 12-month late lumen loss and sustained safety for up to 4 years, including absence of definite and/or probable stent thrombosis.

Crucially, Biosensors has received conditional investigational device exemption approval to conduct a USA-based clinical trial for BioFreedom. This is highly beneficial for the company as the USA is a huge market with an underlying issue of obesity that often manifests itself in heart disease.

Dr Urban is optimistic about the future of the BioFreedom technology, commenting: "This study could potentially change clinical practice by permitting the use of a DCS in conjunction with only 1 month of DAPT."



No fear renal denervation is here

> "We believe this therapy has the potential to dramatically improve the lives of millions of patients with severe high BP and will continue to invest in renal denervation as a potential long-term growth driver."
>
> *Dr Mark D. Carlson, Global Clinical Affairs, St. Jude Medical Inc., Saint Paul, USA*

RENAL denervation has given fresh hope to patients suffering drug-resistant, uncontrolled hypertension at 6 months post-procedure following the success of a next-generation system in major trials.

The second-generation EnligHTN™ renal denervation system, developed by global healthcare company St. Jude Medical, Inc., delivered an average systolic blood pressure (BP) reduction of 25 mmHg points, an 81% response rate to the therapy, and there were no reports of serious device or procedure-related adverse events in the company's international, non-randomised clinical trial: EnligHTN III.

Following the performance of the system and testing outcomes with 6 months of follow-up for 39 eligible subjects, the EnligHTN III study provided promising preliminary results, which confirmed the safe, rapid, and sustained reduction in BP measurements for patients with drug-resistant hypertension.

Prof Stephen Worthley, St. Andrew's Hospital, Adelaide, Australia, a principal investigator of the study, said: "This study demonstrates that the next-generation EnligHTN renal denervation system delivers safe and effective treatment that is aligned with the outcomes of the first-generation system, and ultimately saves time in the procedure room."

Hot on the heels of positive findings in the EnligHTN I and II trials, which showed a safe drop in BP for subjects with drug-resistant hypertension, the EnligHTN system operates by shooting radiofrequency (RF) energy from an ablation catheter to create lesions along the renal nerves, which form a network in the walls of renal arteries - thought to help control BP. This causes a disruption of the nerve supply, leading to reduced systolic and diastolic BP.

Allowing for continuous blood flow to the kidney throughout the operation, the catheter features a unique, non-occlusive basket design, aiding physicians to produce a predictable treatment pattern. Simultaneously administering 60 second ablations from all four catheter electrodes causes early BP reduction, done twice over in each renal artery and drastically reducing operation time.

This powerful tool offers physicians a multi-electrode catheter with an intuitive, faster generator shooting consistent and effective ablations.

"We believe this therapy has the potential to dramatically improve the lives of millions of patients with severe high BP and will continue to invest in renal denervation as a potential long-term growth driver," said Dr Mark D. Carlson, Chief Medical Officer and Vice President of Global Clinical Affairs, St. Jude Medical Inc., Saint Paul, Minnesota, USA.

The future is bright for TAVI technology

> "These features are designed to provide a predictable implantation procedure and may result in improved clinical outcomes."
>
> *Dr Keith Dawkins, Boston Scientific, Natick, USA*

TRANSCATHETER aortic valve implantation (TAVI) technology has taken a big step forward after the Boston Scientific Corporation Lotus™ Valve System showcased a formidable performance at the 6-month mark.

A differentiated second-generation TAVI technology, the Lotus Valve System, delivered strong safety and efficacy results in the REPRISE II trial, with just 1.1% of patients suffering moderate paravalvular aortic regurgitation and a total absence of severe cases.

The Lotus Aortic Valve System consists of a pre-loaded, stent-mounted tissue valve prosthesis and catheter delivery system for guidance and percutaneous placement of the valve. The low profile-delivery system and introducer sheath are designed to enable predictable and precise placement associated with early valve function.

REPRISE II, an ongoing prospective, single-arm study testing the Lotus Valve System in 250 symptomatic patients with severe aortic valve stenosis considered high-risk for surgical valve replacement across Europe and Australia, delivered a spate of promising results, including zero paravalvular aortic regurgitation in an exceptional 79.8% of patients by independent core lab assessment.

Furthermore, the 30-day mean aortic valve pressure gradient measured 11.5±5.2 mmHg, far surpassing the performance goal of 18 mmHg ($p<0.001$) and meeting the primary device performance endpoint of 30-day mean aortic valve pressure gradient. After 6 months, the mean aortic valve pressure gradient remained low and stable at 11.4±4.6 mmHg.

An all-cause mortality rate of 8.4% and a disabling stroke rate of 3.4% rounded off the other key findings of the 6-month study, while no cases of non-study valve implantation, unplanned use of cardiopulmonary bypass, valve embolisation, or valve-in-valve/ectopic valve placement occurred.

Dr Keith Dawkins, Executive Vice President and Global Chief Medical Officer, Boston Scientific, Natick, Massachusetts, USA, was among those encouraged by the system's performance, stating: "These features are designed to provide a predictable implantation procedure and may result in improved clinical outcomes."

Critical cardiac conundrums resolved by FFR

FRACTIONAL flow reserve (FFR) technology has been shown to improve clinical decisions when used to guide cardiac treatment procedures.

Approximately half of patients with coronary artery disease (CAD) experienced an altered course of treatment following the application of St. Jude Medical PressureWire™ FFR technology, according to data from the real-world POST-IT registry, ensuring patients with ischaemia-producing narrowings received appropriate therapy.

Dr Sergio B. Baptista, interventional cardiologist, Hospital Fernando Fonseca, Amadora, Portugal, said: "The results demonstrate that FFR-guided therapy adds important information that alters the current treatment strategy within the cardiology community for percutaneous coronary intervention procedures, furthering my belief that FFR should become the standard of care for treating patients with CAD."

POST-IT, a national, prospective, multi-centre registry enrolled 918 eligible subjects at 19 centres in Portugal. Highlighted were the potential clinical and economic benefits of FFR measurement across a wide range of patients with both stable and unstable CAD. FFR, a physiological index, is used to ascertain the haemodynamic severity of narrowing or lesions in the coronary arteries, and is measured using St. Jude Medical PressureWire™ FFR Aeris. FFR pinpoints which coronary narrowings are responsible for blocking blood-flow to a patient's heart muscle, known as ischaemia, helping to illustrate to the interventional cardiologist which lesions require stenting. This often leads to better patient outcomes and lower healthcare costs.

FFR altered the treatment strategy for over 400 subjects (44.3%), proving that treatment strategies for patients are bolstered through the use of PressureWire FFR measurement systems. Percutaneous coronary intervention-referred subjects rose from 35% to 43% when assessed with FFR-guided therapy.

"Collectively, these findings show that when FFR-guided therapy is used, cardiologists can significantly improve patient management," said Dr Luís F. Raposo, Cardiology Department, Hospital de Santa Cruz, Carnaxide, Portugal. "The findings also suggest that FFR reduces costs to healthcare systems due, in part, to its ability to eliminate further non-invasive tests and potential future procedures."

Dr Mark D. Carlson, Chief Medical Officer and Vice President of Global Clinical Affairs, St. Jude Medical, Saint Paul, Minnesota, USA, said: "These significant new data reaffirm findings from previous clinical trials, including the landmark FAME trails and the RIPCORD study, which demonstrated that patients who received FFR-guided therapy ultimately can have better outcomes than those who received standard angiography alone."

TAVI technology takes big step into the 'real world'

TRANSCATHETER aortic valve implantation (TAVI) technology has taken a leap forward with positive 2-year results following a rigorous 'real-world' study of the CoreValve® System.

The self-expanding valve, developed by Medtronic and approved by the FDA in January 2014 for patients considered at extreme risk for surgery, was evaluated in the Medtronic CoreValve ADVANCE study. Patients tested with the system experienced positive clinical outcomes, showing low rates of mortality and stroke, and demonstrated excellent 2-year valve performance.

96.8% of 1,015 subjects, all of whom had severe aortic stenosis, were treated with the CoreValve System. Subjects displayed low rates of all-cause mortality (25.6%), cardiovascular mortality (16.8%), and major stroke (2.9%) at 2 years, correlating with similarly positive, previously reported 1-month and 1-year data.

87% of subjects experienced dramatic improvement in symptoms across the 2-year duration. Overall, haemodynamic performance was strong and stable; at each follow-up visit, the mean gradients stayed below 10 mmHg, a commonly used threshold of exceptional blood flow.

Dr Axel Linke, principal investigator and Professor of Medicine, University of Leipzig Heart Center, Leipzig, Germany, said: "It is impressive to see that these positive clinical outcomes sustain out to 2 years, affirming the safety and exceptional performance of the CoreValve System."

He later added: "These contemporary real-world data, combined with results from the rigorous randomised trial in the USA, are important in understanding how TAVI performs and [to] help physicians determine which options are best for their patients."

Conducted with experienced TAVI heart teams across 44 centres in 12 countries, the international ADVANCE Study involved subjects receiving CoreValve implants between March 2010 and July 2011.

Subjects 75 years and younger (n=182) were compared with older subjects (n=833) in a separate analysis during the study, with both age groups exhibiting good response to the CoreValve treatment. Both showed similarly low all-cause mortality at 30 days, 12 months, and 2 years (23.6% versus 26.0%, respectively, p=0.448 at 2 years).

Rates of cardiovascular mortality, stroke, myocardial infarction, bleeding, moderate and severe paravalvular leak, or the need for a new permanent pacemaker at either 1 or 2 years were similar in the two age groups.

Although FDA approved, this system is yet to be cleared for use by other patient groups in the USA.

Balloons: the answer to TAVI

BALLOON-EXPANDABLE transcatheter aortic valve implantation (TAVI) valves have been shown to deliver far superior haemodynamic performance and prevention of residual aortic valve regurgitation compared to self-expanding valves.

Dr Mohamed Abdel-Wahab, Head of the Cardiac Catheterization Laboratory, Segeberger Clinic, Bad Segeberg, Germany, one of the study authors who designed the CHOICE trial, which assessed and compared the overall device success of both technologies, said: "If the anatomy is suitable for both valve types (as in the CHOICE population), I would consider the balloon-expandable valve as my first choice because of its more predictable results (at least up to 30 days). Nevertheless, it remains important to continue our follow-up of the trial population and see what happens in the long-term."

241 randomised patients with severe aortic stenosis and at high risk for surgery were given the balloon expandable (n=121) or the self-expanding valve (n=120).

Balloon-expandable group subjects displayed a greater rate of device success compared with self-expandable group subjects (95.9% versus 77.5%, respectively). This has been heavily attributed to a markedly reduced rate of more-than-mild aortic regurgitation in the balloon-expandable group (4.1% versus 18.3%), as well as a more seldom need in this group to implant more than one valve (0.8% versus 5.8%).

"The results of CHOICE in this respect support the development of delivery catheters allowing recapturing and repositioning of self-expanding devices to minimise the consequences of device malpositioning," said Dr Mohamed Abdel-Wahab and colleagues.

However, both valve types showed equally impressive 30-day safety outcomes (18.2% versus 23.1%), while both posted impressive improvements in the New York Heart Association class compared to their baseline levels with a slightly greater rate of improvement in the balloon-expandable group (94% versus 86.7%).

The authors added: "Long-term follow-up of the CHOICE population should be awaited to determine whether differences in device success will translate into a clinically relevant overall benefit for the balloon-expandable valves."

"If the anatomy is suitable for both valve types (as in the CHOICE population), I would consider the balloon-expandable valve as my first choice because of its more predictable results (at least up to 30 days)."

Dr Mohamed Abdel-Wahab, Segeberger Clinic, Bad Segeberg, Germany

EUROPCR 2014 AWARDS

BEST CLINICAL CASE AWARD

Best Clinical Case

Dr Mateusz Orzalkiewicz
Chojnice District Hospital,
Chojnice, Poland

Left main stem pulsation easily missed angiographic phenomenon.

2nd Best Clinical Case

Dr Sridhar Kasturi
Sunshine Heart Institute,
Hyderabad, India

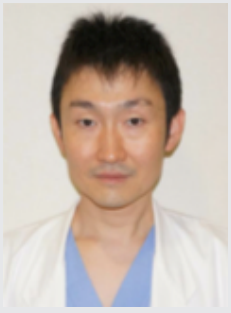
Aortoplasty with stenting of long segment total occlusion of descending thoracic aorta and abdominal aorta in Takayasu aortitis with computed tomography-angiography follow-up.

3rd Best Clinical Case

Dr Amir-Ali Fassa
Hôpital de la Tour,
Geneva, Switzerland

Transseptal mitral valve implantation for severely calcified mitral stenosis.

BEST ABSTRACT AWARD



Best Abstract

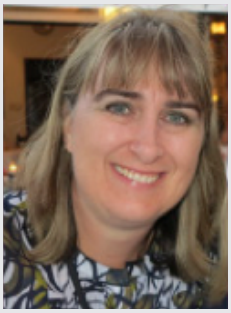
Dr Nobuaki Suzuki
Teikyo University
School of Medicine,
Tokyo, Japan

A randomised comparison of PCI guided by frequency domain OCT and angiography: OPUS-CLASS cohort B study.

2nd Best Abstract

Dr Guido Parodi
Careggi Hospital,
Florence, Italy

Morphine is associated with a delayed activity of oral antiplatelet agents in patients with STEMI undergoing primary PCI.



3rd Best Abstract

Miss Julie Parkinson
Gosford Hospital,
Yattalunga, Australia

An evaluation of peripheral vascular access site complications following cardiac angiography and PCI.

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PERCUTANEOUS RECANALISATION OF CORONARY ARTERY CHRONIC TOTAL OCCLUSIONS: A 2014 UPDATE

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ABSTRACT

Coronary chronic total occlusions (CTOs) are frequently encountered in clinical practice, and their presence influences management decisions; patients with CTOs are more frequently allocated to bypass graft surgery or medical therapy than patients without CTOs. Recent advances in interventional guidewires, catheters, and novel techniques have led to significant improvements in success rates with percutaneous coronary intervention. In this article we review the most recent developments in the percutaneous management of CTOs, the emergence of CTO intervention as a subspecialty in its own right, and discuss future directions for further research and improvement.

Keywords: Chronic total occlusions, ischaemic heart disease, percutaneous coronary intervention, prognosis.

INTRODUCTION

Since the introduction of balloon angioplasty by Andreas Gruentzig in 1977, the ability to cross and safely recanalise coronary chronic total occlusions (CTOs) has represented the greatest technical challenge in interventional cardiology. Historically, percutaneous coronary intervention (PCI) of CTOs has been hindered by reduced immediate success and long-term patency rates, as well as higher rates of complications compared to non-CTO PCI. Over the last decade, substantial advances in guidewires, catheters, and novel techniques have resulted in improved primary success rates and have sparked an intense interest in this topic.[1] In this article, we summarise the most important developments in the field (emphasising recent advancements and progress), describe the CTO centre of excellence concept, and highlight potential avenues for future research.

CTO PREVALENCE AND IMPLICATIONS

In recent reports from North America, the prevalence of CTOs among patients with coronary artery disease (CAD) has varied from 18-31%, rising as high as 89% in patients with prior coronary artery bypass graft surgery (CABG).[2,3] It is widely acknowledged that the presence of a CTO has significant impact on treatment decisions.[4] Historically, most patients with CTOs, particularly those with multivessel disease (MVD), have been referred for CABG or allocated to medical therapy.[4-6] Indeed, the presence of a CTO is one of the most common reasons for CABG referral.[4] PCI is attempted in only 10-13% of CTOs identified during coronary angiography, and only 7% are successfully revascularised.[3] Prior to the 21st century, PCI-CTO success rates were consistently <70%.[7,8] In the SYNTAX trial, successful revascularisation was achieved in only 49.5% of CTOs assigned to PCI and in 68.1% of CTO lesion assigned to CABG,[9] demonstrating that CTOs are sub-optimally revascularised regardless of the modality chosen, representing a difficult challenge for surgeons as well as interventional cardiologists. More recent studies have documented improving success rates for PCI of CTOs at selected centres. Among 1,361 consecutive native coronary artery CTO PCIs performed at three US institutions, from 2006 to 2011, the technical (85.5%), and procedural (84.2%) success rates were significantly

higher than historical comparisons, with a low (1.8%) major complication rate.[10] Of note, 34% of cases were performed with the retrograde approach (PCI is performed by wiring the occlusion through the distal cap with a guide in the vessel that provides collaterals to the occluded artery), an important technique innovation which offers a route to PCI success for lesions which cannot be crossed antegrade (PCI is performed by wiring the occluded vessel through the proximal cap with a guide engaged in the diseased vessel). In this regard, among 801 patients undergoing retrograde CTO PCI in a multicentre Japanese registry between 2009 and 2012 (most of which failed the antegrade approach), the technical and clinical success rates were 84.8% and 83.8%, respectively.[11] However, the rate of peri-procedural myonecrosis may be greater with the retrograde compared to antegrade approach.[12]

Patients with prior CABG who undergo CTO PCI represent a particularly challenging subgroup. These patients tend to be older, with more co-morbidities and more complicated anatomy than CTO patients without prior CABG. Repeat CABG in these patients is associated with high morbidity and mortality and is generally not recommended, particularly in the presence of a patent left internal mammary artery. However, CTO PCI is particularly complex in post-CABG patients given surgically induced vessel tenting and heavy CTO calcification with frequent negative remodelling.[13] Nonetheless, a CTO PCI success rate of 79.7% in post-CABG CTOs has recently been described from a multicentre registry, with an acceptable complication rate of 2.1%.[14] CTO PCI is therefore a viable option for this challenging patient cohort, as an alternative to repeat CABG. Pre-procedural computed tomography angiography, by allowing better characterisation of the degree of calcification, stump morphology, lesion length, post-CABG vessel anatomy, and presence of side-branches compared to angiography alone, is a promising modality that may further improve CTO PCI success rates compared to angiography alone.[15]

CTO age, the presence of bridging collaterals, and the J-CTO score (Multicentre CTO registry in Japan), among others, have traditionally been considered predictors of PCI failure for CTOs.[16] The J-CTO score was derived from an analysis of nearly 500 CTO cases. Independent predictors of failure to cross the lesion within 30 minutes were the presence of calcification, tortuosity in the occluded segment, blunt proximal cap, occlusion length ≥20 mm, and previous failed attempts. One point is recorded for each of the independent predictors present, and the CTO is categorised as easy (J-CTO score 0), intermediate (score 1), difficult (score 2), and very difficult (score ≥3). Contemporary CTO PCI techniques have addressed many (but not all) of these as risk factors (calcification, for example, still remains a major challenge),[17] emphasising the need for a new angiographic scoring system to accurately predict CTO PCI success rates. And despite improvements with contemporary technique and devices, CTO PCI remains a highly technically-demanding procedure, and success rates will vary markedly between institutions and operators, depending on experience and devotion to contemporary approaches.

HISTOPATHOLOGIC AND PHYSIOLOGIC INSIGHTS

The pathophysiology leading to the development of CTOs is not well understood. Virtual histology intravascular ultrasound in 50 CTO lesions after guidewire crossing found fibroatheromas in 84% of lesions, suggesting that most CTO lesions may develop from healed plaque ruptures.[18] For patients to benefit from CTO revascularsation, both myocardial viability and ischaemia should be present. Cardiac magnetic resonance imaging (MRI) is one of the most useful tests to assess viability. In an MRI study of 170 patients with CTOs, 85% had evidence of prior myocardial infarction (MI) by late gadolinium enhancement, although only 25% had Q-waves.[19] Although further studies are required, such patients may not benefit from revascularisation if transmural infarction is present. Conversely, a common misconception is that angiographically evident collaterals protect CTOs from substantial ischaemia, obviating the need for revascularisation. In a recent study, fractional flow reserve (FFR) was measured in 50 CTO target vessels after successful PCI with a 1.5 mm balloon. In all 50 patients the FFR was <0.80 despite the presence of collaterals, representing ischaemia and the potential for benefit after revascularisation.[20] Successful PCI of a CTO also frequently alleviates ischaemia arising from a donor vessel,[21] suggesting that in patients with MVD, a strategy of recanalising the CTO first may in some cases obviate the need to perform PCI of a diseased donor vessel as the donor vessel territory may subsequently be rendered non-ischaemic.

Prognostic Impact

A recently published weighted meta-analysis of 65 studies with 18,061 patients and 18,941 target CTO vessels reported angiographic success in 77% of patients, with complications including death (0.2%), emergent CABG (0.1%), stroke (<0.01%), MI (2.5%), coronary perforation (2.9%), tamponade (0.3%), and contrast nephropathy (3.8%). Compared with successful procedures, unsuccessful procedures were associated with higher rates of perforation (10.7% versus 3.7%, p<0.0001), tamponade (1.7% versus 0%, p<0.0001), and death (1.5% versus 0.4%, p<0.0001). Over time, procedural success rates have increased and complication rates have decreased.[22] Nonetheless, interventionalists treating CTOs must be familiar with recognition and management of complications associated with CTO PCI, which may be serious. Expertise in pericardiocentesis and management of coronary perforations (covered stents, coils, microsphere injection) is mandatory. Complications unique to the retrograde approach, such as donor vessel dissection and thrombosis, collateral vessel perforation, and gear entrapment, should be promptly diagnosed and treated. Injury to septal collaterals is for the most part inconsequential; however, perforation of epicardial collaterals, particularly in patients without prior open heart surgery, can be associated with tamponade and rapid haemodynamic compromise. Experience in managing vascular and haemorrhagic complications is required since most CTO PCIs are performed through 8 French (Fr) femoral sheaths, and the activated clotting time (ACT) is kept in the 300-350 seconds range during retrograde procedures. Judicious use of intravenous contrast agents and radiation are essential since CTO procedures are complex and often prolonged. Pre-procedural hydration and fluid replacement during the procedure is essential. Consultation with radiation physicists is strongly recommended to ensure that settings are programmed to minimise radiation delivery. Protocols should be implemented regarding the maximum dose of radiation allowed as well as the follow-up of patients who have received significant amounts of radiation (e.g. <5 gray).

Several reports have examined the effect of the presence of a CTO and outcomes in acute coronary syndromes (ACS). The presence of a CTO unrelated to the acute event has been associated with higher early and late mortality in patients with ST-segment elevation MI (STEMI) undergoing primary and rescue PCI, and in those with non-STEMI.[23-26]

Acknowledging the limitations of registries, including selection bias, publication bias, and residual confounding, these reports suggest that the presence of CTOs (whether untreated or unsuccessfully treated) negatively impacts clinical survival both in patients with chronic stable angina and in ACS. Other studies have clearly shown associations between successful PCI recanalisation with decreased angina and the need for CABG.[27] Nevertheless, randomised data demonstrating improved survival and/or quality of life with CTO PCI in patients with viable myocardium and ischaemia are lacking. The costs and complexity of designing and executing such a trial are challenging, especially given the ongoing evolution in CTO technique and improving success rates. Nonetheless, such a trial is critical for the widespread acceptance of CTO PCI, beyond patients with refractory symptoms. In this regard there are currently two ongoing randomised trials which are comparing PCI + optimal medical therapy to optimal medical therapy alone in patients with CTOs: the Korean Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion (DECISION-CTO, NCT01078051) trial and the European Study on the Utilization of Revascularization versus Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions (EURO-CTO, NCT01760083) trial. The results of these studies are anticipated in 2018.

CTO PCI in the USA: The 'Hybrid' Approach

A 'hybrid' procedural algorithm has been proposed to provide a standardised approach to CTOs and to facilitate dissemination and adoption of the various crossing techniques (Figure 1).[28] This approach requires operator familiarity with all the available CTO PCI techniques and skillsets (antegrade wire escalation, antegrade dissection/re-entry with dedicated devices,[29] and retrograde wire escalation and dissection re-entry). The operator must become familiar with the numerous specialised guidewires and support catheters that have been developed for these varied approaches.

Planning requires meticulous study of the angiogram, which is obtained by dual injections (simultaneous injections of the occluded [culprit] vessel and the vessel providing collaterals) focusing

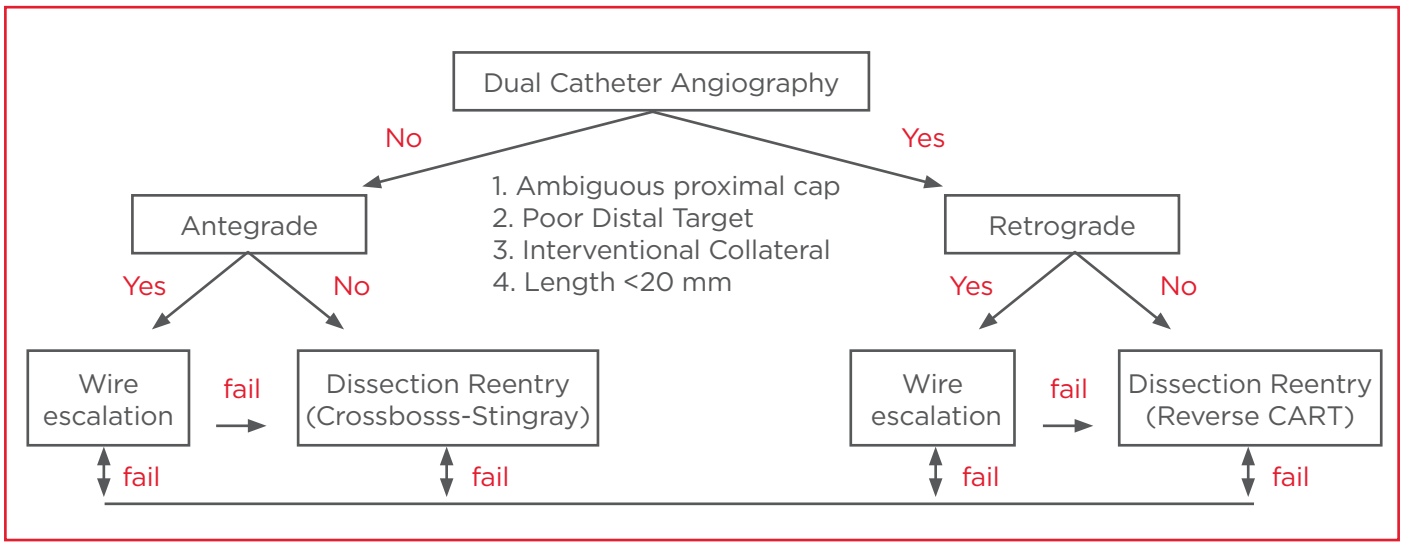

Figure 1: The 'Hybrid' algorithm for chronic total occlusions interventions.
Reproduced from Brilakis et al.[28]

on four angiographic parameters: 1) Presence or absence of proximal cap ambiguity - is it fluoroscopically and/or angiographically evident where the vessel structure continues beyond the proximal cap, increasing the likelihood that the guidewire will remain in the true lumen; 2) distal vessel quality, and presence of a bifurcation at the distal cap that should be preserved; 3) lesion length with a cut-off of 20 mm, since length >20 mm is unlikely to be wired true lumen to true lumen in a 30-minute time frame (16); and 4) presence or absence of 'interventional' collaterals which may be used for retrograde CTO recanalisation. On the basis of these four parameters, the operator can decide on the initial strategy that will provide the safest, most efficient, and most effective way to recanalise the CTO.

By mastering all the techniques of CTO PCI, the operator can switch from one strategy to another efficiently, and thus, complete the case successfully within a reasonable timeframe. For example, an initial strategy of antegrade wire escalation is selected for lesions with a clearly defined proximal cap that are <20 mm in length. But should the wire enter the sub-intimal space, the strategy will quickly change to antegrade dissection re-entry (Figure 2). If, on the other hand, there is a long lesion with an ambiguous proximal cap with a usable contralateral collateral, then a primary retrograde approach will be selected (Figure 3). Flexibility with the various approaches, and timely change of strategies, is at the heart of the hybrid algorithm. The initial experience with the hybrid approach has been very promising since it is teachable, reproducible, efficient, and effective, and has stimulated interest in CTO PCI by a wide range of interventional cardiologists in various clinical settings.

In a single centre, prospective experience of the hybrid approach, a strategy change was required in approximately half the cases.[30] A 'hybrid registry' of 144 cases performed during 'hybrid' workshops at five centres in the US between January 2011 and October 2012 was recently presented at the 2013 CTO Summit (Daniels D, personal communication). Despite including very complex cases, the procedural success rate was 94%, with acceptable resource utilisation (average procedure time 85 minutes and average contrast utilisation 238 mL).[31]

Several questions regarding the hybrid approach need to be addressed, including the procedural safety with this strategy and long-term durability, especially after stent implantation in the sub-intimal space after extensive antegrade or retrograde dissection and re-entry. Angiographic studies examining the incidence of restenosis and reocclusion are underway. Further refinements in the technique, such as limiting the length of sub-intimal stenting, are being evaluated. In addition, the generalisability of this approach to the mainstream interventional community (excluding expert CTO operators) requires evaluation. Results of ongoing hybrid registries in the USA and UK are anticipated in 2014.

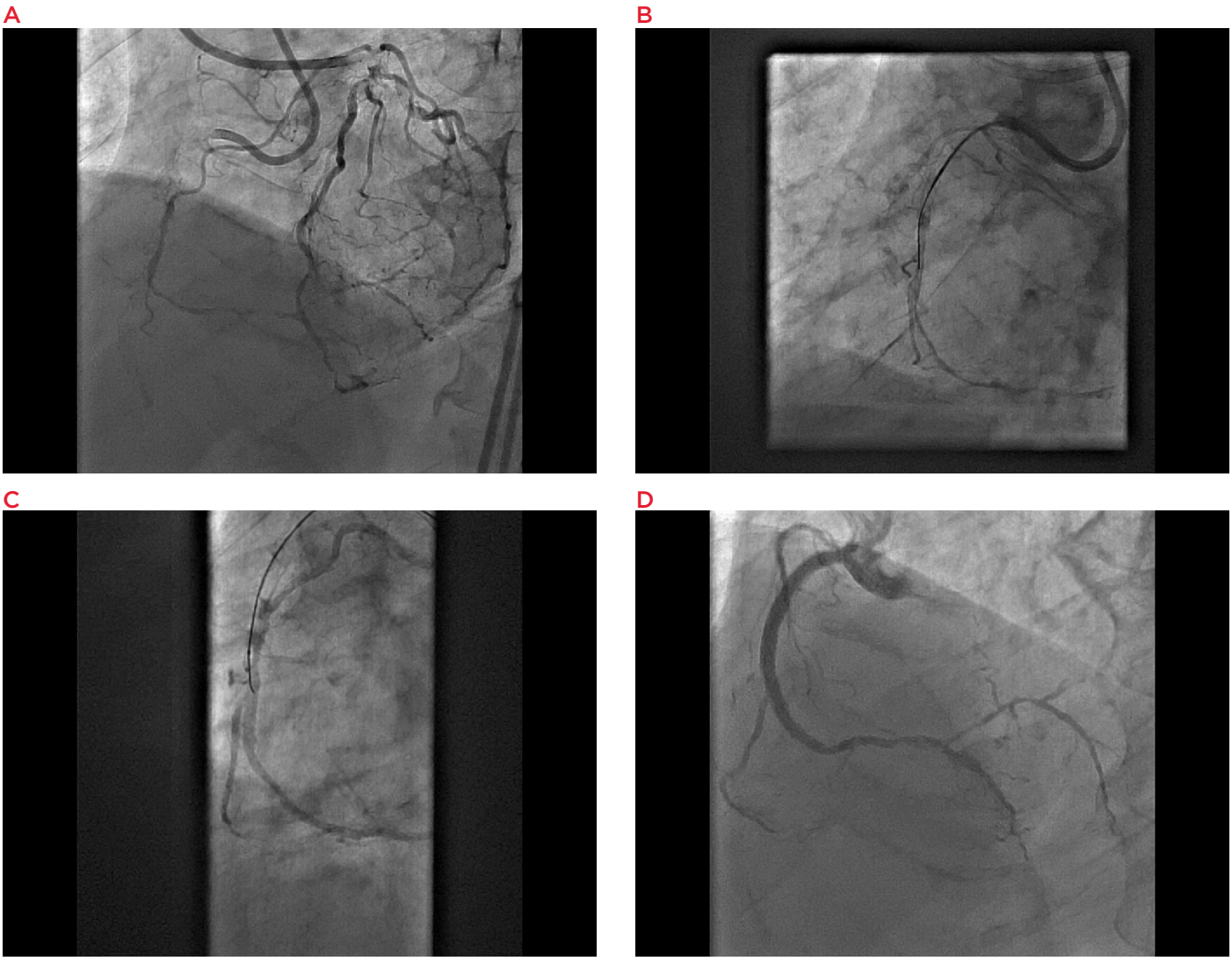

Figure 2: (A) Bilateral coronary injections demonstrate a 2 cm long occlusion of the proximal right coronary artery with a well-defined proximal cap. (B) Antegrade wire escalation was selected as the primary approach, but the wire entered the sub-intimal space. (C) Dissection re-entry is performed with the use of the Stingray balloon and Stingray wire (Boston Scientific) and the true lumen distal to the distal cap is established. (D) An excellent angiographic result is obtained after stenting.

Long-Term Patency Rates After CTO PCI

Although drug-eluting stents (DES) improve late outcomes after CTO PCI compared to bare metal stents (BMS) (Tables 1 and 2),[32-34] clinical and angiographic restenosis rates are higher after DES of CTOs compared to non-CTOs, at least in part due to the diffuseness of disease, calcification, and number and length of stents required. Current generation DES may improve upon the results of first-generation DES after successful CTO recanalisation. In 802 consecutive patients who underwent successful CTO PCI between 2003 and 2010 at a single centre, the restenosis and reocclusion rates were 20% and 7.5%, respectively, with everolimus-eluting stents (EES) demonstrating lower reocclusion rates than other DES (3.0% versus 10.1%, p=0.001).[35] In the CIBELES trial, 207 patients with CTOs were randomised to sirolimus-eluting stents (SES) or EES. Follow-up coronary angiography at 9 months showed similar degrees of late loss with the two devices (0.29±0.60 versus 0.13±0.69 mm, respectively, p<0.01 for non-inferiority), and similar clinical outcomes at 12 months, with a trend for lower stent thrombosis risk in the EES group (3% versus 0%, p=0.075).[36] Second-generation DES provide improved deliverability, and in most settings enhanced efficacy and safety have been demonstrated compared to earlier devices, thereby representing the stents of choice for most CTO operators.[32-41]

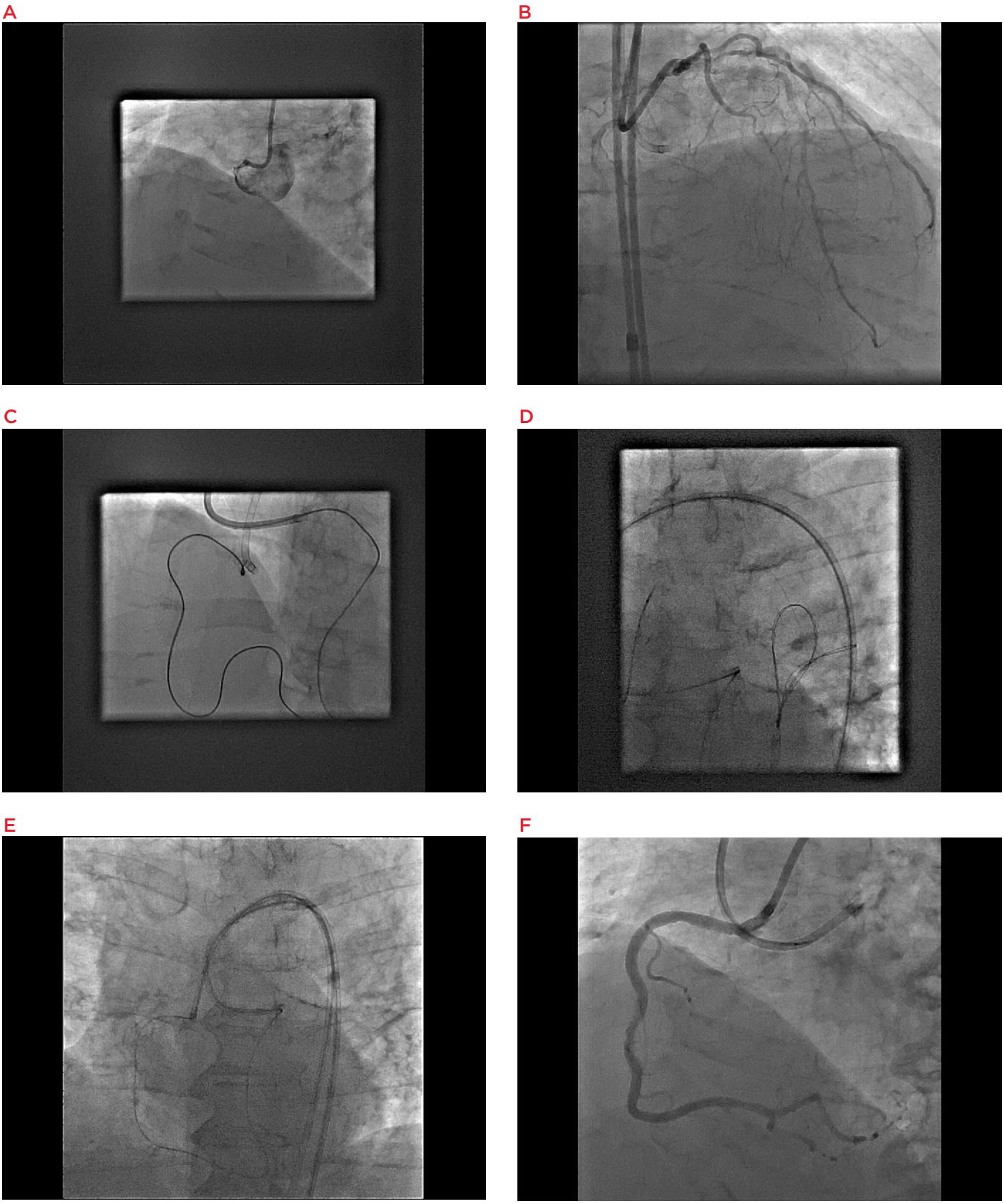

Figure 3: (A) Ostial occlusion of the right coronary artery, with no antegrade options available. (B) Excellent interventional septal collaterals are present from the left anterior descending artery to the posterior descending artery. (C) The collaterals are wired and a Corsair micro-catheter is advanced to the distal cap of the occlusion, which is short. (D) A stiff wire (Confianza Pro 12) crosses the occlusion into the aorta and is snared. (E) The wire is externalised. (F) An excellent angiographic result is obtained after stenting.

Of note, use of the sub-intimal tracking and re-entry (STAR) technique, which involves long, uncontrolled dissections often with poor outflow and compromise of important side-branches, has been reported to have reocclusion rates as high as 57%.[35] Hence, the STAR technique should be avoided and used only as a last resort. If STAR is required, stenting should be avoided to allow dissections to heal, with repeat angiography considered in 6-8 weeks to guide further treatment.

Drug-coated balloons (DCB) and fully bioresorbable vascular scaffolds (BRS) are novel interventional approaches which may be applied to CTOs. Preliminary experience suggests that implanting a BMS followed by DCB is not an attractive CTO approach.[42] LaManna and colleagues[43] have

Table 1: Clinical and angiographic outcomes with drug-eluting versus bare metal stents in chronic total occlusions.

Study	DES Type	Longest Follow-Up (Months)	Angiographic Follow-Up	Event	DES (n/N)	DES Event Rate (%)	BMS (n/N)	BMS Event Rate (%)	P-value
1. SCANDSTENT[28]	SES	7 months or all except MACE (36 months)	SES 95% BMS 89% at 6 months	Death MI TLR TVR MACE Restenosis - In-segment - In-stent Reocclusion Stent thrombosis	0/64 0/64 0/64 3/64 4/59 0/61 0/61 NR 0/64	0 0 0 4.7 6.8 0 0 NR 0	0/63 1/63 21/63 21/63 23/56 21/56 21/56 NR 1/63	0 1.6 33 33 41.1 38 38 NR 1.6	NS NS <0.001 <0.001 <0.001 <0.001 <0.001 NR 0.5
2. PRISON II[30,31]	SES	6 months angiographic; 60 months clinical	SES 94% BMS 94% at 6 months	Death MI TLR TVR MACE Restenosis - In-segment - In-stent Reocclusion Stent thrombosis (definite or probable)	5/100 8/100 12/100 17/100 12/100 NR NR NR 8/100	5.1 8.3 12.5 17.4 12.2 12 7 5	5/100 7/100 27/100 34/100 36/100 NR NR NR 1/100	5.1 7.4 27.3 34.3 36.1 46 39 15	NS NS <0.001 <0.001 <0.001 <0.001 <0.001 NR 0.5 NS NS 0.001 0.004 0.001 <0.001 <0.001 0.16 0.04
3. GISSOC II-GISE[32]	SES	6 months angiographic; 24 months clinical	SES 84% BMS 82% at 6 months	Death MI TLR TVR MACE Restenosis In-segment In-stent Reocclusion Stent thrombosis	2/74 2/74 6.74 11/74 13/74 6/74 5/74 0/74 1/74	2.7 2.7 8.1 15 18 10 8 0 1.4	1/78 4/78 35/78 35/78 39/78 44/78 44/78 11/78 1/78	1.3 6.1 50 50 50 68 68 17 1.3	NS NS <0.001 <0.001 <0.001 <0.001 <0.001 0.001 NS

Table 1 continued.

Study	DES Type	Longest Follow-Up (Months)	Angiographic Follow-Up	Event	DES (n/N)	DES Event Rate (%)	BMS (n/N)	BMS Event Rate (%)	P-value
4. CORACTO[33]	SES with bioabsorbable polymer	6 months angiographic; 24 months clinical	96% at 6 months	Death	2/46	4	1/45	2	NS
				MI	0/46	0	0/45	0	NS
				TLR	NR		NR		
				TVR	5/46	11	27/45	60	<0.001
				MACE	NR		NR		
				Restenosis					
				- In-segment	8/46	17	27/45	60	<0.001
					NR		NR	39	<0.001
				In-stent	0/46	0	7/45	16	<0.001
				Reocclusion	0/46	0	0/45	0	NS
				Stent thrombosis					

DES: drug-eluting stents; BMS: bare metal stents; SES: sirolimus-eluting stent; FU: follow-up; MI: myocardial infarction; TLR: target lesion revascularisation; TVR: target vessel revascularisation; MACE: major adverse cardiac events. *Reproduced from Brilakis ES et al.*[37]

recently published a case of multiple everolimus-eluting BRS (Absorb, Abbot Vascular, Santa Clara, CA, USA) implanted in a right coronary artery ('full polymer jacket'). While a disappearing mechanical scaffold is inherently desirable, especially in diffusely diseased segments that would otherwise require multiple metallic DES, numerous issues regarding this technology - as applied to CTOs - must be addressed, including their greater profile, tendency toward more recoil, and healing properties (particularly with sub-intimal implantation), prior to recommending their routine use in this setting.

ESTABLISHING A CTO CENTRE OF EXCELLENCE

CTO PCI is rapidly evolving into its own subspecialty of interventional cardiology. Optimising success requires long-term commitment to master the wide variety of available techniques, each of which may provide the only route to success in individual cases. A significant learning curve exists; among 1,363 consecutive CTO PCIs performed at three US institutions between 2006 and 2011, the number of years of CTO PCI experience was independently associated with higher technical success rates, lower fluoroscopy time, and less contrast utilisation.[44]

As CTO PCI evolves and the complexity of cases increases we recommend a dedicated CTO PCI programme be initiated at each interested institution, similar to the specialisation required for transcatheter aortic valve replacement. Operators prepared to make a long-term commitment to CTO PCI should be identified, and procedures should ideally be performed working in pairs to maximise experience and quickly overcome the steep learning curve. If possible, engaging in a long-term relationship with an expert is strongly recommended. For purposes of cardiac catheterisation laboratory planning, at least 3 hours should be allocated per case, with a maximum of three cases scheduled per CTO day, at least during the initial phase. It is recommended that specific CTO days are scheduled and that *ad hoc* CTO PCIs are avoided. This allows for careful pre-procedural planning to maximise success, and avoids disruption of catheterisation laboratory workflow. Key safety tasks, including regular monitoring of the ACT, radiation dose, and intravenous contrast volume, are delegated across the entire catheterisation laboratory team. After implementation of quality and performance guidelines, CTO PCI can be performed at most centres with success rates >85%, infrequent complications, and acceptable costs.[45]

Table 2: Results of prospective studies with drug-eluting stents in coronary chronic total occlusions.

Study	Year	Stent	N	FU angio time	Prior CABG	Total stent length (mm)	In-stent restenosis (%)	In-segment restenosis (%)	TLR (%)	TVR (%)
ACROSS-TOSCA 4[38]	2009	SES	200	6 mo	8.5	45.9 (30.2, 62.1)	9.5	12.4	9.8	11.4
PRISON II [39,40]	2006	SES	100	6 mo	3	32 ± 15	7	11	4	8
GISSOC II - GISE[32]	2010	SES	78	8 mo	6.7	41 ± 18	8.2	9.8	8.1	14.9
CORACTO[33]	2010	SES	48	6 mo	NR	45.5 ± 24.8	NR	17.4	NR	10.8
CIBELES[35]	2012	SES EES	101 106	9 mo 9 mo	4 4.7	47 ± 24 50 ± 23	NR NR	10.5 9.1	7.5 6.0	11.6 7.9
CATOS[41]	2012	SES Endeavor ZES	80 80	9 mo 9 mo	NR NR	44.6 ± 20.2 43.4 ± 21.5	NR NR	13.7 14.1	NR NR	13.8 7.5

FU: follow-up; CABG: coronary artery bypass graft surgery; TLR: target lesion revascularisation; TVR: target vessel revascularisation; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent; EES: everolimus-eluting stent; NR: not reported; mo: months.
Reproduced from Brilakis et al.[37]

REFERENCES

1. Stone GW et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. Circulation. 2005;112(15):2364-72.

2. Jeroudi OM et al. Prevalence and management of coronary chronic total occlusions in a tertiary veterans affairs hospital. Catheter Cardiovasc Interv. 2013;doi:10.1002/ccd.25264. [Epub ahead of print].

3. Fefer P et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol. 2012;59(11):991-7.

4. Christofferson RD et al. Effect of chronic total coronary occlusion on treatment strategy. Am J Cardiol. 2005;95(9):1088-91.

5. Grantham JA et al. Chronic total occlusion angioplasty in the United States. JACC Cardiovasc Intv. 2009;2(6):479-86.

6. Moses JW, Karmpaliotis D. Percutaneous revascularization of chronic total coronary occlusions: are the benefits underappreciated? JACC Cardiovasc Interv. 2012;5(4):389-92.

7. Parsad A et al. Trends in outcomes after percutaneous coronary intervention for chronic total occlusions: a 25-year experience from the Mayo Clinic. J Am Coll Cardiol. 2007;49(15):1611-8.

8. Stone GW et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. Circulation. 2005;112(16):2530-7.

9. Farooq V et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. J Am Coll Cardiol. 2013;61(3):282-94.

10. Michael TT et al. Procedural outcomes of revascularization of chronic total occlusion of native coronary arteries (from a multicenter United States registry). Am J Cardiol. 2013;112(4):488-92.

11. Tsuchikane E et al. Japanese multicenter registry evaluating the retrograde approach for chronic coronary total occlusion. Catheter Cardiovasc Interv. 2013;82(5):E654-61.

12. Lo N et al. Periprocedural myocardial injury in chronic total occlusion percutaneous interventions: a systematic cardiac biomarker evaluation study. JACC Cardiovasc Interv. 2014;7(1):47-54.

13. Sakakura K et al. Comparison of pathophysiology of chronic total occlusion with and without coronary artery bypass graft. Eur Heart J. 2013;doi:10.1093/eurheartj/eht422. [Epub ahead of print].

14. Michael TT et al. Impact of prior coronary artery bypass graft surgery on chronic total occlusion revascularisation: insights from a multicentre US registry. Heart. 2013;99(20):1515-8.

15. Rolf A et al. Preprocedural coronary CT angiography significantly improves success rates of PCI for chronic total occlusion. Int J Cardiovasc Imaging. 2013;29(8):1819-27.

16. Morino Y et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. JACC Cardiovasc Interv. 2011;4(2):213-21.

17. Nombela-Franco L et al. Validation of the j-chronic total occlusion score for chronic total occlusion percutaneous coronary intervention in an independent contemporary cohort. Circ Cardiovasc Interv. 2013;6(6):635-43.

18. Guo J et al. A virtual histology intravascular ultrasound analysis of coronary chronic total occlusions. Catheter Cardiovasc Interv. 2013;81(3):464-70.

19. Choi JH et al. Frequency of myocardial infarction and its relationship to angiographic collateral flow in territories supplied by chronically occluded coronary arteries. Circulation. 2013;127(6):703-9.

20. Sachdeva R et al. The myocardium supplied by a chronic total occlusion is

a persistently ischemic zone. Catheter Cardiovasc Interv. 2014;83(1):9-16.

21. Sachdeva R et al. Reversal of ischemia of donor artery myocardium after recanalization of a chronic total occlusion. Catheter Cardiovasc Interv. 2013;82(4):E453-8.

22. Patel VG et al. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. JACC Cardiovasc Interv. 2013;6(2):128-36.

23. Claessen BE et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. Eur Heart J. 2012;33(6):768–75.

24. De Felice F et al. Effect of multivessel coronary artery disease with or without a concomitant chronic total occlusion on 1-year survival in patients treated with rescue angioplasty. J Invasive Cardiol. 2013;25(2):64-8.

25. Hoebers LP et al. The impact of multivessel disease with and without a co-existing chronic total occlusion on short- and long-term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. Eur J Heart Fail. 2013;15(4):425-32.

26. Gierlotka M et al. Impact of chronic total occlusion artery on 12-month mortality in patients with non-ST-segment elevation myocardial infarction treated by percutaneous coronary intervention (from the PL-ACS Registry). Int J Cardiol. 2013;168(1):250-4.

27. Joyal D et al. Effectiveness of recanalization of chronic total occlusions: a systemic review and meta-analysis. Am Heart J. 2010;160(1):179-87.

28. Brilakis ES et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. JACC Cardiovasc Interv. 2012;5(4):367-79.

29. Whitlow PL et al. Use of a novel crossing and re-entry system in coronary chronic total occlusions that have failed standard crossing techniques: results of the FAST-CTOs (Facilitated Antegrade Steering Technique in Chronic Total Occlusions) trial. JACC Cardiovasc Interv. 2012;5(4):393-401.

30. Michael TT et al. Application of the "hybrid approach" to chronic total occlusion interventions: a detailed procedural analysis. J Interv Cardiol. 2014;27(1):36-43.

31. Syrseloudis D et al. Increase in J-CTO lesion complexity score explains the disparity between recanalisation success and evolution of chronic total occlusion strategies: insights from a single-centre 10-year experience. Heart. 2013;99(7): 474-9.

32. Rubartelli P et al. Comparison of sirolimus-eluting and bare metal stent for treatment of patients with total coronary occlusions: results of the GISSOC II-GISE multicentre randomized trial. Eur Heart J. 2010;31(16):2014-20.

33. Reifart N et al. Short and long term comparison (24 months) of an alternative sirolimus-coated stent with bioabsorbable polymer and a bare metal stent of similar design in chronic coronary occlusions: the CORACTO trial. EuroIntervention. 2010;6(3):356-60.

34. Kelbaek H et al. Long-term outcome in patients treated with sirolimus-eluting stents in complex coronary artery lesions: 3-year results of the SCANDSTENT (Stenting Coronary Arteries in Non-Stress/Benestent Disease) trial. J Am Coll Cardiol. 2008;51(21):2011-6.

35. Valenti R et al. Predictors of reocclusion after successful drug-eluting stent-supported percutaneous coronary intervention of chronic total occlusion. J Am Coll Cardiol. 2013;61(5):545-50.

36. Moreno R et al. Randomized comparison of sirolimus-eluting and everolimus-eluting coronary stents in the treatment of total coronary occlusions: results from the chronic coronary occlusion treated by everolimus-eluting stent randomized trial. Circ Cardiovasc Interv. 2013;6(1):21-8.

37. Brilakis ES et al. The role of drug-eluting stents for the treatment of coronary chronic total occlusions. Expert Rev Cardiovasc Ther. 2013;11(10):1349-58.

38. Kandzari DE et al. Clinical and angiographic outcomes with sirolimus-eluting stents in total coronary occlusions: the ACROSS/TOSCA-4 (Approaches to Chronic Occlusions With Sirolimus-Eluting Stents/Total Occlusion Study of Coronary Arteries-4) trial. JACC Cardiovasc Interv. 2009;2(2):97-106.

39. Suttorp MJ et al. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. Circulation. 2006;114(9):921-8.

40. Van den Branden BJ et al. Five-year clinical outcome after primary stenting of totally occluded native coronary arteries: a randomised comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions (PRISON II study). EuroIntervention. 2012;7(10): 1189-96.

41. Park HJ et al. Randomized comparison of the efficacy and safety of zotarolimus-eluting stents vs. sirolimus-eluting stents for percutaneous coronary intervention in chronic total occlusion--CAtholic Total Occlusion Study (CATOS) trial. Circ J. 2012;76(4):868-75.

42. Wöhrle J, Werner GS. Paclitaxel-coated balloon with bare-metal stenting in patients with chronic total occlusions in native coronary arteries. Catheter Cardiovasc Interv. 2013;81(5):793-9.

43. La Manna A et al. Successful retrograde recanalization of chronic total coronary occlusion with multiple bioresorbable vascular scaffolds ('full polymer jacket'): initial experience and rationale. Eur Heart J. 2013;34(37):2925.

44. Michael TT et al. Temporal trends of fluoroscopy time and contrast utilization in coronary chronic total occlusion revascularization: insights from a multicenter united states registry. Catheter Cardiovasc Interv. 2014;doi:10.1002/ccd.25359. [Epub ahead of print].

45. Karmpaliotis D et al. Development of a high-volume, multiple-operator program for percutaneous chronic total coronary occlusion revascularization: procedural, clinical, and cost-utilization outcomes. Catheter Cardiovasc Interv. 2013;82(1):1-8.

CORONARY CHRONIC TOTAL OCCLUSIONS IN THE SETTING OF ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Approximately 10-15% of ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) are found to have a chronic total occlusion (CTO) in a non-infarct related artery (IRA). The presence of a coronary CTO in a non-IRA in STEMI patients is associated with increased mortality and above average deterioration of left ventricular function. A number of mechanisms may be responsible for this worsened prognosis, including impaired healing at the infarct border zone, decreased protection against future cardiovascular events, and potentially increased risk of arrhythmias. This review article aims to provide an overview of published data on the prognostic effect of CTOs in a non-IRA in the setting of primary PCI for acute STEMI. Additionally, observational data on staged PCI of CTOs after primary PCI, and future studies on additional CTO PCI after primary PCI, will be reviewed.

Keywords: Chronic total occlusions, percutaneous coronary intervention, acute myocardial infarction, coronary artery disease.

INTRODUCTION

Coronary chronic total occlusions (CTOs) are frequently encountered during coronary angiography. Recent data suggest a prevalence of approximately 10-15% among patients undergoing diagnostic coronary angiography.[1-3] CTOs are regarded as very complex lesions with relatively low procedural success rates, and, even after successful percutaneous coronary intervention (PCI), restenosis rates are 1.5 to 4-times higher compared with non-occluded coronary artery lesions.[4-6] However, the development of drug-eluting stents (DES), specialised equipment such as CTO guidewires and microcatheters, and advanced techniques such as the retrograde approach have made PCI of CTOs a safe and feasible treatment option. At this time, no randomised controlled trials have been completed that compared PCI of CTOs with optimal medical therapy. However, a meta-analysis of a large number of registries comparing outcomes after successful versus failed PCI of CTOs has reported a significant reduction in residual or recurrent angina, a reduced need for coronary artery bypass graft (CABG) surgery, and reduced mortality after successful CTO PCI.[7]

Recent studies in several independent patient cohorts have shown that a concurrent CTO in a non-infarct related artery (IRA) in patients undergoing primary PCI for ST-segment elevation myocardial infarction (STEMI) is associated with a worsened prognosis.[8-12] This review focuses on currently available clinical data concerning concurrent CTOs in non-IRAs in the setting of acute STEMI.

CORONARY CTOS

Definitions and Epidemiology of Coronary CTOs

A coronary CTO is typically defined as a lesion with a 'Thrombolysis in Myocardial Infarction' (TIMI)

score 0 flow, with an estimated duration of at least 3 months.[13] Another term that is frequently used is a total coronary occlusion (TCO), which is frequently defined as a lesion with TIMI 0 or 1 flow and an estimated duration of <3 months. In current literature, these terms are sometimes used interchangeably. This is unfortunate, as there are important distinctions between CTOs and TCOs, e.g. success rates for PCI of CTOs are lower compared with TCOs, and long-term vessel patency after successful PCI is shorter in CTOs compared with TCOs.

CTOs are relatively common; they are found in approximately 10-15% of cases in studies investigating consecutive patients undergoing diagnostic coronary angiography.[1-3] However, percutaneous revascularisation of CTOs is only considered in a small percentage of cases. In the USA, only 5% of all PCIs were performed in CTO lesions, and this attempt rate did not increase between 2004 and 2007.[3] In recent years, this proportion may have increased as a result of operators specialising in CTOs and the development of novel techniques such as the retrograde approach. Data from a Canadian registry of consecutive patients undergoing non-urgent coronary angiography, with no history of prior CABG surgery, between April 2008 and July 2009 (N=9,377) revealed a prevalence of CTOs in 14.7% of patients.[1] The prevalence in patients with coronary artery disease (CAD), defined as at least one lesion >50% stenosis, was 18.4%. Interestingly, only 40% of patients with a CTO had a history of a prior myocardial infarction (MI).

A recent study in 170 consecutive patients with an angiographically documented CTO undergoing late gadolinium enhancement cardiac magnetic resonance imaging (cMRI) also reported that only 42% of patients had previous ischaemic symptoms consistent with MI.[14] However, contrast enhanced cMRI showed that 86% of patients had evidence of a prior MI. Moreover, a small proportion of CTOs might develop not only as a result of a prior acute thrombotic coronary occlusion, but also as a result of progressive coronary stenosis, ultimately resulting in a silent and frequently asymptomatic occlusion.

Are Coronary CTOs Amenable for Percutaneous Coronary Revascularisation?

Coronary CTOs have been named the 'final frontier' in interventional cardiology.[13] Success rates of CTO PCI are lower than success rates of non-occluded lesions, with reported success rates for CTO ranging from about 70-90%.[3,15,16,17] Moreover, CTOs are associated with relatively high rates of restenosis and re-occlusion.[18] However, the advent of DES has reduced target vessel revascularisation rates to about half the rates observed during the bare metal stent era.[5,19]

Novel equipment such as microcatheters, specialised guidewires, and specialised devices such as the Crossboss™ CTO Crossing Catheter and Stingray® CTO Re-Entry System device (Boston Scientific, Natick, MA, USA) have become available in recent years. Furthermore, specialised CTO techniques were developed, such as several techniques for a retrograde approach to interrogate CTO lesions.[20] These developments have led to increased attention for and understanding of CTO PCI, which has led to increased CTO PCI success rates.[16] Despite the complexity of CTO PCI, recent data on the incidence of procedural complications have been reassuring.[17,21]

Coronary CTOs and MI

Coronary CTOs in the setting of STEMI were investigated for the first time in a prospective cohort of consecutive STEMI patients undergoing primary PCI at the Academic Medical Center (AMC) in the University of Amsterdam, Amsterdam, the Netherlands.[8] In this cohort of 1,463 patients, 839 (59%) had single vessel disease (SVD), 30% had multivessel disease (MVD) without a CTO in a non-IRA, and 11% had MVD with a CTO in a non-IRA. This study showed that patients with MVD without a CTO had a 1-year mortality rate comparable to patients with SVD. Whereas, MVD with a CTO in a non-IRA was associated with increased mortality (hazard ratio [HR] 3.8, 95% CI: 2.4-5.9, p<0.001). This study showed that patients with a CTO in a non-IRA undergoing primary PCI for STEMI, had a 1-year mortality rate of 35%. After these initial observations, several researchers have investigated the prognostic impact of a concurrent CTO in a non-IRA in patients undergoing primary PCI for STEMI. Table 1 shows an overview of studies that investigated mortality in STEMI patients with a concurrent CTO in a non-IRA.

A number of mechanisms may explain the markedly increased mortality rate in STEMI patients with a CTO in a non-IRA (Table 2). First, the presence of a CTO in a non-IRA may result in more pronounced negative left ventricular

Table 1: Mortality in STEMI patients undergoing primary PCI with SVD, MVD without CTO, and MVD with a CTO in a non-IRA.

Study	Year	N of patients	Prevalence of CTOs in non-IRA	Follow-up duration	Mortality in SVD, MVD without CTO, and MVD with CTO		
Van der Schaaf et al.[8]	2006	1,417	11.0%	1 year	8%	16%	35%
Claessen et al.[9]	2009	3,277	13.0%	5 years	14%	20%	38%
TAPAS (Lexis et al.)[11]	2011	1,071	8.4%	25 months	8.5%*		15.6%
HORIZONS-AMI (Claessen et al.)[10]	2012	3,283	8.6%	3 years	4.5%	6.7%	34.3%
Bataille et al.[12]	2012	2,020	8.0%	3 years	5.8%	12.1%	34.1%

STEMI: ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; SVD: single vessel disease; MVD: multivessel disease; CTO: chronic total occlusion; IRA: infarct-related artery.
* SVD and MVD without CTO were combined in this study.

Table 2: Potential mechanisms for increased mortality in STEMI patients with a CTO in a non-IRA.

1 More pronounced negative left ventricular remodelling
2 Higher prevalence of suboptimal markers of reperfusion after primary PCI (e.g. absent myocardial blush grade, incomplete ST-segment resolution)
3 Larger infarct size
4 Increased risk of potentially life-threatening arrhythmias
5 Increased prevalence of cardiogenic shock at hospital admission

STEMI: ST-elevation myocardial infarction; CTO: chronic total occlusion; IRA: infarct-related artery; PCI: percutaneous coronary intervention.

remodelling during the first year after the index STEMI. A CTO in a non-IRA was associated with a further decrease in left ventricular ejection fraction (LVEF) in a cohort of 356 patients with serial measurements of LVEF.[9] A baseline measurement was obtained within 1 month after primary PCI, and a follow-up measurement taken within 1 year after the index event. After multivariate analysis, the presence of a CTO in a non-IRA was an independent predictor for further deterioration of LVEF (OR 3.5, 95% CI: 1.6-7.8, p<0.01). In contrast, MVD without a CTO was not associated with a decrease in LVEF.

Second, two studies showed that STEMI patients with a CTO in a non-IRA had impaired markers of reperfusion after primary PCI when compared to patients with MVD without a CTO and to patients with SVD.[10,11] A substudy from the Thrombus Aspiration during primary PCI in Acute ST-elevation myocardial infarction Study (TAPAS) trial showed higher rates of incomplete ST-segment resolution (63.6% versus 48.2%, p=0.005) and higher rates of myocardial blush Grade 0 or 1 (34.2% versus 20.6%, p=0.006) in patients with (versus without) a concurrent CTO.[11] In a substudy from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, patients with a CTO in a non-IRA were found to be more likely to have a post-procedural TIMI flow Grade <3, absent myocardial blush, and incomplete ST-segment resolution.[10]

A third mechanism may be that STEMI patients with a CTO in a non-IRA develop larger infarcts. The aforementioned substudy from TAPAS showed that patients with a CTO in a non-IRA

had higher median levels of maximal myocardial-band of creatinin kinase (CK-MB). A fourth mechanism may be that the presence of a CTO in a non-IRA may lead to an increased susceptibility for life-threatening arrhythmias.[22]

Finally, the presence of a CTO in a non-IRA in STEMI patients is associated with higher rates of cardiogenic shock at hospital admission. In an observational study by Conde-Vela et al.[23] in a cohort of 630 STEMI patients treated with primary PCI, the presence of a CTO in a non-IRA was associated with an increased prevalence of cardiogenic shock at hospital admission, with an OR of 4.48 (95% CI: 2.1-9.1, p<0.001). Hoebers et al.[24] also described a higher prevalence of CTO in patients with (versus without) cardiogenic shock (29% versus 11%).

Coronary CTOs and MI in Selected Subgroups

Cardiogenic shock

The impact of a CTO in a non-IRA in STEMI patients has been studied in several patient subgroups. Two studies investigated STEMI patients presenting with cardiogenic shock,[25,26] defined according to clinical criteria used in the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial:[27] hypotension (systolic blood pressure <90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure ≥90 mmHg), and end-organ hypoperfusion (cold extremities or a urine output of <30 ml/hour and a heart rate of ≥60 beats/minute). Both studies showed that the presence of a CTO in a non-IRA was strongly associated with the occurrence of cardiogenic shock at admission. Moreover, a CTO in a non-IRA was independently associated with increased mortality in this extremely high-risk subgroup.[25,26]

Diabetes mellitus (DM)

STEMI patients with diabetes are known to have more extensive CAD. Approximately 35% of STEMI patients without diabetes have MVD compared with 60-70% of diabetic patients.[28-31] In a cohort of 539 STEMI patients with DM undergoing primary PCI, the prevalence of CTOs was also increased; 21% of diabetic patients had a CTO in a non-IRA compared with only 12% of patients without DM (p<0.01).[31] In diabetic STEMI patients undergoing primary PCI, the presence of a CTO in a non-IRA was an independent predictor of 5-year mortality (HR 2.2, 95% CI: 1.3-3.5, p<0.01).

Chronic kidney disease (CKD)

STEMI patients with CKD (defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2) were recently shown to have an increased prevalence of a CTO in a non-IRA (13% in patients with CKD versus 7% in patients without CKD, p=0.0003) in a Canadian cohort of patients (n=1,873) undergoing primary PCI.[32] In patients with CKD, the presence of a CTO was not an independent predictor of mortality. In contrast, a CTO in a non-IRA was an independent predictor of mortality in patients without CKD. Therefore, the clinical impact of a CTO in a non-IRA may be overshadowed by the presence of CKD.

Should We Treat Concurrent CTOs in Acute MI?

The strong association between the presence of a concurrent CTO in a non-IRA in STEMI patients raises the obvious question of whether revascularisation of these CTOs after primary PCI may lead to improved outcomes. Theoretically, this may promote healing at the infarct border zones, improve regional myocardial function, result in less pronounced left ventricular remodelling, and potentially improve electrical stability. In patients with stable CAD, successful CTO PCI has been demonstrated to improve LVEF and reduce left ventricular dimensions.[33-35]

A retrospective study by Yang et al.[36] described 136 STEMI patients with a CTO in a non-IRA who underwent primary PCI, all of whom underwent a staged procedure at 7-10 days after the index procedure to attempt a PCI of the concurrent CTO. This was successful in 64% of patients. During 2-year follow-up, cardiac mortality was lower (8.0% versus 20.4%, p=0.036) in patients with a successful (compared with an unsuccessful) CTO PCI. Moreover, the rate of major adverse cardiac events (MACE: composed of death, recurrent MI, repeat revascularisation, and re-hospitalisation because of heart failure) at 2 years was significantly lower in patients with successful CTO PCI (38.8% versus 21.8%, p=0.042). After multivariable analysis, successful CTO PCI remained associated with reduced mortality and reduced MACE rates at 2 years.

The ongoing Evaluating Xience V and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions after ST-elevation Myocardial Infarction (EXPLORE) trial[37] is enrolling STEMI patients with a CTO in a non-

IRA after successful primary PCI. 300 patients are randomised to either elective PCI of the CTO in a staged procedure within 7 days or to optimal medical therapy. The primary endpoints of this trial are: LVEF and left ventricular end-diastolic volume measured by cardiac MRI at 4-month follow-up. This trial has currently enrolled 80% of patients and will deliver important data regarding the potential beneficial effect of percutaneous recanalisation of concurrent CTOs in STEMI patients.

CONCLUSIONS

Approximately 10-15% of STEMI patients undergoing primary PCI are found to have a CTO in a non-IRA. The presence of a coronary CTO in a non-IRA in STEMI patients is associated with increased mortality, and above average deterioration of left ventricular function. A number of mechanisms may be responsible for this worsened prognosis, including impaired healing at the infarct border zone, decreased protection against future cardiovascular events, and potentially increased risk of arrhythmias. Currently, no prospective studies investigating additional revascularisation of the concurrent CTO have been completed. However, retrospective data suggest a potential benefit of CTO revascularisation in a staged procedure after the primary PCI.[36] The currently ongoing EXPLORE trial will deliver prospective evidence about the potential benefit of staged CTO PCI for this particular patient population.

REFERENCES

1. Fefer P et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol. 2012;59(11):991-7.

2. Råmunddal T et al. Chronic total occlusions in Sweden - report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). J Am Coll Cardiol. 2012;60(17 S):doi:10.1016/j.jacc.2012.08.092.

3. Grantham JA et al. Chronic total occlusion angioplasty in the United States. JACC Cardiovasc Interv. 2009;2(6):479-86.

4. Caixeta A et al. 5-year clinical outcomes after sirolimus-eluting stent implantation insights from a patient-level pooled analysis of 4 randomized trials comparing sirolimus-eluting stents with bare-metal stents. J Am Coll Cardiol. 2009;549(10):894-902.

5. Van den Branden BJ et al. Five-year clinical outcome after primary stenting of totally occluded native coronary arteries: a randomised comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions (PRISON II study). EuroIntervention. 2012;7(10):1189-96.

6. Godino C et al. Coronary chronic total occlusions: mid-term comparison of clinical outcome following the use of the guided-STAR technique and conventional anterograde approaches. Catheter Cardiovasc Interv. 2012;79(1):20-7.

7. Joyal D et al. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. Am Heart J. 2010;160(1):179-87.

8. van der Schaaf RJ et al. Impact of multivessel coronary disease on long-term mortality in patients with ST-elevation myocardial infarction is due to the presence of a chronic total occlusion. Am J Cardiol. 2006;98(9):1165-9.

9. Claessen BE et al. Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. JACC Cardiovasc Interv. 2009;2(11):1128-34.

10. Claessen BE et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. Eur Heart J. 2012;33(6):768-75.

11. Lexis CP et al. Impact of chronic total occlusions on markers of reperfusion, infarct size, and long-term mortality: a substudy from the TAPAS-trial. Catheter Cardiovasc Interv. 2011;77(4):484-91.

12. Bataille Y et al. Prevalence, predictors and clinical impact of unique and multiple chronic total occlusion in non-infarct-related artery in patients presenting with ST-elevation myocardial infarction. Heart. 2012;98(23):1732-37.

13. Stone GW et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. Circulation. 2005;112(15):2364-72.

14. Choi JH et al. Frequency of myocardial infarction and its relationship to angiographic collateral flow in territories supplied by chronically occluded coronary arteries. Circulation. 2013;127:703-9.

15. Mehran R et al. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. JACC Cardiovasc Interv. 2011;4:952-61.

16. Rathore S et al. Retrograde percutaneous recanalization of chronic total occlusion of the coronary arteries: procedural outcomes and predictors of success in contemporary practice. Circ Cardiovasc Interv. 2009;2(2):124-32.

17. Patel VG et al. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. JACC Cardiovasc Interv. 2013;6(2):128-36.

18. Valenti R et al. Predictors of reocclusion after successful drug-eluting stent-supported percutaneous coronary intervention of chronic total occlusion. J Am Coll Cardiol. 2013;61(5):545-50.

19. Colmenarez HJ et al. Efficacy and safety of drug-eluting stents in chronic total coronary occlusion recanalization: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55(17):1854-66.

20. Garcia S et al. Chronic total occlusions: patient selection and overview of advanced techniques. Curr Cardiol Rep. 2013;15(2):334.

21. Werner GS et al. Contemporary success and complication rates of percutaneous coronary intervention for chronic total coronary occlusions: results from the ALKK quality control registry of 2006. EuroIntervention. 2010;6(3):361-6.

22. Nombela-Franco L et al. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO Primary Study). Circ Arrhythm Electrophysiol.

2012;5(1):147-54.

23. Conde-Vela C et al. Cardiogenic shock at admission in patients with multivessel disease and acute myocardial infarction treated with percutaneous coronary intervention: related factors. Int J Cardiol. 2007;123(1):29-33.

24. Hoebers LP et al. The impact of multivessel disease with and without a co-existing chronic total occlusion on short- and long-term mortality in ST-elevation myocardial infarction patients with and without cardiogenic shock. Eur J Heart Fail. 2013;15(4):425-32.

25. van der Schaaf RJ et al. Effect of multivessel coronary disease with or without concurrent chronic total occlusion on one-year mortality in patients treated with primary percutaneous coronary intervention for cardiogenic shock. Am J Cardiol. 2010;105(7):955-9.

26. Bataille Y et al. Deadly association of cardiogenic shock and chronic total occlusion in acute ST-elevation myocardial infarction. Am Heart J. 2012;164(4): 509-15.

27. Hochman JS et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. N Engl J Med. 1999;341(9):625-34.

28. van der Schaaf RJ et al. Primary percutaneous coronary intervention for patients with acute ST elevation myocardial infarction with and without diabetes mellitus. Heart. 2006;92(1):117-8.

29. van der Schaaf RJ et al. Long-term impact of multivessel disease on cause-specific mortality after ST elevation myocardial infarction treated with reperfusion therapy. Heart. 2006;92(12):1760-3.

30. Mak KH et al. Influence of diabetes mellitus on clinical outcome in the thrombolytic era of acute myocardial infarction. GUSTO-I Investigators. Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries. J Am Coll Cardiol. 1997;30(1):171-9.

31. Claessen BE et al. Prevalence and impact of a chronic total occlusion in a non-infarct-related artery on long-term mortality in diabetic patients with ST elevation myocardial infarction. Heart. 2010;96(24):1968-72.

32. Bataille Y et al. Interaction of chronic total occlusion and chronic kidney disease in patients undergoing primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. Am J Cardiol. 2013;112(2):194-9.

33. Kirschbaum SW et al. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. Am J Cardiol. 2008;101(2):179-85.

34. Sirnes PA et al. Improvement in left ventricular ejection fraction and wall motion after successful recanalization of chronic coronary occlusions. Eur Heart J. 1998;19(2):273-81.

35. Danchin N et al. Effect of late percutaneous angioplastic recanalization of total coronary artery occlusion on left ventricular remodeling, ejection fraction, and regional wall motion. Am J Cardiol. 1996;78(7):729-35.

36. Yang ZK et al. Impact of successful staged revascularization of a chronic total occlusion in the non-infarct-related artery on long-term outcome in patients with acute ST-segment elevation myocardial infarction. Int J Cardiol. 2013;165(1):76-9.

37. van der Schaaf RJ et al. Rationale and design of EXPLORE: a randomized, prospective, multicenter trial investigating the impact of recanalization of a chronic total occlusion on left ventricular function in patients after primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. Trials. 2010;11:89.

RECENT ADVANCES IN SURGICAL AND PERCUTANEOUS MITRAL VALVE THERAPIES - IMPLICATIONS OF AN INTEGRATED APPROACH TO MITRAL REGURGITATION

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ABSTRACT

Surgical mitral valve (MV) repair has evolved to become the standard of care for severe mitral regurgitation (MR) with superior acute and long-term results compared to valve replacement. Minimally-invasive surgical techniques have been successful in reducing operative trauma while yielding equivalent or even superior results compared to conventional sternotomy. However, due to elevated operative risk, growing numbers of patients are not referred for surgery, especially elderly patients with reduced ventricular function and functional MR who often present with relevant comorbidities. For these patients, transcatheter-based therapies represent an attractive option. While most interventional techniques are still in experimental or early clinical stages, relevant clinical experience has been gathered with the MitraClip device. More recently, devices for transcatheter MV implantation have entered the clinical stage.

For successful implementation of an interdisciplinary MV programme, integration of surgical and interventional treatment modalities within heart centres is of paramount importance. This is best accomplished by an interdisciplinary heart team consisting of cardiologists and cardiac surgeons. An integrated approach to MV disease will help relieve under-treatment of patients with severe MR and will benefit a true heart centre as a whole by increasing the overall caseload of MV patients, as well as volumes and outcome of MV surgery by more adequate patient allocation for different treatment options.

Keywords: Mitral regurgitation, mitral valve repair, minimally-invasive, transcatheter mitral valve repair, MitraClip, heart team.

INTRODUCTION

Mitral regurgitation (MR) is among the most frequent entities in valvular heart disease, with a prevalence of 1.7% in Western societies. In patients >75 years, relevant MR, as defined by international guidelines, is present in approximately 10% of the population.[1,2] Furthermore, due to increasing life expectancy and a growing prevalence of cardiovascular risk factors, increasing patient numbers, especially with functional MR and chronic heart failure, can be anticipated.[3]

Since the basic pathophysiological mechanism of MR was classified by Alain Carpentier[4] in the 1980s, reconstructive MV surgery has been established as the gold standard treatment. By refinement of surgical techniques, mitral valve repair (MVR) can be performed with low perioperative risk and excellent long-term outcome.[5] Minimally-invasive techniques (MITs) have reduced operative trauma and have become the standard-of-care at specialised centres.[6] This expertise is the benchmark for any novel interventional approach. These less invasive approaches are urgently needed since a growing share of patients with

relevant MR are poor surgical candidates.[7] It is for this growing population of high-risk patients that interventional MV therapies represent an adequate adjunct to surgical therapies.

SURGICAL MVR

Modern Surgical Techniques

MVR has proven superior compared to prosthetic valve replacement with regards to perioperative risk and long-term outcome.[8,9] Therefore, MVR with preservation of the subvalvular apparatus has to be strived for whenever possible. Depending on the pathology, different surgical techniques are well established. Annuloplasty is indicated in almost every case. Annuloplasty rings allow for downsizing in case of annular dilatation or to stabilise additional valvuloplasty. Different rings are available depending on the individual pathology with the aim of restoring leaflet coaptation.

In degenerative MR, annuloplasty is usually complemented by valvuloplasty. While, in the past, resection of excessive leaflet tissue of the posterior mitral leaflet (PML) was frequently performed, today leaflet-sparing techniques with limited PML triangular resection and/or implantation of neochords are preferred. Neochords are anchored to the papillary muscles and sutured to the free edges of PML or anterior mitral leaflet (AML). By adjusting the length of the neochords, prolapse is corrected to the level of the annular plane.[10]

When correcting large prolapse, SAM phenomenon ('systolic anterior motion') can occur leading to systolic obstruction of the left ventricular (LV) outflow tract. A 'sliding plasty' can be performed to reduce the height of the PML to avoid SAM. Alternatively, dedicated annuloplasty rings with increased anterior-posterior diameter can be used.

The Alfieri-stitch is another technique that can be helpful in selected cases. Using a suture, free edges of PML and AML are connected at the origin of the regurgitant jet creating a 'double-orifice' of the MV.[11]

Despite a large armamentarium of surgical reconstructive techniques, MVR is not always possible. If prosthetic valve replacement is indicated, preservation of the subvalvular apparatus is of paramount importance.[12]

Minimally Invasive Surgery

Beginning in the mid-1990s, MITs for MVR were developed. At specialised centres, minimally-invasive MVR via left antero-lateral minithoracotomy has become the standard access, suitable for a wide range of patients (Figure 1). Contraindications include severe pleural adhesions or pronounced atherosclerosis of peripheral vessels, precluding groin cannulation, and representing a risk of atheroembolism or aortic dissection during retrograde perfusion.

Patients are positioned with slight elevation of the right hemithorax. Via a 4-5 cm skin incision, access is gained through the fourth or fifth intercostal space. Cranial to the incision, an endoscope is inserted for videoscopic vision. Cross-clamping of the aorta is performed by a transthoracic clamp ('Chitwood clamp') or using the 'endo-clamp' technique. The latter technique can be helpful in 'redo cases' to avoid dissection of adhesions of the ascending aorta. Continuous insufflation of CO_2 minimises the risk of air embolisation. Implementation of extracorporeal circulation is achieved by cannulation of arteria and vena femoralis (Figure 1A). Access to the MV is gained via direct left atrial incision. Reconstructive techniques are identical to those used in sternotomy approaches.

Apart from isolated MVR, additional tricuspid valve repair, correction of atrial septal defects, extirpation of atrial myxoma, or atrial ablation for atrial fibrillation can also be performed via the minimally-invasive approach.

Clinical Results

Compared to the conventional sternotomy approach, several advantages have been shown when using MITs. A certain learning curve with initially prolonged operative times is usually without evident clinical consequences. Regarding acute as well as long-term outcome, minimally-invasive MV surgery is non-inferior to sternotomy approaches.[13] In one of the largest published series operative mortality was 0.2% after minimally-invasive surgery compared to 0.3% after conventional MVR.[14] Freedom from repeat MV surgery is similar after both approaches with rates above 90% up to 7 years of follow-up. Advantages of MITs were demonstrated regarding transfusion requirements, re-exploration for bleeding, postoperative ventilation times, or duration of hospital stay.

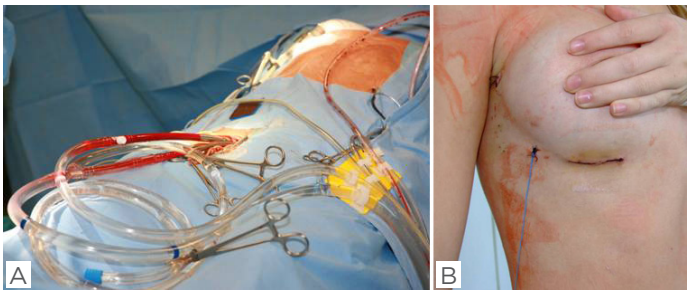

Figure 1: A) Implementation of extracorporeal circulation by cannulation of femoral vessels; B) result after minimally-invasive mitral valve repair via right antero-lateral minithoracotomy.

Also, less postoperative pain, quicker reconvalescence, and improved cosmesis (Figure 1B) speak in favour of minimally-invasive MVR.

After minimally-invasive MVR was introduced, concerns regarding increased incidence of cerebrovascular events were expressed. In a large current meta-analysis[13] this effect was not found. In our own single-centre experience of >400 consecutive cases since 2001, no periprocedural stroke was observed. Routine use of the technique has allowed us to perform >80% of all isolated MV procedures by minimally-invasive access. Cardiopulmonary bypass times and aortic cross-clamp times are no longer different compared to the standard sternotomy technique. Finally, by reduced complication rates and shorter duration of hospital stay, minimally-invasive MVR can be performed cost-effectively.[15]

INTERVENTIONAL MVR

Even though surgical MVR is an established therapeutic concept for patients with relevant MR, a large proportion of patients are denied surgery. According to the European Heart Survey, only 50% of patients receive surgical treatment.[7] This is true especially in patients of advanced age, reduced LV function, and relevant comorbidities. Furthermore, results after surgical MVR for functional MR are less favourable compared to degenerative MR. Surgical correction of secondary MR leads to some 'reverse remodelling' and moderate improvement of LV function.[16] However, proof of survival advantage is pending.[17,18] Recently, results of a multicentre study suggested non-inferiority of prosthetic MV replacement compared to MVR in patients with severe ischaemic MR regarding LV remodelling. While MV replacement provided more durable results regarding recurrence of MR, no significant differences were found with respect to clinical endpoints. However, the trial was only powered to detect differences in the primary endpoint, i.e. reverse remodelling.[19]

A number of percutaneous approaches to MR have been developed. According to their mode of action, they can be categorised into systems meant for direct or indirect annuloplasty or for direct valvuloplasty.

Coronary Sinus (CS) Techniques

The anatomical proximity of the CS to the posterior aspect of the mitral annulus (MA) and the uncomplicated transvenous access have led to the development of different systems for indirect annuloplasty. The Carillon Mitral Contour System (Cardiac Dimensions®, Inc., Kirkland, WA, USA) consists of a central nitinol element connecting distal anchors and a proximal anchor. After transjugular access the anchoring portions are placed in the vena cordis magna and proximal CS. By stepwise foreshortening of the central element, the device allows for remodelling of the posterior periannular tissue.

Results of the prospective, multicentre AMADEUS trial (Carillon Mitral Annuloplasty Device European Union Study[20]) have been published. Implantation of the device was successful in 30 of 48 patients (63%). In 18 patients implantation was impossible or the device was retracted due to dislocation, coronary artery compression, or failure to reduce MR. After successful implantation, 23% of patients had serious adverse events. At 6 months, clinical improvement by a mean of one New York Heart Association (NYHA) functional class was observed. The device carries Conformité Européenne (CE) mark.

The Monarc System (Edwards Lifesciences, Irvine, CA, USA) has self-expanding distal and proximal anchoring segments connected by a central spring. This spring is held under tension by resorbable spacers. During the first weeks following implantation, the central portion foreshortens successively and reduces septal-lateral circumference of the MA. 1-year data of the multicentre EVOLUTION-I trial[21] have been published. In 82% of 72 patients, successful implantation was documented. In 30%, compression of coronary arteries was noted. The primary safety endpoint was reached by 91% and 82% at 30 days and 12 months, respectively.

In 50%, reduction of MR by ≥1 Grade was noted at 12 months. In light of these results, the device is no longer available.

The Viacor PTMA system (Percutaneous transvenous mitral annuloplasty; Viacor, Inc., Wilmington, MA, USA) is a multi-lumen catheter introduced through the subclavian vein. Nitinol rods of differing stiffness are introduced to cause anterior displacement of the posterior MA. As the proximal port of the multi-lumen catheter is left in an infraclavicular subcutaneous pouch, exchange of nitinol rods is possible at later time points. The PTOLEMY-I trial (Percutaneous transvenous mitral annuloplasty)[22] has investigated clinical effects following implantation. Only 9 of 27 patients received permanent implants; 4 patients were followed until the end of the study, and all other patients experienced complications requiring surgical removal of the system. These results prompted the company to stop further development of the device.

Limitations of CS techniques

CS techniques have important limitations. Spatial relation of CS and MA is highly variable. This distance increases in patients with severe MR.[23,24] From surgical literature it is known that annuloplasty needs to address posterior and anterior MA, and annuloplasty rings need to be anchored at fibrous trigons. Systems inserted into the CS only compress the posterior aspect of the MA.[25] Finally, many patients do not qualify because, in up to 80%, circumflex artery compression may occur. Therefore, most CS approaches have been abandoned.

Direct Annuloplasty

Several devices for direct annuloplasty exist mimicking surgical annuloplasty. The issue of circumflex artery compression inherent with CS approaches is circumvented by these techniques. One of the devices with early clinical experience is the Valtech Cardio B (Valtech Cardio, Or Yehuda, Israel), which is delivered via a transvenous, transseptal route, and uses nitinol screws inserted into the atrial aspect of the MA in a commissure-to-commissure fashion. In a second step, a wire is tightened to allow for cinching of the annulus. Experimental and early clinical data have been presented.[26]

The Mitralign system (Mitralign Inc., Tewksbury, Massachusetts, USA) delivers pledgets via a transventricular route and after puncture of the MA to the atrial aspect. Pledgets are cinched by a suture. A CE mark study is currently being persued.[27]

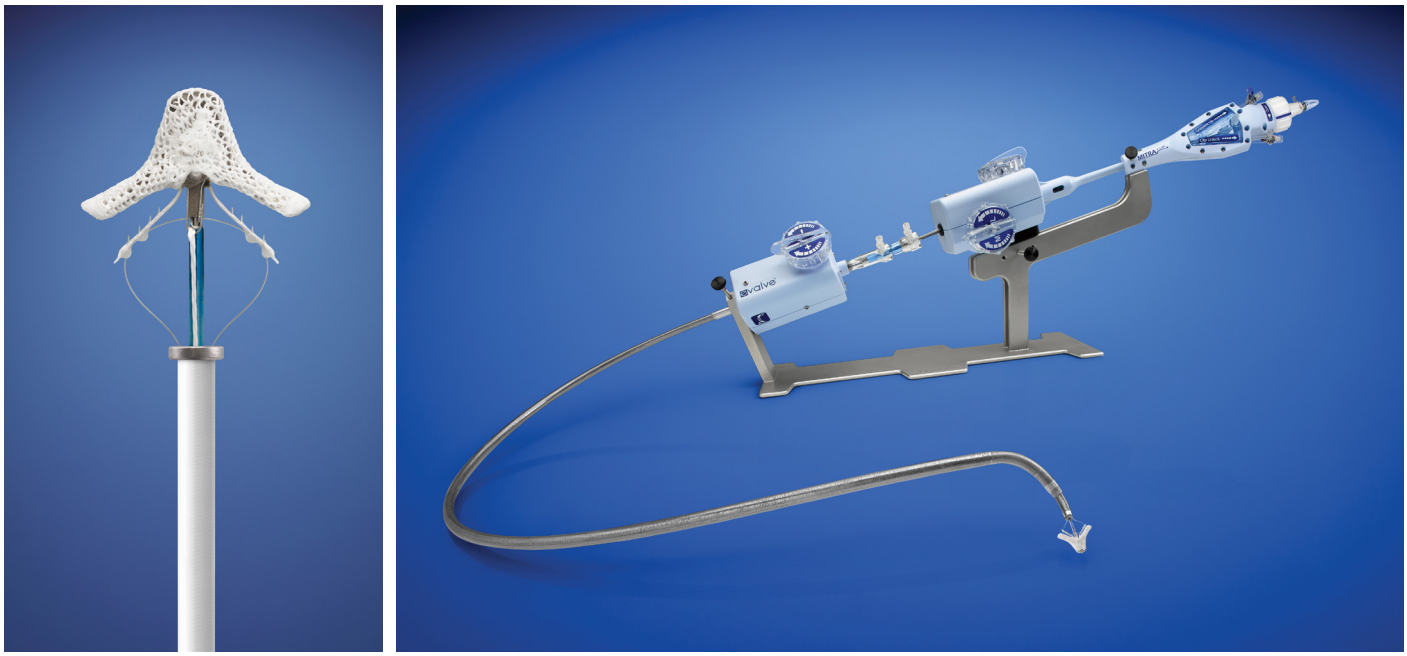

Figure 2: The MitraClip system consists of a polyester-covered cobalt-chromium clip. It represents the interventional extension of the surgical 'edge-to-edge' technique.
Reproduced from Abbott Vascular, Menlo Park, CA, USA.

Interventional Edge-to-Edge Repair Technique

The MitraClip system (Abbott Vascular, Menlo Park, CA, USA) is a catheter-based extension of the surgical Alfieri technique.[11] The device consists of a polyester-covered cobalt-chromium clip (Figure 2). It is introduced by a 24 French (Fr) delivery catheter via the femoral vein into the right atrium and, after transseptal puncture, advanced into the left atrium. Under 2D and 3D echocardiographic and fluoroscopic guidance (Figure 3) the clip is positioned above the MV, opened, and advanced into the left ventricle. Subsequently, it is retracted so that the free edges of AML and PML are loaded onto the clip at the origin of the regurgitant jet; closure of the clip results in a 'double-orifice' MV (Figure 4).

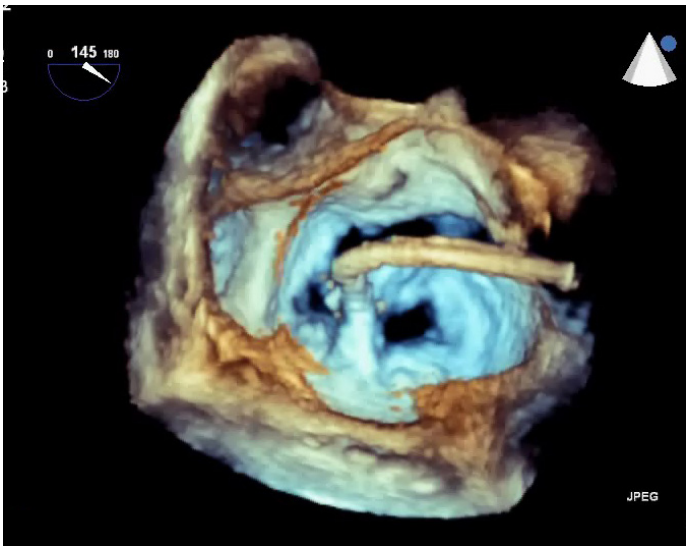

Figure 3: The MitraClip procedure requires optimal visualisation by 2D and 3D echocardiography.

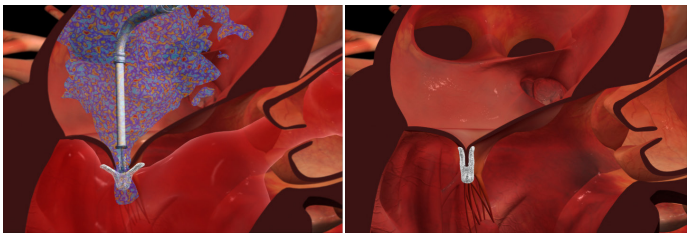

Figure 4: The MitraClip is introduced via the femoral vein and advanced to the right atrium. After transseptal puncture it is positioned above the mitral valve at the origin of the regurgitant jet and inserted into the left ventricle. By retraction of the clip, the free edges of mitral leaflets are loaded onto the clip arms. Closure of the clip results in approximation of the free leaflet edges.
Reproduced from Abbott Vascular, Menlo Park, CA, USA.

Before deployment, the clip can be opened and repositioned or completely retrieved. The implantation results are assessed under physiological haemodynamic conditions. One or more additional clips can be implanted if necessary.

Clinical results

The MitraClip system was initially evaluated in the EVEREST-I (Endovascular Valve Edge to Edge Repair Study) and EVEREST-II trials.[28,29] Out of 107 patients, acute success with residual MR ≤Grade 2+ was noted in 74%. In 66% of successfully implanted patients, MR was ≤Grade 2+ at 12 months. Severe adverse events were documented in 9% at 30 days. Randomisation for the EVEREST-II trial allocated 279 patients in a 2:1 ratio to MitraClip or surgery.[30] Degenerative MR was present in 73% of cases. Primary efficacy endpoint was defined as survival, freedom from reoperation, and freedom from MR ≥Grade 2+ at 12 months, and it was reached in 55% of interventional and 73% of surgical patients in an intent-to-treat analysis (p=0.007). The combined safety endpoint (incidence of severe adverse events to 30 days) was reached in 15% of interventional and 48% of surgical patients (p<0.001), even though transfusion of ≥2 units represented the majority of adverse events. Excluding transfusion, no significant difference in safety was seen (p=0.23). In both interventional and surgical cohorts, ventricular remodelling, improved NYHA functional class, and improved quality of life were noted. It has to be emphasised that 20% of MitraClip patients underwent secondary MV surgery. In 46% of interventional patients MR was ≥Grade 2+ at 12 months. Further follow-up resulted in MitraClip FDA approval in October, 2013. Efficacy of the MitraClip device is currently evaluated in randomised controlled trials against best medical therapy in the COAPT (ClinicalTrials.govID:NCT01626079) and RESHAPE-HF (ClinicalTrials.govID:NCT01772108) trials.

Extensive real-world experience with the MitraClip system exists in Europe. The first-in-Europe implantation was performed at the University Heart Center in Hamburg, Germany, in January, 2008. In an interim analysis of 51 patients,[31] marked reduction of MR and an excellent safety profile of the procedure was documented. Until January 2014, >500 patients have been treated. This represents the world´s largest single-centre experience. Meanwhile 2-year data of 202 successfully treated patients (74±9 years, 65%

male, logEuroSCORE I 25[16-43]%) from our centre have been reported.[32] 140 patients were treated for secondary MR, while primary MR was present in 62 patients. Freedom from MR ≥Grade 2+ was 89% at 2 years.

Transapical Implantation of Neochordae

A novel device for transapical implantation of neochordae has been evaluated clinically, and recently, received CE mark (NeoChord DS1000, NeoChord Inc., Minneapolis, Minnesota, USA). Via standard transapical access, the delivery catheter is inserted into the left ventricle. Under 2D and 3D echocardiographic guidance, the free edge of the prolapsing segment of PML or AML are grasped. Colour-sensitive fibre optics ensure grasping of sufficient leaflet tissue. Neochordae are subsequently externalised through the LV apex and fixed at adequate length under echo guidance. Clinical feasibility and safety have recently been demonstrated in the Transapical Artificial Chordae Tendineae (TACT) trial and further evaluation is being pursued in a post-market registry at present.[33]

COMMENTARY

Refinement of reconstructive techniques has made surgical MVR the reference treatment for patients with relevant MR. Surgery can be performed with low perioperative complication rates and excellent long-term outcomes. Therefore, surgery may also be justified in asymptomatic patients. In Germany, rates of MVR as compared to prosthetic valve replacement have constantly increased.[34] MIT have further improved surgical results and have become the standard of care at specialised centres.

Many interventional treatment strategies for MR have been pursued in the past. However, only the MitraClip system has extensive clinical experience. For patients with elevated surgical risk due to advanced age, reduced LV function, and/or relevant comorbidities it represents an adequate alternative. In a recent analysis, we found that interventional and surgical patients differ fundamentally.[35] Interventional patients had significantly higher overall clinical risk profiles compared to surgical patients (p<0.001). Also, MR was of functional or mixed aetiology in 25.3% of surgical compared to 77.8% in interventional patients (p<0.001). While surgery was significantly more likely to reduce MR to ≤Grade 2+ compared to MitraClip treatment (p=[log rank]<0.001), risk-adjusted survival was not significantly different at 6 months between the two modalities (p=0.642).

In the years following the introduction of an interventional MV programme at our centre, surgical MV activity has increased.[36] This increase in surgical caseload amounted to 32.2% from 2007-2012, and it was well above the national background, which showed an increase in caseload during the same timeframe of 10.2%.[37] The overall caseload of interventional and surgical MV patients increased by 71.3% from 2007-2012. In summary, it seems likely that in addition to some crossover of patients initially considered for surgery but then deemed to be high-risk, MitraClip patients stem mainly from an 'on-top recruitment' process. Thus, addition of a MitraClip programme likely relieved undertreatment of patients with relevant MR.

Regarding risk profiles of surgical patients there were also several changes since implementation of a MitraClip programme. Although mean logEuroSCORE I of surgical patients remained unchanged, risk profile decreased significantly regarding several important parameters, such as presence of ischaemic MR, coronary artery disease, status post myocardial infarction, or status post previous cardiac surgery (all p<0.01). In parallel, the adjusted MVR rate (excluding cases of MV stenosis or severe MV endocarditis) increased from 80-89% (p=0.02), while 30-day mortality decreased from 7.2-4.2% (p=0.22) for all MV patients. For isolated MVR, 30-day mortality was 1.5% (6/406 patients) in all patients during the study period. The trend of improved surgical outcomes may be explained by more adequate patient selection.

Recently, MitraClip therapy has been incorporated into international guidelines for treatment of primary or secondary MR in inoperable or high-risk patients.[2] Patient selection, performance of the procedure, and post-procedural care should be performed by an interdisciplinary team of cardiologists and cardiac surgeons.

FUTURE PERSPECTIVES

For the future, an increasing clinical relevance of endovascular therapies for treatment of MR can be anticipated. New devices for repair are entering the clinical stage for specific subsets of patients.

Even more recently, very early clinical experience has been gathered with devices for transapical or transatrial transcatheter MV implantation, such as the Neovasc Tiara (Neovasc Inc., Richmond, BC, Canada), the Fortis (Edwards Lifesciences, Inc., Irvine, CA, USA), or the CardiAQ device (CardiAQ Valve Technologies, Inc., Irvine, CA, USA). These new devices have the conceptual advantages of potentially abolishing MR altogether without risk of recurrence. Also, treatment of multiple aetiologies of MR by one device seems possible.

In summary, the field of transcatheter MV therapies is quickly evolving with multiple new repair and replacement strategies in early clinical use. At present, all devices have to be restricted to inoperable patients or to compassionate use settings. However, once clinical proof of safety and efficacy has been demonstrated, extension to a broader patient spectrum seems likely. For a successful clinical programme, an interdisciplinary heart team of multiple specialities, but mandatorily including cardiologists and cardiac surgeons, is needed to ensure optimal patient care and careful evaluation of new techniques against the current surgical gold standard.

REFERENCES

1. Nkomo VT et al. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.

2. Vahanian A et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2012;33(19):2451-96.

3. Rosamond W et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2008;117(4):e25-146.

4. Carpentier A. Cardiac valve surgery – the "French correction". J Thorac Cardiovasc Surg. 1983;86(3):323-37.

5. David TE et al. Late outcomes of mitral valve repair for floppy valves: implications for asymptomatic patients. J Thorac Cardiovasc Surg. 2003;125(5):1143-52.

6. Conradi L et al. Minimally-invasive mitral valve surgery: evolution of the technique to the standard of care for mitral repair. Thorac Cardiovasc Surg. 2010;58(Suppl 1):S119.

7. Mirabel M et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J. 2007;28(11):1358-65.

8. Lawrie GM. Mitral valve repair vs replacement. Current recommendations and long-term results. Cardiol Clin. 1998;16(3):437-48.

9. Mohty D et al. Very long-term survival and durability of mitral valve repair for mitral valve prolapse. Circulation. 2001;104(12 Suppl 1):11-7.

10. Perier P et al. Toward a new paradigm for the reconstruction of posterior leaflet prolapse: midterm results of the "respect rather than resect" approach. Ann Thorac Surg. 2008;86(3):718-25.

11. Alfieri O et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. J Thorac Cardiovasc Surg. 2001;122(4):674-81.

12. David TE et al. Left ventricular function after mitral valve surgery. J Heart Valve Dis. 1995;4 Suppl 2:S175-80.

13. Modi P et al. Minimally invasive mitral valve surgery: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2008;34(5):943-52.

14. Mihaljevic T et al. One thousand minimally invasive valve operations: early and late results. Ann Surg. 2004;240(3):529-34.

15. Reichenspurner H et al. Video and robotic-assisted minimally invasive mitral valve surgery: a comparison of the Port-Access and transthoracic clamp techniques. Ann Thorac Surg. 2005;79(2):485-90.

16. Bach DS, Bolling SF. Improvement following correction of secondary mitral regurgitation in end-stage cardiomyopathy with mitral annuloplasty. Am J Cardiol. 1996;78(8):966-9.

17. Wu AH et al. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol. 2005;45(3):381-7.

18. Mihaljevic T et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol. 2007;49(22):2191-201.

19. Acker MA et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med. 2014;370:23-32.

20. Schofer J et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. Circulation. 2009;120(4):326-33.

21. Harnek J et al. Transcatheter implantation of the MONARC coronary sinus device for mitral regurgitation: 1-year results from the EVOLUTION phase I study (Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation). JACC Cardiovasc Interv. 2011;4(1):115-22.

22. Sack S et al. Percutaneous transvenous mitral annuloplasty: initial human experience with a novel coronary sinus implant device. Circ Cardiovasc Interv. 2009;2(4):277-84.

23. Choure AJ et al. In vivo analysis of the anatomical relationship of coronary sinus to mitral annulus and left circumflex coronary artery using cardiac multidetector computed tomography: implications for percutaneous coronary sinus mitral annuloplasty. J Am Coll Cardiol. 2006;48(10):1938-45.

24. Tops LF et al. Noninvasive evaluation of coronary sinus anatomy and its relation to the mitral valve annulus: implications for percutaneous mitral annuloplasty. Circulation. 2007;115(11):1426-32.

25. Lansac E et al. Percutaneous mitral annuloplasty through the coronary sinus: an anatomic point of view. J Thorac Cardiovasc Surg. 2008;135(2):376-81.

26 Maisano F et al. Direct access transcatheter mitral annuloplasty with a sutureless and adjustable device: preclinical experience. Eur J Cardiothorac Surg. 2012;42:524-9.

27 Mandinov L et al. Early insight into Mitralign direct annuloplasty for treatment of functional mitral regurgitation. Interventional Cardiology

Review. 2011;6:170-2.

28 Feldman T et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. J Am Coll Cardiol. 2005;46(11):2134-40.

29. Feldman T et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol. 2009;54(8):686-94.

30. Feldman T et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med. 2011;364(15):1395-406.

31. Franzen O et al. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. Eur Heart J. 2010;31(11):1373-81.

32. Rudolph V et al. Aetiology of mitral regurgitation differentially affects 2-year adverse outcomes after MitraClip therapy in high-risk patients. Eur J Heart Fail. 2013;15(7):796-807.

33. Seeburger J et al. Off-pump transapical implantation of artificial neo-chordae to correct mitral regurgitation: the TACT trial (Transapical Artificial Chordae Tendinae) proof of concept. J Am Coll Cardiol. 2014;63:914-9.

34. Beckmann A et al. Cardiac surgery in Germany during 2012: a report on behalf of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg. 2014;62(1):5-17.

35. Conradi L et al. Surgical or percutaneous mitral valve repair for secondary mitral regurgitation: comparison of patient characteristics and clinical outcomes. Eur J Cardiothorac Surg. 2013;44(3):490-6.

36. Conradi L et al. Towards an integrated approach to mitral valve disease: implementation of an interventional mitral valve programme and its impact on surgical activity. Eur J Cardiothorac Surg. 2013;44(2):324-8.

37. Funkat AK et al. Cardiac Surgery in Germany during 2011: a report on behalf of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg. 2012;60(6):371-82.

TRANSCATHETER AORTIC VALVE IMPLANTATION: REVIEW AND CURRENT STATE OF THE ART

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ABSTRACT

Since the introduction of transcatheter aortic valve implantation (TAVI) 12 years ago, the treatment options for severe, symptomatic aortic valve stenosis in high-risk patients have significantly increased. Because of the growing implementation of TAVI in clinical practice, knowledge of the outstanding clinical outcome of TAVI and TAVI-related limitations is expanding. In this review, potential complications, including stroke, vascular complications, paravalvular regurgitation, and conduction disturbances, are discussed. To reduce the incidence of these limitations, new valves are being designed and clinically evaluated. The ultimate goal is to reduce potential complications and expand the use of TAVI to lower-risk patient cohorts.

Keywords: Aortic valve stenosis, valvular heart disease, prosthetic valves, transcatheter aortic valve implantation (TAVI), stroke, aortic regurgitation, vascular complications, permanent pacemaker.

AORTIC VALVE STENOSIS

Aortic valve stenosis is one of the most common acquired valvular diseases in elderly patients (>75 years) in Western countries, with a prevalence of 3.4% of severe aortic valve stenosis.[1] The progressive narrowing of the degenerative aortic valve, due to aortic valve sclerosis, causes an increasing pressure gradient between the left ventricle and the ascending aorta. The left ventricle can compensate to overcome this pressure gradient by progressive myocardial hypertrophy. As long as ventricular compensation is present, symptoms do not occur and patient prognosis remains uninfluenced. However, once hypertrophy reaches its limit by losing compliance, diastolic dysfunction initiates, and further thickening and calcification of the aortic valve - together with progressive myocardial dysfunction - will lead to the onset of symptoms. Once symptoms occur, the prognosis is very poor; the average survival of patients that experience angina, syncopes, or heart failure symptoms due to aortic valve stenosis is only 5, 3, and 2 years, respectively.[2]

The actual gold standard treatment for severe, symptomatic aortic valve stenosis is surgical aortic valve replacement (AVR). The aortic valve is replaced by a mechanical or biological valve prosthesis (depending on the clinical picture and the age of the patient). Absence of important comorbidities leads to low operative mortality, even in elderly patients.[3]

However, one in three patients are rejected for AVR, because of a too high operative risk (e.g. old age, increased surgical risk score such as EuroSCORE) or the presence of important comorbidities (pulmonary hypertension, porcelain aorta, etc.).[4] Until recently, a pending medical therapy (digoxin, diuretics, angiotensin converting enzyme-inhibitors or angiotensin receptor blockers), potentially combined with balloon aortic valvuloplasty, was proposed for those patients.[5] However, prognosis of medically treated patients remains limited.

Non-surgical, percutaneous treatment of patients with severe symptomatic aortic valve stenosis was initiated in 1985, with the introduction of balloon aortic valvuloplasty.[6-8] In 1986, Alain Cribier reported on balloon aortic valvuloplasty carried out in three elderly patients with acquired severe aortic valve stenosis. The transvalvular systolic pressure gradient was considerably decreased at the end of the procedure, during which there were no complications. An increased valve opening was confirmed by angiography and echocardiography. A subsequent clinical course showed a pronounced functional improvement.[6] Unfortunately, a high rate of restenosis, occurring several months to years after balloon valvuloplasty, and the occurrence of aortic regurgitation, remains an important limitation of this technique. In 1987, the development of larger peripheral vascular stents created technical perspectives for the design of a specific 'cardiac' stent to maintain opening of the aortic valve.[9] In 1992, the first stent-based porcine bioprostheses were implanted in animal models.[10] Ten years later (2002), the first-in-man non-surgical aortic valve implantation was performed by Alain Cribier.[11] In 2012, TAVI or percutaneous aortic valve implantation was adopted in the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines as a treatment for severe, symptomatic aortic valve stenosis in patients with high surgical risk.[5]

Types of Percutaneous Aortic Valves

To date, a significantly expanding number of percutaneous bioprostheses are approved by the Conformité Européenne (CE). The Edwards-SAPIEN THV™ valve (Edwards Lifesciences, Irvine, California, USA) and CoreValve® (Medtronic, Inc., Minneapolis, Minnesota, USA) are the valves with the most clinical experience and published data to date (Figure 1).

More recently, the following valves also received CE approval: Edwards SAPIEN 3 (Edwards Lifesciences, Irvine, California, USA), JenaClip JenaValve™ (JenaValve Technology GmbH, Munich, Germany), Symetis Acurate™ (Symetis, Lausanne, Switzerland), Direct Flow Medical® Transcatheter Aortic Valve System (Direct Flow Medical, Santa Rosa, California, USA), Portico™ (St. Jude Medical, St. Paul, Minnesota, USA), Medtronic Engager™ (Medtronic, Minneapolis, Minnesota, USA), and Lotus™ Valve System (Boston Scientific, Boston Scientific, Natick, Minnesota, USA). These are the most recently approved transcatheter valve types (Figure 2).[12,13]

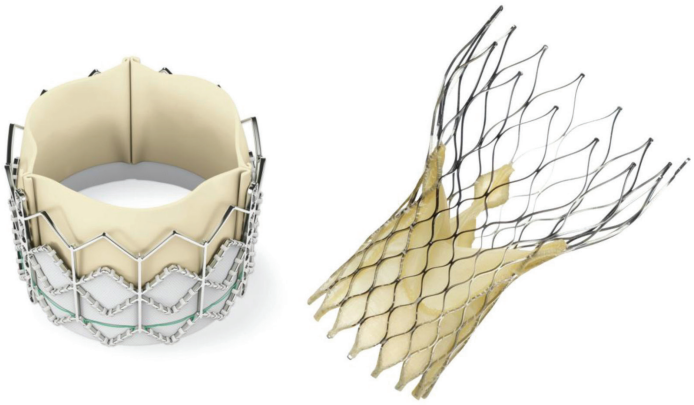

Figure 1: Left: Edwards-SAPIEN (Edwards Lifesciences, Irvine, California, USA), and right: CoreValve® (Medtronic, Inc., Minneapolis, Minnesota, USA); the valves with the most clinical experience and published data until now.

Edwards SAPIEN

The Edwards SAPIEN THV™ prosthesis is a balloon expandable valve, consisting of a cylindrical frame of a cobalt chromium alloy. In this stent, three valve cusps of bovine pericardial tissue are sealed. The lower part of the stent frame is covered with a skirt of polyethylene terephthalate. This bioprosthesis is available with a diameter of 23 mm or 26 mm. After nose cone modifications of the delivery system, Retroflex3™ is currently used. The diameter of the delivery system varies from 22 French (Fr) up to 24 Fr. The second generation of this valve, Edwards SAPIEN XT™ is available in 20 mm, 23 mm, 26 mm, and 29 mm, with resp. 16, 16, 18, and 20 Fr delivery sheaths (Novaflex™). Ascendra™ delivery system is used for transapical approach.

The Edwards SAPIEN 3 transcatheter heart valve comprises a balloon-expandable frame with bovine pericardial tissue valve.[14,15] The valve is covered by an outer polyethylene terephthalate cuff to enhance paravalvular sealing. The transfemoral delivery system (Commander, 14 Fr eSheath for the 23 mm and 26 mm valves, and 16 Fr eSheath for the 29 mm SAPIEN 3 valve) enables advancing or retracting the valve several millimetres up or down within the annulus. For transapical implantation, the Certitude is the new corresponding delivery system that also features a smaller nose cone.[16]

Figure 2: Most recent CE-approved transcatheter aortic valves.
A: JenaValve™ (JenaValve Technology GmbH, Munich, Germany); B: Symetis Acurate™ (Symetis, Lausanne, Switzerland); C: Direct Flow Medical® Transcatheter Aortic Valve System (Direct Flow Medical, Santa Rosa, California, USA); D: Portico™ (St. Jude Medical, St. Paul, Minnesota, USA); E: Medtronic Engager™ (Medtronic, Minneapolis, Minnesota, USA); F: SAPIEN 3 (Edwards Lifesciences, Irvine, California, USA); G: Lotus™ Valve System (Boston Scientific, Boston Scientific, Natick, Minnesota, USA).

Table 1: Results of the PARTNER trial (Edwards SAPIEN) and the ADVANCE registry (Medtronic CoreValve).

	TAVI (n)	30-day outcomes				Longer mortality
		Stroke	New PM	Grade AR ≥II	Mortality	
Edwards SAPIEN PARTNER Cohort A[18,19]	248	5.5%	3.8%		3.4%	1 year: 24.3%, 2 years: 33.9%
Cohort B[17,20]	178	6.7%	3.4%	12.5%	5.0%	1 year: 30.7%, 2 years: 43.3%
Medtronic CoreValve ADVANCE[21,22]	996	3.0%	26.4%	13.0%	4.5%	1 year: 17.9%
US Pivotal trial (Iliofemoral)[25]	471	2.4%	22.2%	11.5%	7.9%	1 year: 24.0%

PM: pacemaker; AR: aortic regurgitation.

The PARTNER (Placement of Aortic Transcatheter Valve) trial is a unique randomised trial, designed to evaluate TAVI compared to AVR in high-risk patients (cohort A, n=699), and TAVI compared to conservative treatment in inoperable patients (cohort B, n=358), with the Edwards SAPIEN prosthesis.[17,18] The results of PARTNER cohort A proved that TAVI is comparable to AVR for survival up to 3 years after valve implantation (50%, n.s.). Mortality within 30 days was lower than expected (TAVI: 3.4%, AVR: 6.5%, p=0.070).[19] In PARTNER cohort B, no difference was found for mortality within 30 days after the procedure for patients treated with TAVI or optimal medical treatment, but 2 years mortality after the interventions differed significantly (optimal medical treatment: 2 years mortality 68%, TAVI: 2 years mortality 43%, p<0.001).[20] Within 30 days after TAVI, both in cohort A and cohort B, the incidence of stroke or transient ischaemic attack (TIA) was resp. 5.5% and 6.7%, and the incidence of new pacemaker implantation was resp. 3.8% and 3.4% (Table 1). Moderate-to-severe aortic regurgitation (AR) was present in 12.5% after TAVI.

CoreValve revalving system

The CoreValve prosthesis is a self-expandable stent, with a supra-annular porcine pericardium valve. These leaflets form a sealing skirt on the stent frame to reduce paravalvular leakage. The stent is manufactured from nitinol, an alloy of titanium and nickel, which has a temperature-related shape memory. Initial sheaths were 25 Fr, but since 2010 the Accutrack™ delivery system (18 Fr) is available for transfemoral implantation of prostheses of size 26 mm, 29 mm, and 31 mm. Medtronic Evolut™

Table 2: Overview of current available data of various transcatheter aortic valves.

	N	30-day outcomes				Longer mortality
		Stroke	New PM	Grade AR ≥II	Mortality	
JenaValve™ Multicentre CE-mark study[26] JUPITER registry[27]	 66 101	3.0%	9.1%	 13.6% 2.3%	 7.6% 14.9%	
Symetis Acurate™ [28]	40	5.0%	7.5%	3.4%	12.5%	6 months: 17.5%
Direct Flow Medical® DISCOVER trial[29]	 33			 3.0%	 3.0%	
Portico™ valve first-in-men[30]	10	10.0%	0.0%	10.0%	0.0%	
Medtronic Engager™ European Pivotal trial[31]	 61	 3.5%	 27.6%	 0.0%	 9.9%	 6 months: 16.9%
SAPIEN 3[15]	26	0.0%		0.0%	3.8%	
Lotus™ Valve System REPRISE I trial[34] REPRISE II trial[35]	 11 60	 27% 8.6%	 36% 29.3%	 1.9%	 1.7%	

PM: pacemaker; AR: aortic regurgitation.

is available in 23 mm size, is 10 mm shorter in height, and is modified to fit better in the aortic root.

The ADVANCE Registry is the best monitored, prospective, multicentre study as regarding to the CoreValve prosthesis, with the inclusion of 1,015 patients in experienced TAVI sites.[21,22] It is important to mention that the clinical endpoints were all defined according to the 'Valve Academic Research Consortium' (VARC) and were all monitored by an independent event committee. The 30 day mortality was comparable to the 30 day mortality of the PARTNER trial (4.5%).[23,24] All-cause mortality at 1 year was 17.9%.[21] No differences were found in survival between men and women. Within 30 days after TAVI, the incidence rate of stroke or TIA was 3.0% and the incidence of new pacemaker implantation was 26.4% (Table 1). The need for permanent new pacemaker implantation, however, did not influence 1 year survival. Moderate-to-severe AR was present in 15% after TAVI. The CoreValve US Pivotal trial has two cohorts: the first is a randomised controlled study in high-risk patients (CoreValve versus AVR), and the second is a non-randomised study in extreme-risk patients that can be treated with TAVI by iliofemoral access.[25] In the latter (n=471), a significant reduction in all-cause mortality and in major stroke compared to the objective performance goal (estimated mortality risk and stroke risk with medical therapy only) was achieved by transfemoral TAVI.

Other percutaneaous aortic valves

The JenaValve™ is a self-expandable nickel-titanium alloy frame with porcine valve. The valve is fixed on the native aortic valve leaflets and there is no high radial force needed to anchor in the aortic root. This valve is specifically designed for transapical approach. The results of the multicentre prospective CE-mark study were promising.[26] The JUPITER Registry, which will provide long-term outcomes of the JenaValve™, is still ongoing.[27]

The Symetis Acurate™ is also a self-expandable nickel-titanium alloy frame with porcine valve.[28] The conical form during the implantation centres the valve in the correct place. The upper part of the cone anchors itself, and the skirt seals the valve in the native annulus to minimise paravalvular leakage.

The Direct Flow Medical® consists of bovine pericardium to form leaflets and has a plastic polymer frame.[29] The Portico™ resembles the Medtronic CoreValve, but has more open cells. In order to prevent suboptimal positioning of the prosthesis, this transcatheter valve is fully re-sheathable and repositionable, until fully deployed.[30] Bovine pericardium leaflets are used in the design

of the Medtronic Engager™ for transapical TAVI.[31] The Multicentre European Engager Pivotal trial is still ongoing.[32] A central marker in the nitinol frame (including bovine pericardium) of the Lotus Valve helps positioning of the valve.[33-35] A novel Adaptive Seal™ technology leads to minimised AR, and the device can be fully retrieved, redeployed, or repositioned, even after full valve deployment and prior to release. An overview of the current available data of these newer transcatheter aortic valves is given in Table 2.

Patient Selection

Due to the complex condition of high-risk patients, the final clinical decision for an individual patient to be suitable for undergoing AVR/TAVI/medical treatment relies on a multidisciplinary heart team discussion, with (interventional) cardiologists, cardiac surgeons, and other involved specialists.

Anatomical factors

There are several necessary anatomic evaluations specific to TAVI.[36] Non-invasive evaluation of the dimensions of the aortic annulus, such as transoesophageal echocardiography, magnetic resonance imaging, and multidetector computed tomography (MDCT, Figure 3), must be carried out in order to select the optimal size of the valve.[36] Arterial access is generally assessed with angiography or contrast MDCT. Most arteries are compliant and can accommodate slightly larger sheaths, but this is not always the case in diffusely diseased, tortuous, or calcified arteries. The aorta should be evaluated with angiography or contrast MDCT to assess delivery and implantation of the specific valve type, aortic root, and calcification, together with the risk of coronary obstruction.

Clinical factors

Not only is technical and anatomical evaluation necessary in the discussion of whether TAVI has to be performed, but also the likelihood of functional and survival benefit. Patients in whom a significant improvement in quality and duration of life is likely have to be distinguished from those in whom the intervention will not be beneficial due to advanced age and comorbidities.

Surgical risk scores (e.g. EuroSCORE, Society of Thoracic Surgeons mortality score) could be helpful in patient selection; however, they do not take TAVI-related risk factors into account, are in general not accurate enough to predict prognosis after TAVI, and are not based on elderly patients (75 years and older).[37] Geriatric syndromes (falling, dementia, malnutrition), together with frailty, which are frequently seen in elderly patients and remain an important preoperative risk factor, are not included in these surgical risk scores, although frailty is significantly related to functional decline and prognosis.[38,39] Therefore, multidimensional geriatric evaluation of these patients may be useful in predicting outcome and optimal patient selection.[36]

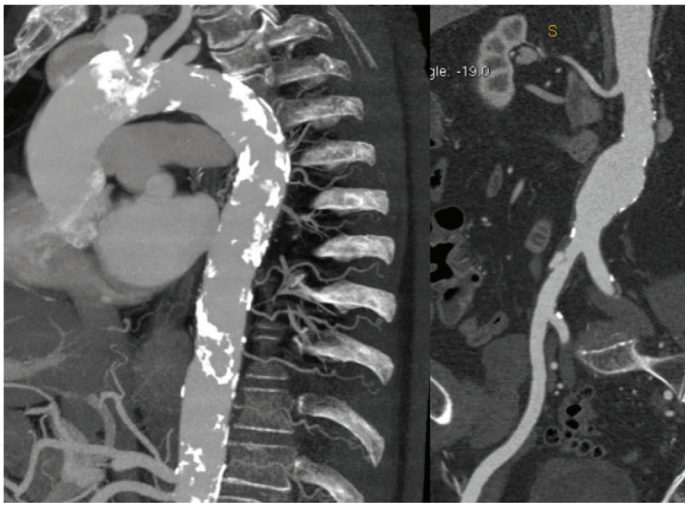

Figure 3: Evaluation of aorta and calcifications and tortuosity of peripheral arteries by computed tomography.

Procedure

In general, TAVI is performed under general anaesthesia or sedation.[39] Femoral access remains, until now, the preferred and most frequently used approach. The native valve can be predilated by balloon valvuloplasty during rapid ventricular pacing. The transcatheter valve is deployed by angiographic or echographic guidance (Figure 4). Successful implantation of the valve will immediately decrease the pressure gradient over the aortic valve. Guidewires and catheters are withdrawn, and the femoral artery is sealed surgically or by use of a specific closure device.

The femoral artery has been the most popular access site. Although originally requiring a surgical cut-down, most experienced groups now utilise a percutaneous puncture and suture pre-closure technique, avoiding the need for open surgical access. Current consensus, with some exceptions, strongly favours transfemoral arterial access as the preferred, default approach for TAVI.[36]

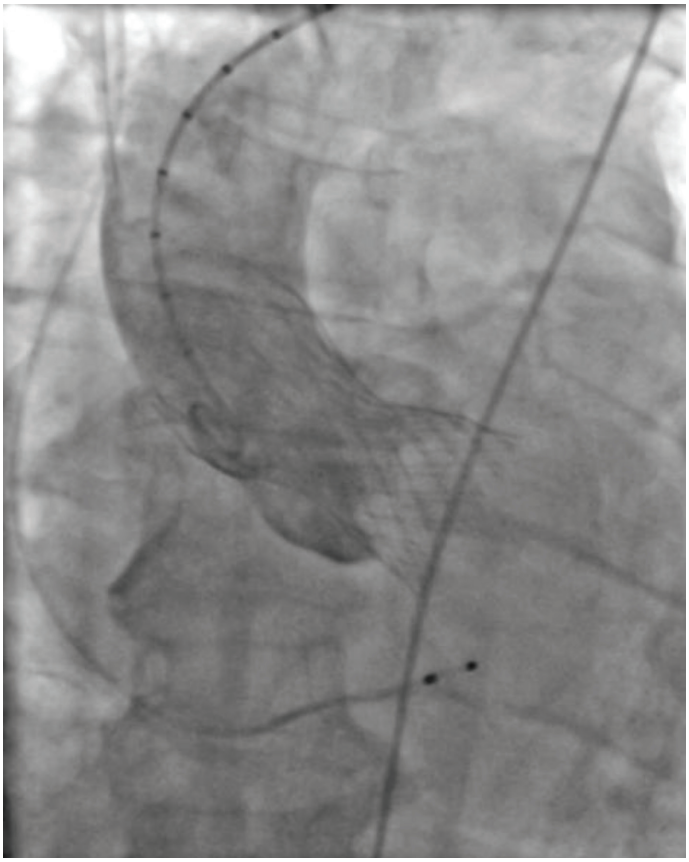

Figure 4: Implantation of CoreValve™, guided by aortography.

However, many patients have small or diseased femoral arteries. On occasion, surgical retroperitoneal approach is utilised to gain access to the larger iliac artery in patients with femoral disease. Subclavian (transaxillary) access has gained popularity as an alternative access. Importantly, the subclavian route can damage the left internal mammary artery, which is important to patients with previous coronary artery bypass graft.

Antegrade implantation of the aortic transcatheter valve has several advantages, due to transapical approach, with direct access to the left ventricle through an intercostals thoracotomy: a low risk of vascular complications, a direct pathway to the aortic valve, and easier crossing of the diseased aortic valve. Nevertheless, direct myocardial/mitral injury, bleeding, haemodynamic instability, and postoperative respiratory and thoracotomy pain, remain points of concern. The transapical procedure is generally associated with the Edwards SAPIEN valve and newer valves (JenaClip JenaValve™, Medtronic Engager™, Portico™, Symetis Acurate™).

Complications

Acute periprocedural and late complications may occur. Left ventricular rupture, tamponade, and coronary obstruction can be fatal complications during the TAVI procedure, but are fortunately rare. Stroke, vascular (access-related) complications, AR, and conduction abnormalities are more frequently occurring adverse events; their specific definitions are recently described in the Valve Academic Consortium-2 Consensus Document.[24]

Stroke or TIA

The definition of stroke according to VARC is 'an acute episode of focal or global neurological dysfunction caused by the brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction.'[24] Another type of ischaemic event is TIA, which is a transient type of dysfunction, without acute infarction.

Procedural stroke (acute, <24 hours) has an incidence of 1.5% after TAVI. During the first month after TAVI (subacute), stroke and TIA have an incidence of resp. 3-6.7% and 0.9%, and resp. 10% and 2.3% 1 year after TAVI (late).[19-21,40,41] If stroke occurs, this has a negative impact on the prognosis and the quality of life of patients who underwent TAVI.[41]

The aetiology of neurological events during or after TAVI is clearly multifactorial. Embolic causes of these cerebrovascular events are, however, often assumed, with material of the native aortic root dislodged by introduction and control of the guidewire, balloon valvuloplasty, manipulation of the delivery system, and by the deployment of the transcatheter valve. Embolic protection devices are developed to avoid stroke.[42,43] Deflection shields are used to cover supra-aortic arteries, and intraluminal filters can retrieve embolic debris in the carotid arteries. These devices are, however, also introduced by catheterisation, which can, in turn, increase embolisation of calcified material. Available data supporting their evidence are limited.

Thrombin or platelet deposition before endothelialisation of the prosthesis can occur after TAVI and might be a risk for embolisation. Duration and type of antithrombotic therapy after TAVI is not clearly defined. Also post-procedural (new or continued) atrial fibrillation is a proven risk factor for post-procedural stroke or TIA and was related to anticoagulant therapy. Nuis et al.[44] reported five patients developing new onset atrial

fibrillation without anticoagulant therapy, suffering strokes. Amat-Santos[45] reported a stroke incidence of 40% (no anticoagulants) compared to 2.9% in those who did receive anticoagulant therapy. Therefore, sustained anticoagulant therapy, mostly consisting of clopidogrel/aspirin during 3-6 months after TAVI, is recommended. In case of atrial fibrillation, coumarin is combined with aspirin or clopidogrel.

Vascular complications

Vascular access-related complications occur most following transfemoral approach, leading to potentially serious arterial bleeding and increased patient mortality. The rate of vascular complications varies from 9.5-51.6% of TAVI patients.[46] Early vascular complications are related to increased late mortality after TAVI, due to haemodynamic instability, increased transfusion need, and longer hospitalisation.[47] Therefore, evaluation of iliofemoral vasculature on tortuosity, calcifications, and diameters is important to determine if femoral approach is safely feasible.

An important risk factor of the development of vascular complications is the sheath size. The development of smaller sheaths (from 22 Fr to 18 Fr), and smaller delivery systems, is important to decrease the incidence of major vascular complications. Also, improved design of closure devices for sealing the access site puncture is important.

AR

Moderate-to-severe AR (Grade ≥2/4) occurs in around 15-20% of the TAVI patients and, as described in several papers, has a significant negative impact on survival.[48,49] During TAVI, the native valve is crushed between the aortic wall and the prosthesis. This debris of calcifications can prevent appropriate sealing of the prosthesis in the aortic root, which increases the risk of paravalvular AR. Also, malpositioning of the valve (too high, too low under the native annulus) and incorrect sizing of the prosthesis (annulus – prosthesis mismatch) cause AR after TAVI.[48-51]

Quantification of AR after TAVI can be done by angiography, by echocardiographic evaluation, and by invasive haemodynamics. Angiographic evaluation is based on grading the amount of contrast regurgitating into the left ventricle, which relates to the severity of the leakage (Grade I to IV).[52] This technique is very easy to use but remains a subjective evaluation depending on the observer, the amount of contrast used, and overlapping structures. Non-invasive transthoracic echocardiographic evaluation of AR in non-TAVI patients is typically done by integrating colour flow, vena contracta, and pressure half-time, together with signs of haemodynamic impact of AR (LV size, LV function, LV pressures).[24] However, in TAVI patients, assessment of AR by echocardiography usually appears to be much more difficult because of the echo reflections of the stent and the frequent presence of multiple (excentric) jets (valvular, paravalvular, multiple locations).[51]

Haemodynamic evaluation of AR post TAVI is suggested by AR index, defined as '(diastolic blood pressure – left ventricular end diastolic pressure)/ systolic blood pressure x 100'.[53,54] This objective parameter is available during the TAVI procedure but it is based on invasive pressures, which can be influenced by age and procedural factors. Validation of this method is necessary. Which of these techniques is preferred for AR quantification after TAVI remains a matter of debate.

Reduction of the grade of AR might be done by post-balloon dilatation (increasing the expansion of the valve), snaring of the valve (adaptation of the implantation depth), or implantation of a second valve (valve-in-valve).

Conduction disturbances

Left bundle branch block (LBBB) and atrioventricular block (AVB), with the need for permanent pacemaker implantation, are the most important and the most frequently observed new conduction disturbances after TAVI. The occurrence of conduction disturbances depends on valve design and valve position. LBBB is reported in 29-65% of the patients implanted with Medtronic CoreValve®, in contrast to 4-18% of the patients treated with Edwards SAPIEN.[55] The assumed cause of this difference relies on the difference in design of the valves: Edwards SAPIEN includes only the native aortic valve, in contrast to CoreValve, which overlaps left ventricular outflow tract (LVOT) and the aortic sinuses. The overlap of LVOT could potentially cause damage to the underlying conduction tissue of the heart. Inconsistent data have been published on whether LBBB after TAVI increases the risk of mortality.[55-58] Most conduction abnormalities occur during balloon aortic valvuloplasty before the effective

TAVI (46%), 25% with the crossing of the aortic valve with guidewires and delivery systems, and the other 29% during expansion of the prosthesis.[59] In line with LBBB, high degree AVB after TAVI is more frequent after CoreValve implantation (14-44%, Edwards SAPIEN: 0-12%). This leads to more pacemaker implantation in patients with CoreValve implanted (18-49%), in contrast to Edwards SAPIEN treated patients (0-12%).

Deep implantation of the prosthesis under the native annulus and pre-existing right bundle branch block are risk factors to total AVB, and therefore, to the need for permanent pacemaker implantation.[60]

In the Future

The most challenging aspect of TAVI for high or very high-risk patients is optimal patient selection. Geriatric aspects have an influence on patient outcome and can be useful in determining whether or not a patient is capable of undergoing AVR or TAVI.[39,61] Therefore, a specific TAVI-score to evaluate this, taking into account a frailty index, imposes itself.[62]

With the scope to reduce complications - such as paravalvular leakage and conduction disturbances - other transcatheter valves, guidewires, and delivery systems are designed with the ability of the valve being retrievable to allow optimal deployment. Bourantas et al.[43] made an overview of these second -generation transcatheter valves.

The experience of TAVI in high-risk patients is helpful in expanding the use of TAVI to treatment for medium-risk patients suffering from aortic valve stenosis (PARTNER II, SURTAVI), or patients with biscuspid aortic valve.[63] Also, TAVI may be used in patients with a degenerative bioprosthesis or in patients suffering from AR.[64,65] The TAVI-experience is also useful in expanding transcatheter approaches to pulmonary and mitral valve interventions.[66]

CONCLUSION

TAVI is an outstanding, relatively new treatment for high-risk patients with severe, symptomatic aortic valve stenosis. Although there were excellent results from the PARTNER and the ADVANCE studies, important complications including stroke, vascular complications, paravalvular AR, and conduction disturbances may occur after TAVI, and so need to be considered. The development of adapted transcatheter valves and devices will reduce these complications.

REFERENCES

1. Osnabrugge RLJ et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013;62(11):1002-12.

2. Ross J Jr, Braunwald E. Aortic stenosis. Circulation. 1968;38(1 Suppl):61-7.

3. Varadarajan P et al. Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: results from a cohort of 277 patients aged > or =80 years. Eur J Cardiothorac Surg. 2006;30(5):722-7.

4. Iung B et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J. 2005;26(24):2714-20.

5. Vahanian A et al. Guidelines on the management of valvular heart disease (version 2012): the joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2012;33(19):2451-96.

6. Cribier A et al. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: an alternative to valve replacement? Lancet. 1986;327(8472):63-7.

7. Cribier A et al. Percutaneous transluminal balloon valvuloplasty of adult aortic stenosis: report of 92 cases. J Am Coll Cardiol. 1987;9(2):381-6.

8. Safian RD et al. Balloon aortic valvuloplasty in 170 consecutive patients. N Engl J Med. 1988;319(3):125-30.

9. Sigwart U et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med. 1987;316(12):701-6.

10. Andersen HR et al. Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs. Eur Heart J. 1992;13(5):704-8.

11. Cribier A et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation. 2002;106(24):3006-8.

12. Clayton B et al. Transcatheter aortic valve insertion (TAVI): a review. B J Radiol. 2014;87(1033):20130595.

13. Bourantas CV et al. Transcatheter aortic valve update 2013. EuroIntervention. 2013;9 Suppl:S84-90.

14. Binder RK et al. Transcatheter aortic valve replacement with the SAPIEN 3: a new balloon-expandable transcatheter heart valve. JACC Cardiovasc Interv. 2013;6(3):293-300.

15. Dvir D et al. Preliminary clinical experience using the SAPIEN 3 device. JACC. 2013;62(18S1):B239.

16. Ribeiro H et al. Transapical implantation of the SAPIEN 3 valve. J Card Surg. 2013;28(5):506–9.

17. Leon MB et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363(17):1597-607.

18. Smith CR et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-98.

19. Kodali SK et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012;366(18):1686-95.

20. Makkar RR et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med. 2012;366(18):1696-704.

21. Linke A et al. One year outcomes in real world patients treated with tavi: the advance study. EuroIntervention. 2013;EuroPCR Abstracts 2013.

22. Bosmans J et al. TCT-814 health related quality of life following transcatheter aortic valve implantation: results from the CoreValve advance study. J Am Coll Cardiol. 2012;60(17 Suppl):doi: 10.1016/j.jacc.2012.08.860. [Epub ahead of print].

23. Leon MB et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the valve academic research consortium. J Am Coll Cardiol. 2011;57(3):253-69.

24. Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60(15):1438-54.

25. Popma JJ. CoreValve US Pivotal trial extreme risk iliofemoral study results. Presented at TCT, 2013,San Francisco, USA.

26. Treede H et al. Transapical transcatheter aortic valve implantation using the JenaValve™ system: acute and 30-day results of the multicentre CE-mark study. Eur J Cardiothorac Surg. 2012;41(6):e131-e8.

27. Ensminger S et al. TCT-736 interim results of the jupiter registry on long-term performance and safety of the transapical JenaValve. J Am Coll Cardiol. 2013;62(18S1):B224.

28. Kempfert J et al. Transapical aortic valve implantation using a new self-expandable bioprosthesis (ACURATE TA™): 6-month outcomes. Eur J Cardiothorac Surg. 2013;43(1):52-6.

29. Schofer J et al. 30-day outcome of the 18 F-direct flow medical valve in patients with severe aortic stenosis - results from the DISCOVER trial. Eur Heart J. 2013;34(Suppl 1): doi:10.1093/eurheartj/eht310.P5428. [Epub ahead of print].

30. Willson AB et al. Transcatheter aortic valve replacement with the St. Jude Medical Portico valve: first-in-human experience. J Am Coll Cardiol. 2012;60(7):581-6.

31. Sündermann SH et al. Feasibility of the Engager™ aortic transcatheter valve system using a flexible over-the-wire design. Eur J Cardiothorac Surg. 2012;42(4):e48-e52.

32. Holzhey D et al. Intermediate follow-up results from the multicenter engager European pivotal trial. Ann Thorac Surg. 2013;96(6):2095-100.

33. Meredith IT et al. Boston Scientific Lotus valve. EuroIntervention. 2012;8 Suppl Q:Q70-4.

34. Meredith IT et al. The repositionable Lotus Aortix Valve Replacement System: six-month outcomes in the REPRISE I Feasibility study. JACC. 2013;61(10S):doi:10.1016/S0735-1097(13)61868-9.

35. Meredith I et al. Thirty day outcome for the first 60 patients in the REPRISE II study. Presented at EuroPCR; 2013.

36. Webb JG, Wood DA. Current status of transcatheter aortic valve replacement. J Am Coll Cardiol. 2012;60:483-92.

37. D'Ascenzo F et al. Inaccuracy of available surgical risk scores to predict outcomes after transcatheter aortic valve replacement. J Cardiovasc Med (Hagerstown). 2013;14(12):894-8.

38. O'Sullivan C et al. Preinterventional screening of the TAVI patient: how to choose the suitable patient and the best procedure. Clin Res Cardiol. 2014. [Epub ahead of print].

39. Schoenenberger AW et al. Predictors of functional decline in elderly patients undergoing transcatheter aortic valve implantation (TAVI). Eur Heart J. 2013;34(9):684-92.

40. Holmes DR Jr et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol. 2012;59(13):1200-54.

41. Eggebrecht H et al. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. EuroIntervention. 2012;8(1):129-38.

42. Ghanem A et al. Novel approaches for prevention of stroke related to transcatheter aortic valve implantation. Expert Rev Cardiovasc Ther. 2013;11(10):1311-20.

43. Bourantas CV et al. Future perspectives in transcatheter aortic valve implantation. Int J Cardiol. 2013;168(1):11-8.

44. Nuis RJ et al. Frequency and causes of stroke during or after transcatheter aortic valve implantation. Am J Cardiol. 2012;109(11):1637–43.

45. Amat-Santos IJ et al. Incidence, predictive factors and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. J Am Coll Cardiol. 2012;59(2):178–88.

46. Généreux P et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol. 2012;59(25):2317-26.

47. Czerwińska-Jelonkiewicz K et al. Vascular complications after transcatheter aortic valve implantation (TAVI): risk and long-term results. J Thromb Thrombolysis. 2013;doi:10.1007/s11239-013-0996-7. [Epub ahead of print].

48. Généreux P et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. J Am Coll Cardiol. 2013;61(11):1125-36.

49. Athappan G et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol. 2013;61(15):1585-95.

50. Stähli BE et al. Aortic regurgitation after transcatheter aortic valve implantation: mechanisms and implications. Cardiovasc Diagn Ther. 2013;3(1):15-22.

51. Fassa AA et al. Mechanisms and management of TAVR-related complications. Nat Rev Cardiol. 2013;10(12):685-95.

52. Bekeredjian R, Grayburn PA. Valvular heart disease: aortic regurgitation. Circulation. 2005;112(1):125-34.

53. Sinning JM et al. Prospective evaluation of the aortic regurgitation index in TAVI patients. Eur Heart J. 2013;34(Suppl 1):doi:10.1093/eurheartj/eht310.P5398.

54. Sinning JM et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol. 2012;59(13):1134-41.

55. van der Boon RM et al. Clinical implications of conduction abnormalities and arrhythmias after transcatheter aortic valve implantation. Curr Cardiol Rep. 2014;16(1):429.

56. Testa L et al. Clinical impact of persistent left bundle-branch block after transcatheter aortic valve implantation with CoreValve revalving system. Circulation. 2013;127(12):1300-7.

57. Urena M et al. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol. 2012;60(18):1743-52.

58. Houthuizen P et al. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. Circulation. 2012;126(6):720-8.

59. Nuis RJ et al. Timing and potential mechanisms of new conduction abnormalities during the implantation of the Medtronic CoreValve System in patients with aortic stenosis. Eur Heart J. 2011;32(16):2067-74.

60. Koos R et al. Electrocardiographic and imaging predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. J

Heart Valve Dis. 2011;20(1):83-90.

61. Cribier A. Development of transcatheter aortic valve implantation (TAVI): a heart-warming adventure. European Geriatric Medicine. 2013;4(6):401-6.

62. Grube E et al. The year in cardiology 2013: valvular heart disease (focus on catheter-based interventions). Eur Heart J. 2014;doi:10.1093/eurheartj/eht558. [Epub ahead of print].

63. Lim GB. Valvular disease: TAVI safe and effective for patients with a bicuspid aortic valve. Nat Rev Cardiol. 2013;10(8):432.

64. Mylotte D et al. Transcatheter heart valve implantation for failing surgical bioprostheses: technical considerations and evidence for valve-in-valve procedures. Heart. 2013;99(13):960-7.

65. Roy DA et al. Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. J Am Coll Cardiol. 2013;61(15):1577-84.

66. Fishbein GA et al. Transcatheter aortic valve implantation: status and challenges. Cardiovasc Pathol. 2013;doi:10.1016/j.carpath.2013.10.001. [Epub ahead of print].

CORONARY BIFURCATION DISEASE AND BIFURCATION STENTING: A PRACTICAL APPROACH

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ABSTRACT

Approximately 20% of percutaneous coronary interventions (PCIs) are performed to treat coronary bifurcations. PCIs in bifurcation lesions have been associated with lower procedural success rates and worse clinical outcomes than non-bifurcation lesions. In addition, PCIs in bifurcation are renowned for being technically demanding. Indeed, there are several challenges in percutaneous treatment of bifurcation lesions to take into account, including: 1) localisation, size, and angle of bifurcation branches in coronary tree (e.g. left main versus others); 2) disease extension at bifurcation (true versus pseudo-bifurcation lesions); 3) stenting technique; and finally 4) choice of the most appropriate device. Several studies have been published in each of these settings, but therapeutic strategies are still linked mostly to clinical setting and operator experience. In this review, we have summarised the most important aspects and clinical studies on bifurcation lesion treatment with the aim to give the readers a practical approach to bifurcation PCI.

Keywords: Atherosclerotic disease, percutaneous coronary intervention, bifurcation disease.

BIFURCATION DEFINITION AND CLASSIFICATION

The first step in approaching a bifurcation lesion is its identification and definition. The European Bifurcation Club (EBC)[1] has proposed the following practical definition: "A coronary artery narrowing occurring adjacent to, and/or involving the origin of a significant side branch (SB)." Practically speaking, a significant SB is a branch that you do not want to lose during revascularisation. Although there are currently at least six different classifications of bifurcation lesions (where in all of them, a combination of letters and/or digits describes the angiographic position of the lesions in the bifurcation, Figure 1), which require significant efforts for memorisation; the most user-friendly and easy-to-remember is the Medina classification.[2] Such classification consists of recording any narrowing in excess of 50% in each of the three arterial segments of the bifurcation in the following order: proximal main vessel, distal main vessel, and proximal SB. Such classification is the most standardised and utilised nowadays to indicate the presence of a significant stenosis (1) or the absence of stenosis (0). A true bifurcation presenting a significant disease of both main branches (MB) and SB will then be indicated as 1.1.1; 0.1.1; or 1.1.0 Medina class. The main limitation of this classification is the absence of any information on lesion length, especially for the SB, and angiographic features (e.g. presence of calcifications, bifurcation angle). Indeed, the severity of SB and the angle between the two branches have been shown to significantly impact on treatment technique choice and actually on long-term clinical outcome.[3] However, apart from the fact that the presence of quantifiable variables would be recorded under "yes" or "no", the addition of these simple angiographic parameters and possibly others (e.g. eccentric location of the MB lesion, TIMI flow) would negate the simplicity of the Medina classification.

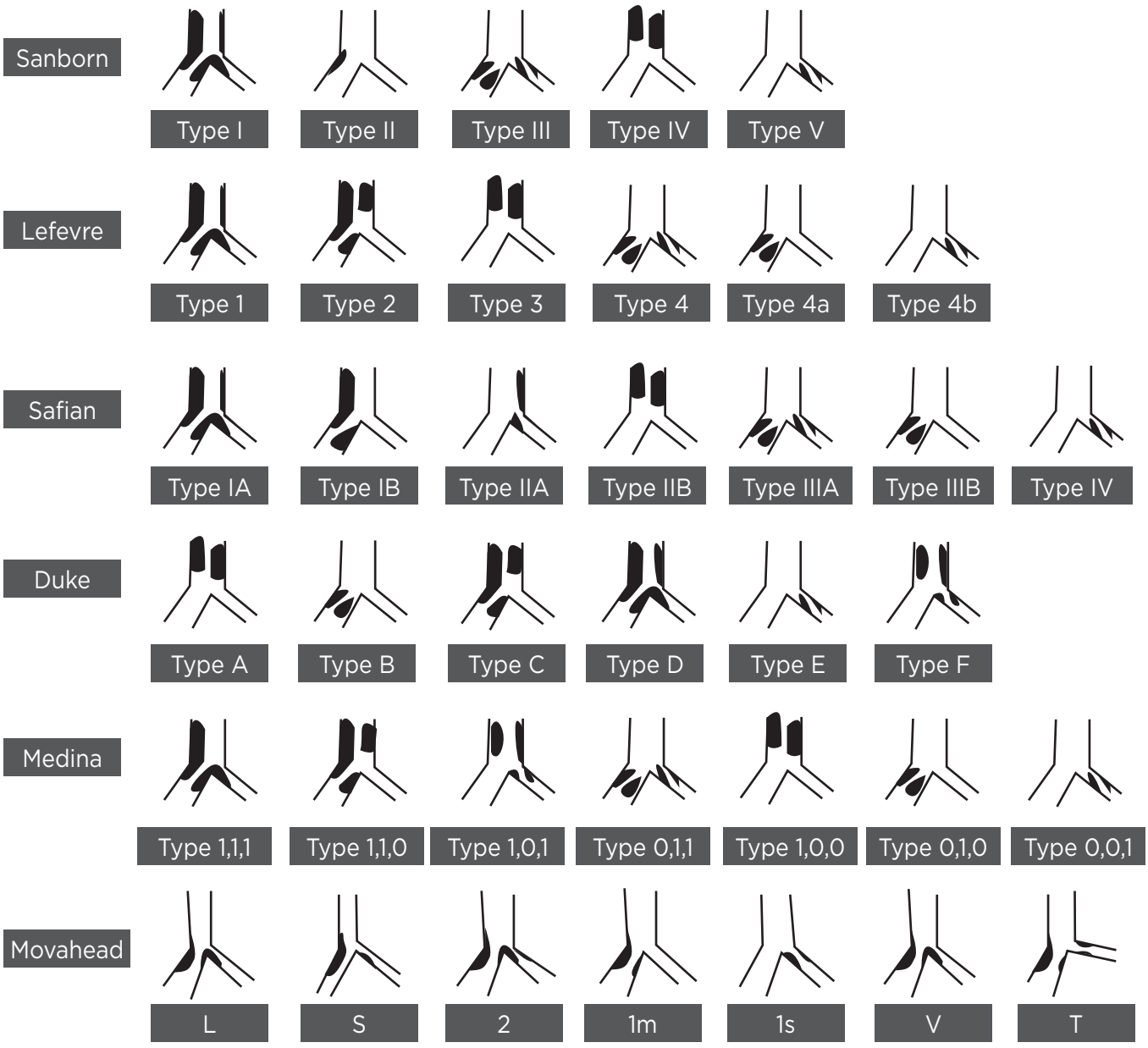

Figure 1: Published classification of coronary bifurcation lesions.

After bifurcation classification, it is very important to consider its localisation in the coronary tree. In this setting, we think that left main coronary artery (LMCA) disease with involvement of distal bifurcation is a different entity than other bifurcation lesion location and should then be approached differently as outlined below in this review.

As stated above, bifurcation lesions could be divided into true bifurcation (Medina 1.1.1; 1.0.1; 0.1.1) where MB and SB are both significantly narrowed (>50% diameter stenosis), and non-true bifurcations, which include all the other lesions involving a bifurcation. This distinction is likely the most important for the choice of the technical approach; indeed, non-true bifurcation should always be treated with a one-stent strategy. On the other hand, in true bifurcation lesion we must consider some anatomical characteristics of the SB such as the length of disease (i.e. localised only to the ostium or extending beyond it), its size (i.e. <2.5 mm), angle (i.e. <70°), and plaque distribution at the level of the carina.

In this setting, a new comprehensive classification of bifurcation lesions that is simple, practical, and inclusive of other important features of coronary bifurcation lesions has been recently published. This classification is based on a system composed of a single prefix (B, for bifurcation lesion) to which up to three main suffixes are added, describing important anatomical features of the lesion:[4]

the proximal segment size (suffix S, for small), atherosclerotic disease burden (one or two-branch disease), and the bifurcation angle (V or T angle). It is known that if the proximal segment is too small (small is defined as less than two-thirds of the sum of the diameters of both branch vessels) the kissing stenting technique cannot be utilised. The second suffix describes the involvement of the disease area of the bifurcation branches, namely, if both ostia at the bifurcation site are involved, the number '2' is used; if the MB only is involved, '1m' is used; and if the SB only is involved, '1s' is used. Thus, a B2 lesion in this classification is a true bifurcation. The bifurcation angle is another important feature of bifurcation lesions. Steep angulations have been found to be associated with higher risk of abrupt vessel closure,[5] SB occlusion,[6] and major adverse cardiac events.[3] In this classification, the third suffix describes the angulation of bifurcation branches: suffix V applies to angles of <70°, and the suffix T applies to angles of >70°. Thus, a B2V lesion is a true bifurcation with an angle <70° between MB and SBs.

A comparison of known classifications, with a detailed algorithmic approach to coronary bifurcation interventions was recently published[7] as a guide to interventional cardiologists for technical decision-making based on lesion characteristics.

TECHNICAL STRATEGY

Techniques used for treatment of coronary bifurcation lesions must be accurately defined for at least two reasons. First, it is important to compare various techniques with an intention-to-treat (ITT) analysis with respect to success rate, procedure duration, X-ray exposure, volume of contrast media used, and long-term follow-up. Second, impact of elaborate techniques on the outcome can be major.[8] The EBC has strived to include all potential technical strategies by describing four ways of beginning the procedure.[9] This classification can be summarised with the acronym 'MADS' (Figure 2). Each letter of the acronym represents the initial step of first stent placement: M (Main) stent implantation in the proximal main vessel; A (Across) stent implantation across the SB; D (Distal) stent implantation at the ostium or both distal branches; and S (Side) where the SB is stented first with or without protrusion. Each of these families contains several possible techniques with one or two-stent implantation. For example, M as the initial step may be followed by the opening of the stent towards both branches (SKIRT technique),[10,11] with subsequent successive or simultaneous stent placement in one or both distal branches. The second family (A) may be the first and the last step of the procedure but may also be followed by the opening of a stent cell with or without kissing balloon (KB) inflation towards the SB,[12] and, if necessary, by the delivery of a second stent in the SB in a T,[13] or Internal Crush, configuration.[14,15] The third family (D) can start creating a new carina by stent implantation in the proximal segments (simultaneous kissing stent [SKS]).[16,17] A technique of V-stenting configuration can also be achieved by successive delivery of the stents. Thus, each technical approach in bifurcation lesion considers the possibility of one or two-stent utilisation.

This strategic choice is of paramount importance in the treatment of bifurcation lesions. We are aware that for most operators the effectiveness of drug-eluting stents (DES) in reducing restenosis and revascularisation in complex lesions, such as bifurcations, can encourage the utilisation of two stents. However, regardless of technical approach, DES have become the preferred stent platform for treatment of coronary bifurcation. Indeed, many studies showed that DES implantation in bifurcation lesion can increase the risk of stent thrombosis (ST), but this is not clearly linked to two-stent techniques.[9,18,19] There are no solid data to support the supposition that two stents are more thrombogenic than one, that is, provided that correct stent placement has been performed and compliance with antiplatelet therapy is maintained. On the other hand, in the setting of acute myocardial infarction, a two-stent technique has been associated with an increased risk of ST.[20]

Although there is no convincing evidence that discourages using a DES platform and a two-DES strategy in bifurcation lesions, we still feel that a simple technique – if feasible – should always be the preferred one, even in the case of complex lesion subset. In this setting, the recent 5-year follow-up results of the Nordic study[21] demonstrated that the clinical outcomes after simple provisional SB stenting remained at least equal to the more complex strategy of planned stenting of both main vessel and SB. However, it is important to note that the Nordic trial is a small trial, considerably underpowered given the low major adverse cardiac events (MACE) rate found. A properly powered study should include approximately 20,000 patients but an inclusion of this order of

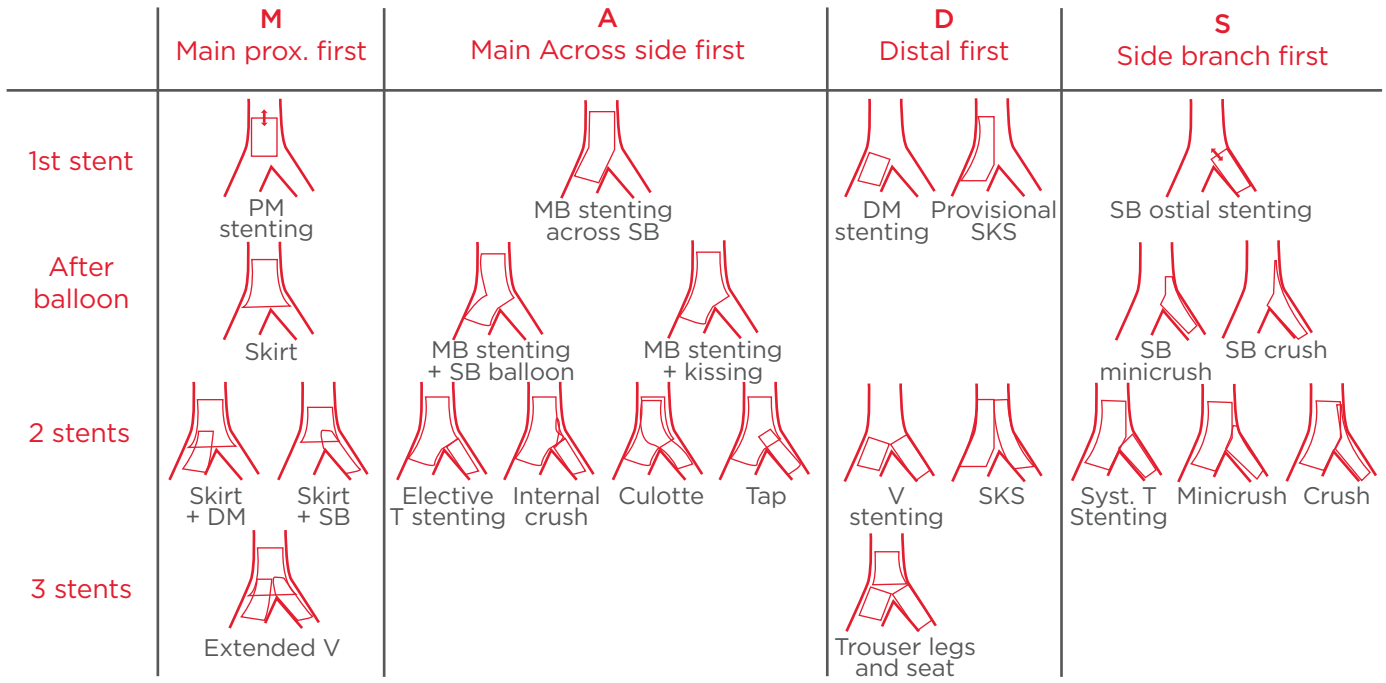

Figure 2: MADS classification of different bifurcation treatment techniques.

magnitude would not be feasible in the complex lesion subset of a bifurcation study. Furthermore, ischaemia testing was not performed in the trial, and there were no objective data to compare relief of ischaemia; however, MACE was adjudicated by a blinded events committee and should not have been influenced by the open design of the study. Finally, the study included only first-generation DES and this is another major limitation that must be kept in mind[21] (Table 1).

Several other studies[17,20,22-27] demonstrated that routine stenting of both branches offers no clear advantage over a provisional strategy of stenting MB only with balloon angioplasty of the SB. However it is also important to consider that, if it is true that there are bifurcations requiring one stent as a default treatment and a second stent when the result is suboptimal, then there are also bifurcation lesions in which two stents need to be implanted as an ITT from the beginning (indeed, approximately 30% of true bifurcation lesions require two stents and this percentage is about 50% for LMCA). Again, the distinction of these strategies is linked to SB relevance, extension of disease, and territory distribution of the involved vessels. The preliminary assessment by the operator of clinical relevance of SB disease for the patient's symptoms and disease burden in SB (ostial versus disease extending from 10 to 20 mm or more distally) is fundamental to perform a tailored approach for each bifurcation. Practically, in bifurcation lesions the objective is to conclude the procedure with both branches open ('keep it open' strategy), associated with an optimal stenting result in the MB.

Furthermore, an optimal angiographic result with minimal residual stenosis in SB may not be physiologically important if the operator utilises fractional flow reserve (FFR) examination[28] to assess the final result. Thus, we believe that each bifurcation is different and no single strategy can be applied to every situation.

In practice, two wires should be placed in most bifurcations for protecting SB from closure as a result of plaque shift or stent struts during MB stenting. Moreover, the SB wire facilitates rewiring. In the French multicentre TULIPE study,[29] the absence of this jailed wire was associated with a greater rate of re-interventions during follow-up. Two stents as ITT should be the technique used when the disease in the SB extends beyond the ostium and when the SB diameter and territory of distribution are relatively large. In all other conditions, SB provisional stenting should be the procedure of choice.

If SB is either very small for stenting or functionally irrelevant, we feel that the best strategy, after

Table 1: Published randomised controlled trials in bifurcation disease.

Study	No. Patients	Two-Stent strategy	Type of DES	Thienopyridine duration, mo	Intention to treat	Angio follow-up (months)	Clinical follow-up (months)
Pan et al.	91	Any	SES	12	Yes	6	11
Colombo et al.	85	Any	SES	3	No	6	6
NORDIC	413	Any	SES	6-12	Yes	8	6
Ferenc et al.	202	T-stenting	SES	6-12	Yes	9	12, 24
BBC ONE	500	Crush or Culotte	DES	9	Yes	-	9
CACTUS	350	Crush	SES	6	Yes	6	6, 12
DK-CRUSH2	370	DK-Crush	DES	12	Yes	8	6, 12

Adapted from Louvard et al.[53]

stenting MB, is to avoid rewiring or post-dilating SB. Conversely, when SB is suitable for treatment but disease is localised only to the ostium, the preferred strategy is the provisional technique: after stenting MB, the operator should rewire SB, remove the jailed wire, and perform final kissing inflation (FKI). If the result remains unsatisfactory (suboptimal result, plaque shift with >75% residual stenosis or TIMI flow grade <3, in a SB >2.5 mm) or SB balloon dilation is complicated by a flow-limiting SB dissection, then SB stenting should be performed. Finally, if SB is suitable for stenting and presents a diffuse disease beyond the ostium, we prefer a two-stent strategy as ITT.[30]

TECHNICAL STRATEGY FOR LM BIFURCATION DISEASE

The LM is responsible for supplying ~75% of the left ventricular (LV) cardiac mass in patients with right dominant type or balanced type and 100% in the case of left dominant type. As a result, severe LM disease will reduce flow to a large myocardium territory, placing the patient at high risk for life-threatening events. The LM is generally divided into three anatomic regions: the ostium or origin of the LM from the aorta, a mid-portion, and the distal portion. The LM differs from the other coronary arteries in its relatively greater elastic tissue content, which can explain elastic recoil and high restenosis rate following balloon angioplasty. The segment of the LM that extends beyond the aorta displays the same layered architecture as that of the other coronary arteries. Atherosclerotic lesions tend to form at specific regions of the coronary vasculature where there is a low shearstress area. In the LM bifurcation, intimal atherosclerosis is accelerated primarily in an area of low shear stress in the lateral wall, close to the left anterior descending artery (LAD) and left circumflex artery (LCx) bifurcation. Thus, the carina is frequently free of disease and this can explain the reason why single-stent strategy (provisional stenting) can be successfully performed in patients with no or moderate disease by angiography.

In a systematic review and meta-analysis of 1,278 patients published by our group,[31] we have shown that treating unprotected (U)LMCA lesions with DES is associated with a 5.5% (3.3–7.7%) risk of death, a 16.5% (11.7–21.3%) MACE rate, and a TLR rate of 6.5% (3.7–9.2%). Distal LM disease is a predictor of MACE and TLR; however, it is the presence of high-risk features that predicts death. Our review also shows that most series have reported low rates of ST (0–2%), apart from the Price et al.[32] group (4%). Data about safety and efficacy of PCI compared with coronary artery bypass grafts (CABG) in patients with LMCA disease have been further summarised in two important meta-analyses, published in 2011.

These two papers reviewed a total of 1,611 patients[6,11,33,34] randomised in the LEMANS,[35] SYNTAX left main cohort,[36] PRECOMBAT,[37] and a study by Boudriot et al.,[38] and reached similar conclusions; the primary endpoint of 1 year MACE was non-significantly different in the PCI cohort

compared with the CABG cohort (14.5% versus 11.8%; OR 1.28; 95% CI: 0.95-1.72; p=0.11). As in each of the individual studies analysed, the rate of stroke was lower in the PCI group than in the CABG group (0.1% versus 1.74%; OR 0.15; 95% CI: 0.03-0.67; p=0.013), whilst higher rates of target vessel revascularisation (TVR) were observed in the PCI cohort (11.4% versus 5.4%; OR 2.25; 95% CI: 1.54-3.29; p<0.001). Thus, according to such evidence, we can assert that PCI is comparable to CABG for the treatment of ULMCA with respect to the composite of major adverse cardiovascular or cerebrovascular events at 12-month follow-up, as well as having a lower risk of stroke and a higher risk of TVR.

These differences should be kept in mind by operators in the clinical decision-making process when evaluating the choice of best treatment according to the patient's risk profile. However, the best suggestion that we can give to the readers for safely performing PCI in LM stem is careful patient selection. There are four important areas to consider when selecting patients for LM PCI: 1) knowing the data from literature and guidelines; 2) evaluating the patient in terms of clinical presentation (stable, functional class, ACS, STEMI, shock); 3) evaluating the patient in terms of clinical characteristics (age, diabetes, renal function, cognitive status, valvular disease, carotid disease, previous cardiac intervention, other co-morbidities, EuroSCORE); 4) reviewing the angiographic characteristics of the patient (LV function, LM anatomy [distal/non-distal lesion, calcification, bifurcation angle, diseased LCx ostium, trifurcation], mitral valve disease, number of lesions, diffuse disease, complexityof additional lesions [length, calcifications, bifurcations], chronic total occlusion - particularly right coronary artery [RCA] total occlusion - diffuse calcified and porcelain aorta, possibility of complete or incomplete revascularisation, number of stents needed, overlapping, SYNTAX score); 5) knowing the own local centre experience; 6) knowing the evolution of techniques and the different technology for PCI and CABG.

A patient presenting with good LV function, non-distal and non-calcified LM stenosis, ostial LM lesions and mid-shaft LM lesions, and very few additional lesions on the other coronary vessel has been shown to have excellent outcomes following LM stenting. Conversely, a patient with heavy calcified LM disease, reduced LV function, diabetic (particularly if insulin-dependent), with multivessel disease (particularly with low EuroSCORE), and/or distal LM bifurcation lesion with reduced LV function or with occluded RCA or with additional complex lesions on the other coronary vessels (high SYNTAX score), is definitively a better surgical candidate. Finally, a recently published score, the NERS Score II system - which consisted of seven clinical and nine angiographic variables – demonstrated, for values ≥19, an enhanced MACE sensitivity and specificity (84.0% and 76.0%, respectively), significantly higher compared with the SYNTAX score. A NERS Score 2 ≥19 was the only independent predictor of cumulative MACE (hazard ratio: 3.27; 95% CI: 1.86 to 5.23; p≤0.001) and ST (OR: 22.15; 95% CI: 12.47-57.92; p≤0.001) at follow-up after LM stenting.[39]

DEDICATED BIFURCATION STENT AND NEW TREATMENT DEVICES

There is still a debate regarding the choice of the best device, including the new dedicated bifurcation stents, the bioresorbable scaffolds (BRS), and drug eluting balloons (DEB), and including adjunctive procedures such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), and FFR for assessing the best approach and the results in the interventionalist armamentarium to treat bifurcation lesions.

As stated before - unless clinically contraindicated - DES should always be utilised. Conversely, the safety and efficacy of dedicated stents are still under evaluation. The main advantage of most dedicated bifurcation stents is to allow the operator to perform the procedure on a bifurcation lesion without the need to rewire the SB. Dedicated bifurcation stents can be broadly divided into three categories (Table 2):

1. MB dedicated devices (Stentys self-expanding stent, Stentys SA; Axxess Plus, Devax, Irvine, CA, USA).

2. SB dedicated devices (e.g. Sideguard, Cappella Inc., Auburndale, Massachusetts; Tryton, Tryton Medical, Newton, Massachusetts). The Tryton and Sideguard are designed to treat the SB first and require re-crossing into the SB after MB stenting for FK.

3. MB and SB dedicated devices: the Medtronic coronary Y-stent (Medtronic, Minneapolis, MN), The Taxus® Bifurcation Stent System (Boston Scientific

Corporation; Natick, MA), Antares® Coronary Stent System (TriReme Medical, Inc., Pleasanton, CA), Abbott Vascular Side Branch Access (more commonly referred to as Xience SBA) stent (Abbott Vascular, Redwood City, CA), Y-Med sideKicK™ (Y-Med, Inc., San Diego, CA), Invatec Twin- Rail™ (Invatec S.r.l., Italy), and Minvasys Nile Croco® (Minvasys, Gennevilliers, France).

The Axxess Plus stent was the first available on the market of dedicated bifurcation devices designed to elute an anti-restenostic drug (Biolimus A9). The Axxess Plus stent is a self-expanding, nickel-titanium, conically-shaped stent that is placed at the level of the carina. Recently, results of the 3-year follow-up of the Diverge Trial have been published, demonstrating the good safety of this dedicated stent in terms of cumulative MACE.[40] However the lack of randomised, long-term clinical studies for this class of dedicated devices makes their utilisation a niche in the percutaneous management of bifurcation disease.

Table 2: Characteristics of dedicated stents.

Stent	Stent Material	Drug-Eluting	GCS	Stent Delivery System	Mechanism of Stent Expansion
Devax AXXESS™	Nitinol	Biolimus A9	7F	Single wire rapid exchange system	Self expandable
Stentys bifurcation stent	Nitinol	No/Yes*	6F	Single wire rapid exchange system (second wire needed for SB access)	Self expandable; balloon to open access to SB
Tryton Side Branch Stent™	Cobalt chromium	No	6F	Single balloon, single wire rapid exchange system	Balloon expandable
Cappella Sideguard®	Nitinol	No	6F	Single balloon, single wire rapid exchange system	Balloon deployed; self-expandable
Medtronic coronary Y-stent	Cobalt alloy	No	6F	Double balloon, dual wire, single catheter	Balloon expandable (single inflation)
Taxus® bifurcation stent	Platinum alloy	Paclitaxel	7F	Double balloon, dual wire, side exchange catheter	Balloon expandable (single inflation)
Antares® coronary stent	Stainless steel	No	6F	Single balloon, rapid exchange system, with second wire in peel-away lumen	Balloon expandable (single inflation)
Abbott Vascular side-branch access stent	Cobalt chromium	Everolimus	7F	Double balloon, dual wire, joined mandrel tip; MB rapid exchange and SB over-the-wire	Balloon expandable (single inflation)
Y-Med sideKicK™	Cobalt chromium	No	5F	MB fixed wire platform with rapid exchange steerable SB wire	Balloon expandable
Invatec Twin-Rail™	Stainless steel	No	6F	Double balloon, dual rapid exchange, single catheter	Balloon expandable (single inflation)
Minvasys Nile Croco®	Cobalt chromium	No/Yes*	6F	Double balloon, dual rapid exchange system, with 2 independent catheters	Balloon expandable

GCS: guilding catheter size (French); MB: main branch; SB: side-branch.
*paclitaxel is eluted in newer stent iteration.
Devax Inc., Lake Forest, CA; Stentys, Inc., Princeton, NJ; Tryton Medical, Durham, NC; Cappella Medical Devices, Galway, Ireland; Medtronic, Minneapolis, MN; Boston Scientific, Natick, MA; TriReme Medical, Pleasanton, CA; Abbott Vascular, Redwood City, CA; Y-Med, San Diego, CA; Invatec, Italy; Minvasys, Gennevilliers, France.
Adapted from Movahed.[54]

Recently, bioresorbable vascular scaffold (BVS) adoption introduced a unique potential in the treatment of coronary lesions, as they provide temporary vessel scaffolding and then slowly disappear, thereby allowing for the restoration of the vessel wall physiology and vasomotion. Initial preclinical and clinical results appear promising but data are limited to simple lesions, and there is no evidence in the context of randomised control trials that would allow direct comparison of the efficacy of the BVS with the effectiveness of new-generation DES. Albeit the feasibility of using BVS in bifurcation lesions is unknown, a recent study by Colombo and co-authors,[41] utilising an *in-vitro* arterial model, including main-vessel stenting with ballooning of the SB with low-pressure final kissing balloon inflation through the BVS struts (Absorb everolimus-eluting BVS - Abbott Vascular, Santa Clara, California), T-stenting, and crush and culotte procedures, demonstrated that intervention of bifurcation lesions using BVS appears feasible.

DEB technology can represent a potential alternative to DES to prevent restenosis. There are several commercially available DEB in Europe with different carriers and paclitaxel as the active drug. The potential advantage of DEB utilisation in bifurcation lesions is that there is no distortion of the original anatomy of the bifurcation, but there is a reduction of strut deformation, lower risk of polymer fracture, and finally, homogeneous administration of the drug to the vessel wall. In this setting, the potentially homogeneous drug delivery to the vessel wall is indeed one of the more frequently stated advantages of DEB over DES,[42,43] as opposed to a very spatially defined delivery due to release from the comparably narrow stent struts (surface coverage of <20%), as reported by Hwang et al.[44] However, a recent *in vitro* study by Seidlitz and co-authors[45] suggested that it seems crucial to carefully design coatings to avoid vast drug losses during the advancement to the site of expansion, while at the same time allowing for sufficient transfer upon expansion against the vessel wall. The results of the study further indicate that using a micro-pipetting technique with tightly folded balloons may lead to an inhomogeneous distribution of coatings with little coating located deep within the folds. This finding, which is contradictory to common assumptions about this dosage form, emphasises the necessity to further characterise device performance *in vitro*, and indirectly implies an inhomogeneous drug distribution also with paclitaxel-eluting balloon.

In the bifurcation clinical setting, the DEBIUT study failed to demonstrate angiographic superiority of DEB (Dior - Eurocore GmbH, Bonn, Germany) as compared to bare metal stents (BMS), with similar late luminal loss and binary restenosis rates in both treatment groups; DES showed better angiographic results than both DEB and BMS; the reduced duration of dual antiplatelet therapy to 3 months appeared to be safe in combination with DEB and BMS.[46] Finally, it is important to keep in mind that DES implantation in coronary bifurcation lesions is an off-label indication, and DES utilisation in large, real-world registries is associated with higher event rates compared with on-label use of DES, which is consistent with a higher-risk clinical and lesion profile. However, event rates with off-label use of DES are lower compared with off-label use of BMS.[47]

IMAGING AND FUNCTIONAL GUIDE IN BIFURCATION TREATMENT

Intravascular imaging constitutes an important contribution to treatment for bifurcation disease, assisting in the evaluation of: 1) longitudinal plaque distribution; 2) plaque composition; 3) mother and daughter vessel reference diameters; 4) precise stent landing zone analysis; and 5) SB ostium analysis (diseased or not), and after for: 1) stent expansion and apposition; 2) SB ostium assessment; 3) final vessel sizes (stent over or under-expansion); and 4) proximal or distal dissection. IVUS has major spatial resolution and seems preferable, improving the safety of coronary bifurcation stenting using DES;[1] however, a recent retrospective Italian registry published by our group did not associate it with significant clinical benefits.[48]

The detailed assessment of the bifurcation by OCT pre-intervention may aid tailoring the treatment strategy. The expected ability to assess the risk of carina shift or SB closure may influence the decision to protect a SB with a wire and whether or not to pre-dilate it. The exact determination of vessel dimension and distribution of the disease in the bifurcation segment could influence the decision of whether to plan a simple or a complex approach up-front, ensuring adequate coverage of all diseased areas where needed. A final OCT pullback after a complex bifurcation procedure often points to areas of under-expansion, malapposition, or an excessive amount of free floating struts, which are not visible on angiography and can be corrected with additional high-pressure

post-dilation or KB inflation. In addition, high-speed optical frequency domain imaging (OFDI) can be used to create 3D reconstructions of implanted stent structures with excellent quality and at high resolutions. Utilising this technique, OCT may be used to guide the procedure preserving SB patency without compromising the MB, obtaining the optimal vessel dimensions and reducing malapposition of stent struts and the amount of unplanned floating struts. Although not available in all centres, 3D OCT would be of great help for the operator, providing insight into the take-off of SBs as well as aiding in the understanding and planning of optimal treatment strategy.[49,50]

FFR is a pressure-derived flow index, which represents the amount of flow reduced by a specific stenosis. FFR-guided revascularisation strategy is known to be better than angiography-guided revascularisation in various lesion subsets. In particular, FFR can give useful information for the interventional decision-making process of small SB with an angiographically-significant ostial lesion after MB stenting, which may not be functionally significant by FFR analysis. FFR can be used in bifurcation, appearing feasible, safe, and effective.[1,34] In this setting, Koo and co-authors[28] demonstrated that a suboptimal angiographic result in SB after MB stenting should not be an indication to perform SB stenting. In this study, 94 jailed SB were evaluated by FFR and the conclusions can be summarised as follows: no lesions with a quantitative coronary angiography (QCA) percentage stenosis <75% had an FFR <0.75, and among those with a percentage stenosis >75%, only 27% were functionally significant. Moreover, no TVR occurred in those with percentage stenosis <75%, suggesting that most of these lesions do not have functional significance and should not be treated despite 'critical' angiographic appearance.

A particular aspect that needs to be addressed is the utilisation of FFR for LM disease. Although LMCA disease was an exclusion criteria within the DEFER and FAME trials, FFR has nevertheless been used for evaluation of the physiological significance of indeterminate ULMCA lesions. However, a number of important caveats of this approach warrant further consideration. At present, there are a lack of randomised data from larger multicentre studies confirming the long-term safety of this approach. Also, it remains debatable as to whether an FFR <0.75 versus an FFR of <0.80 should be regarded as the appropriate ischaemic threshold.

Some authors suggest the complementary use of IVUS to assess LMCA severity if the LMCA FFR is between 0.80 and 0.85.[51] At least 50-60% of ULMCA lesions involve distal bifurcation, often with significant involvement of the ostia of both daughter branches. Therefore, an FFR pullback should be undertaken starting within both daughter branches to localise the most significant distribution of disease across the region bordering the distal LMCA segment and ostia of both daughter branches. FFR readings across the LMCA segment will be influenced by the presence of lesions within distal coronary segments as well as the amount of functional myocardial territory supplied by these lesions. It is important to keep in mind that stenoses within the LAD or LCx territories will artificially increase the FFR measured across the LMCA stenosis,[52] and therefore, PCI to these lesions would unmask the true haemodynamic significance of the stenosis within the LMCA segment.

In conclusion, based on the current available level of evidence, we recommend the use of FFR for the assessment of (angiographic indeterminate) isolated ostial or midshaft LMCA stenoses in patients who are considered more appropriate candidates for coronary arterial bypass grafting. In those patients with distal/bifurcation LMCA lesions and in those with diffuse/distal coronary arterial disease, we strongly recommend the liberal use of IVUS. Furthermore, in those patients considered likely candidates for ULMCA PCI, IVUS remains crucial for assessing the degree of lumen compromise and the extent, distribution, and morphology of plaque, as well as for the immediate post-procedural quantification of stent deployment.

CONCLUSION

Coronary bifurcation disease is a very challenging subset in interventional cardiology. A provisional approach with MB stenting is the preferred choice in most bifurcations lesions but it is very important to select the most appropriate approach for each bifurcation based on anatomical variables and operator experience. Regardless of strategy choice (one versus two stents), DES have dramatically improved the long term outcomes and should be the preferred device. We believe that the future prospective is primarily related to the development and refinement of dedicated bifurcation stents, which may simplify the procedure by adapting to the complex anatomy of bifurcation disease, and, at the same time, improving the long-term clinical

outcomes. BVS represents the last frontiers in the treatment of bifurcation disease and those devices may indeed offer the unique opportunity to simplify the procedure with a 'cross-over' approach, since the SB will be jailed for only a few months.

REFERENCES

1. Stankovic G et al. Consensus from the 7th European Bifurcation Club meeting. Eurointervention. 2013;9(1):36-45.

2. Medina A et al. A new classification of coronary bifurcation lesions. Rev Esp Cardiol. 2006;59(2):183.

3. Dzavik V et al. Predictors of long-term outcome after crush stenting of coronary bifurcation lesions: importance of the bifurcation angle. Am Heart J. 2006;152(4):762–9.

4. Movahed MR, Stinis CT. A new proposed simplified classification of coronary artery bifurcation lesions and bifurcation interventional techniques. J Invasive Cardiol. 2006;18(5):199-204.

5. Tan K et al. Clinical and lesion morphologic determinants of coronary angioplasty success and complications: current experience. J Am Coll Cardiol. 1995;25(4):855-65.

6. Aliabadi D et al. Incidence and angiographic predictors of side branch occlusion following high-pressure intracoronary stenting. Am J Cardiol. 1997;80(8):994-7.

7. Movahed MR. Coronary artery bifurcation lesion classifications, interventional techniques and clinical outcome. Expert Rev Cardiovasc Ther. 2008;6(2):261-74.

8. Ge L et al. Clinical and angiographic outcome after implantation of drug-eluting stents in bifurcation lesions with the crush stent technique: importance of final kissing balloon post-dilation. J Am Coll Cardiol. 2005;46(4):613–20.

9. Steigen TK et al. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. Circulation. 2006;114:1955–61.

10. Alberti A et al. "Skirt" technique for coronary artery bifurcation stenting. J Invasive Cardiol. 2000;12(12):633-6.

11. Kobayashi Y et al. The skirt technique: a stenting technique to treat a lesion immediately proximal to the bifurcation (pseudobifurcation). Catheter Cardiovasc Interv. 2000;51(3):347–51.

12. Ormiston JA et al. Stent deformation following simulated side-branch dilatation: a comparison of five stent designs. Catheter Cardiovasc Interv. 1999;47(2):258–64.

13. Lefèvre T et al. Stenting of bifurcation lesions: a rational approach. J Interv Cardiol. 2001;14(6):573–86.

14. Sianos G et al. Bifurcation stenting with drug eluting stents: illustration of the crush technique. Catheter Cardiovasc Interv. 2006;67(6):839–45.

15. Porto I et al. "Crush" and "reverse crush" technique to treat a complex left main stenosis. Heart. 2006;92(8):1021.

16. Sharma SK. Simultaneous kissing drug-eluting stent technique for percutaneous treatment of bifurcation lesions in large-size vessels. Catheter Cardiovasc Interv. 2005;65(1):10–6.

17. Sharma SK et al. Simultaneous kissing stents (SKS) technique for treating bifurcation lesions in medium-to-large size coronary arteries. Am J Cardiol. 2004;94(7):913-7.

18. Iakovou I et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA. 2005;293(17):2126–30.

19. Kuchulakanti PK et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation. 2006;113(8):1108–13.

20. Ong AT et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. J Am Coll Cardiol. 2005;45(6):947–53.

21. Maeng M et al. Long-term results after simple versus complex stenting of coronary artery bifurcation lesions: Nordic Bifurcation Study 5-year follow-up results. J Am Coll Cardiol. 2013;62(1): 30-4.

22. Myler RK et al. Lesion morphology and coronary angioplasty: current experience and analysis. J Am Coll Cardiol. 1992;19:1641–52.

23. Suzuki N et al. Percutaneous coronary intervention of bifurcation coronary disease. Minerva Cardioangiol. 2007;55(1):57–71.

24. Tsuchida K et al. The clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularization Therapies Study part II (ARTS II). Eur Heart J. 2007;28(4): 433–42.

25. Thuesen L et al. Comparison of sirolimus-eluting and bare metal stents in coronary bifurcation lesions: subgroup analysis of the Stenting Coronary Arteries in Non-Stress/Benestent Disease Trial (SCANDSTENT). Am Heart J. 2006;152(6):1140–5.

26. Yamashita T et al. Bifurcation lesions: two stents versus one stent--immediate and follow-up results. J Am Coll Cardiol. 2000;35(5):1145–51.

27. Ge L et al. In-hospital and nine-month outcome of treatment of coronary bifurcational lesions with sirolimus-eluting stent. Am J Cardiol. 2005;95: 757–60.

28. Koo BK et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. J Am Coll Cardiol. 2005;46(4):633-7.

29. Brunel P et al. Provisional T-stenting and kissing balloon in the treatment of coronary bifurcation lesions: results of the French multicenter "TULIPE" study. Catheter Cardiovasc Interv. 2006;68(1):67–73.

30. Latib A, Colombo A. Bifurcation disease: what do we know, what should we do? JACC Cardiovasc Interv. 2008;1(3):218-26.

31. Biondi-Zoccai GG et al. A collaborative systematic review and meta-analysis on 1278 patients undergoing percutaneous drug-eluting stenting for unprotected left main coronary artery disease. Am Heart J. 2008;155:274-83.

32 Price MJ et al. Serial angiographic follow-up of sirolimus-eluting stents for unprotected left main coronary artery revascularization. J Am Coll Cardiol. 2006;47:871-7.

33. Capodanno D et al. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: a meta-analysis of randomized clinical data. J Am Coll Cardiol. 2011;58(14):1426-32.

34. Ferrante G et al. Percutaneous coronary intervention versus bypass surgery for left main coronary artery disease: a meta-analysis of randomised trials. EuroIntervention. 2011;7(6):738-46.

35. Buszman PE et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol. 2008;51(5):538-45.

36. Morice MC et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary

intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the synergy between percutaneous coronary intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation. 2010;121(24):2645-53.

37. Park SJ et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med. 2011;364(18):1718-27.

38. Boudriot E et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol. 2011;57(5):538-45.

39. Chen SL et al. The anatomic- and clinical-based NERS (New Risk Stratification) Score II to predict clinical outcomes after stenting unprotected left main coronary artery disease. Results from a mlticenter, prospective, registry study. JACC Cardiovasc Interv. 2013;6(12):1233-41.

40. Buysschaert I et al. Three-year clinical results of the Axxess Biolimus A9 eluting bifurcation stent system: the DIVERGE study. Eurointervention. 2013;9(5):573-81.

41. Džavík V, Colombo A. The absorb bioresorbable vascular scaffold in coronary bifurcations: insights from bench testing. JACC Cardiovasc Interv. 2014;7(1):81-8.

42. Waksman R, Pakala R. Drug-eluting balloon: the comeback kid? Circ Cardiovasc Interv. 2009;2:352–8.

43. Wohrle J. Drug-coated balloons for coronary and peripheral interventional procedures. Curr Cardiol Rep. 2012;14:635–41.

44. Hwang CW et al. Physiological transport forces govern drug distribution for stent-based delivery. Circulation. 2001;104:600–5.

45. Seidlitz A et al. In vitro determination of drug transfer from drug-coated balloons. PLoS One. 2013;31;8(12):e83992.

46. Belkacemi A et al. Coronary bifurcation lesions treated with the drug-eluting balloon: a preliminary insight from the DEBIUT study. EuroIntervention. 2011;7(Suppl K):K66-9.

47. Brodie BR et al. Outcomes and complications with off-label use of drug-eluting stents: results from the STENT (Strategic Transcatheter Evaluation of New Therapies) group. JACC Cardiovasc Interv. 2008;1(4):405-14.

48. Biondi-Zoccai G et al. Does the target vessel impact on results of percutaneous coronary intervention for bifurcation lesions? Insights from the I-BIGIS registry. J Invasive Cardiol. 2013;25(12):660-5.

49. Farooq V et al. Three-dimensional optical frequency domain imaging in conventional percutaneous coronary intervention: the potential for clinical application. Eur Heart J. 2013;34(12): 875-85.

50. Farooq V et al. New insights into the coronary artery bifurcation hypothesis-generating concepts utilizing 3-dimensional optical frequency domain imaging. JACC Cardiovasc Interv. 2011;4(8):921-31.

51. Fearon WF. The case for FFR (rather than IVUS) to assess borderline left main stenosis. Presented at: 8th Annual CTO Summit and Left Main Coronary Interventions Course. 14–16th February, 2011, New York.

52. Pijls NH et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. Circulation. 2000;102:2371-7.

53. Louvard Y et al. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! Catheter Cardiovasc Interv. 2008;71(2):175-83.

54. Movahed MR. Coronary artery bifurcation lesion classifications interventional techniques and clinical outcome. Expert Rev Cardiovasc Ther. 2008;6(2):261-74.

CORONARY ARTERY BIFURCATION LESIONS: A REVIEW OF CONTEMPORARY TECHNIQUES IN PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

Percutaneous intervention of coronary bifurcation lesions continues to challenge interventional cardiologists. Nonetheless, the past decade has seen an explosion in the development of clinical novel techniques and well-conducted trials validating the relative efficacy and safety of these techniques. For the most part, consensus has emerged regarding the preferred technique, that being provisional stenting of the side-branch (SB), based on the results of several randomised trials that, with the exception of one, have shown no benefit of a two-stent approach, utilising any one of several techniques, including the crush, culotte, or other modifications. Only the double-kiss (DK) crush appears to confer better clinical outcomes, possibly because of the superiority of the technique in optimising access to the SB. Trial data are still pending regarding the efficacy of two-stent techniques in patients with complex SB lesions and with large-calibre SBs. The use of second-generation drug-eluting stents is associated with better results compared to historical data. Preliminary data from studies utilising dedicated bifurcation stents similarly shows favourable results. Bifurcation stenting using bioresorbable vascular scaffolds is at an early stage, with prospective trial data needed to validate this technology for the use in this subset of patients. Modern imaging tools such as intravascular ultrasound and optical coherence tomography, as well as physiological assessment of SB lesions, are now utilised in decision-making regarding stent strategy, though trial data showing better outcomes with routine use of these tools are lacking.

Keywords: Bifurcation, stenting, crush, culotte, provisional stenting.

INTRODUCTION

Coronary artery bifurcation lesions comprise one of the more complex lesion subsets routinely faced in interventional cardiology, accounting for up to 20% of all coronary disease treated by percutaneous coronary intervention (PCI).[1]

The technical difficulties inherent in the treatment of bifurcation lesions, associated with their lower success and higher complication rates compared with non-bifurcation lesions, have always been the object of intense research activity, with publication of contemporary studies in the past few years contributing significantly to the decision-making process.[2-8] In this review article we will examine the main techniques for the treatment of bifurcation lesions and discuss the evidence to support their use.

Anatomical Classification

Bifurcation lesions are challenging to categorise, since they are variable not only in their anatomy (location of plaque, plaque burden, angle between branches, site of bifurcation, and size of branches), but also in the dynamic anatomic changes during treatment caused by dissections and carina shift.[9] Despite these challenges complicating classification of bifurcation lesions, many definitions have been proposed in an effort to unify this common clinical situation. Louvard and colleagues[9] proposed that a bifurcation lesion is a coronary artery narrowing occurring adjacent to, and/or involving, the

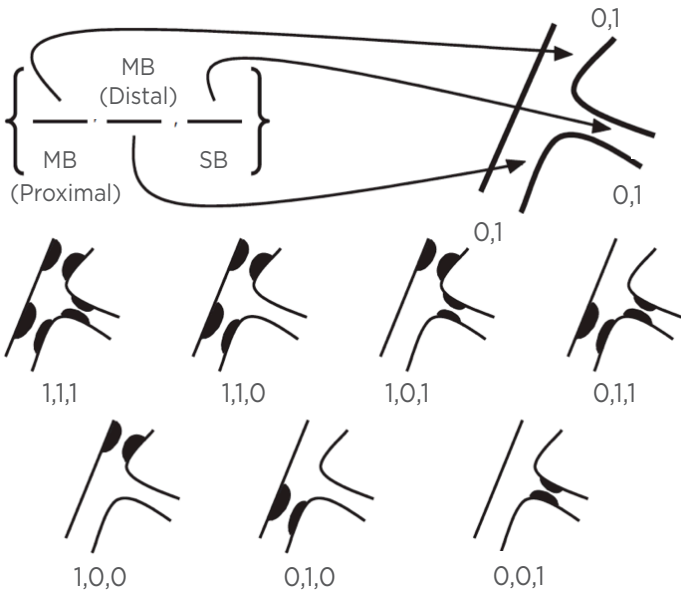

Figure 1: The Medina classification of coronary bifurcation lesions.
Adapted from Medina et al.[10]

origin of a significant side-branch (SB); being a significant SB it should not be lost in the global patient context (symptoms, location of ischaemia, branch responsible for symptoms or ischaemia, viability, collateralising vessel, left ventricular function, and so forth). Indeed, the Medina classification, a simple and straightforward classification that provides all the information contained in other systems, has prevailed and is nowadays used worldwide (Figure 1).[10] The classification entails recording any narrowing exceeding 50% in each of the three arterial segments of a bifurcation in the following order: proximal main vessel (MV), distal MV, and the SB; 1 is used to indicate the presence of a significant stenosis and 0 the absence of stenosis (Figure 1). Based on the Medina classification, lesions classified as 1,1,1, 1,0,1, and 0,1,1 are considered 'true bifurcation', as they involve a significantly diseased SB.

BIFURCATION STENT TECHNIQUES

The introduction of drug-eluting stents (DES) in the last decade has created an expectation of better long-term outcomes when treating bifurcation lesions. Despite reducing the incidence of restenosis in comparison with balloon angioplasty and/or bare metal stent deployment, the majority of contemporary studies have failed to demonstrate a benefit in routinely choosing a two-stent technique over a provisional SB stent approach.[11] Although the provisional technique has been the prevailing strategy for many years, various two-stent techniques have become popular in the DES era.[12-14] Below is a brief description of the most commonly used bifurcation techniques.

Provisional SB Stent Technique

This technique, considered by the majority of experts to be the preferred strategy for the majority of bifurcation interventions, consists of deploying a single stent in the MV, with a second stent then being deployed in the SB only in case of an unsatisfactory SB result (thrombolysis In myocardial infarction [TIMI] flow <3 or residual angiographic stenosis >70% after balloon dilatation). A common variation includes pre-dilatation of the SB. In case of dilation of the SB, a final kissing balloon inflation (FKBI) is recommended.[3]

Crush Technique Variations

The crush technique, first reported by Antonio Colombo and colleagues,[14] consists of placing one stent in the MV and one in the SB, with the main-vessel stent being positioned more proximally in order to completely cover the crushed proximal end of the SB stent. After the SB stent is deployed, it is crushed by the stent positioned in the MV, flattening the protruding cells of the SB stent. Hereafter, the wires are recrossed and FKBI is performed.[14] The downsides of this technique lie in the difficulty in recrossing the SB through the multiple layers of metal after deployment of both stents, and residual stenosis of SB ostium.

The mini-crush modification simply consists of protruding less SB stent material in the MV, this being associated with greater success in recrossing the struts.[15] The crush technique requires the use of a 7 or 8 French (Fr) guiding catheter. The development of the balloon crush technique, whereby the SB stent is initially crushed by a balloon rather than a stent in the MV, has allowed the use of a 6 Fr guiding catheter, and thus, the ability to perform the crush utilising radial access.[16] Subsequent variations have included the DK crush and the modified balloon or double crush.[17,18] In both techniques, access to the SB is improved by first dilating the struts of the crushed SB stent with a balloon prior to deployment of the MV stent.

In the DK crush, kissing balloon (KB) inflation is performed after crushing the SB stent with a balloon. This technique facilitates access to the SB in addition to optimising stent apposition at the SB ostium;[4,5] it has been shown to perform favourably

against provisional stenting in a randomised trial.[4] In the double crush technique, the dilated SB stent struts are crushed by a balloon to prevent winging of the MV portion of the stent, and thus, facilitating positioning of the MV stent. Following deployment of the MV stent (the second crush), the SB struts are again recrossed and dilated using a high-pressure inflation. The procedure is then completed with a FKBI. Registry data have shown excellent long-term results using this technique.[19]

A final crush variation is the reverse crush technique, the main indication for which is as bailout in a provisional SB stenting strategy, with unacceptable SB result after main-vessel stenting, when the SB angle is too narrow for an effective T-stent approach. In this case, a second stent is advanced into the SB, after balloon dilatation to open the MV struts. The SB stent should be deployed no more than 2-3 mm into the MV, with a balloon positioned at the bifurcation level in the MV. For the most part, this technique has been supplanted by the T and protrusion (TAP) technique in which, rather than protruding the provisional SB stent so far into the MV that it needs to be crushed, the SB stent is deployed with a slight protrusion in the carinal aspect of the bifurcation, resulting in slight protrusion of the SB stent into the MV.[20] If the SB is large, and the bifurcation angle acute, this procedure could potentially result in excessive protrusion of the SB stent into the MV lumen. In such unusual cases, a reverse crush may remain a better option.

The Culotte Technique

This consists of deploying two stents in vessels of somewhat similar luminal diameters.[21] It results in complete coverage of the bifurcation at the expense of an excess of metal covering of the proximal segment. After balloon predilatation of both branches, the first stent should be delivered in the more angulated vessel, facilitating access into the other vessel. After opening the stent struts, a second stent is advanced through them and deployed in overlap with the first stent at the proximal segment. The procedure is completed with a FKBI. The culotte technique provides excellent coverage of the SB ostium. Similar to the crush technique, it leads to a high concentration of metal with a double-stent layer at the carina and at the proximal part of the bifurcation. The main disadvantage of the technique is that rewiring both branches through the stent struts can be difficult and time consuming.

T-Stenting and Modified T-Stenting Techniques

The original T-stenting technique consists of positioning a stent first at the ostium of the SB, without stent protrusion into the MV. After deployment of the stent and removal of balloon and wire from the SB, a second stent is advanced in the MV. A wire is then re-advanced into the SB, and a FKBI is performed.[22] Modified T-stenting is done by simultaneous positioning of stents at the SB and MV. The SB stent is deployed first, then after wire and balloon removal from the SB, the MV stent is delivered.[12] This technique is best suited for a right angle bifurcation, although the TAP modification allows for the use of this technique when the bifurcation angle is more acute.

A Systematic Approach

The European Bifurcation Club has devised a systematic classification and approach to the treatment of coronary bifurcation lesions.[9] This classification of techniques, MADS (main, across, distal, side) is based on the manner in which the first stent is implanted, which often corresponds to a technical strategy related to the importance of the vessel treated first[9] (Figure 2).

All considerations regarding the best treatment strategy for bifurcation lesions are based on the premise that the SB is large enough (≥2 mm) with a sufficient territory of distribution to justify preoccupation with its patency. If the SB is small (<1.5 mm) and supplies a small area of myocardium, it can be ignored, and a stent can be placed in the MV across the SB ostium. In the medium size SB (2-2.75 mm), a strategy of wiring and reassessment after MV pre-dilatation is appealing. In general, predilation of the SB prior to stent deployment is not recommended, as predilation can cause a dissection of the ostium and render subsequent recrossing of the ostium through MV stent struts problematic.[23] If an unsatisfactory result of the SB is observed after stenting the MV, balloon dilatation of the SB is the first option. A stent placement in the SB is generally required only when flow in the SB is reduced. In the NORDIC study, patients randomised to provisional SB stenting had further intervention in the SB only if the TIMI flow was <3.[6]

Treatment of coronary bifurcations frequently requires simultaneous insertion of two balloons or two stents; therefore, an appropriately sized guiding catheter should be selected. With the currently available low-profile balloons, it is possible to insert

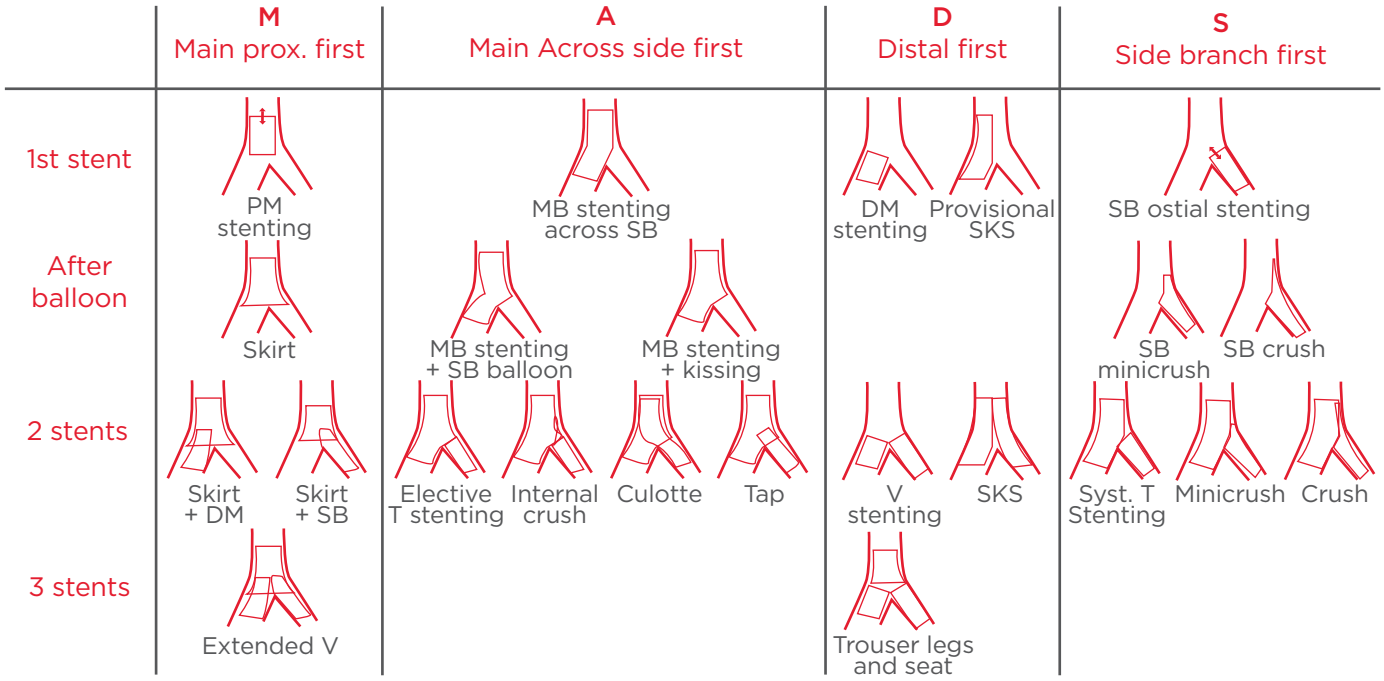

Figure 2: MADS classification of different bifurcation treatment techniques.
Adapted from Stankovic et al.[23]

two balloons inside a large-lumen 6 Fr guiding catheter with an internal lumen diameter of more than 0.070 in (1.75 mm). If two stents are needed, they can only be inserted one after the other, not simultaneously, in a large-lumen 6 Fr guiding catheter. Because most commonly used two-stent techniques do not require simultaneous deployment of the MV and SB stents, 6 Fr access is usually the first option, especially because it allows a radial approach in virtually all patients.

The Evidence

Several randomised trials utilising DES have compared multiple strategies for the treatment of bifurcation lesions. The larger, contemporary trials are summarised in Table 1. Most of these studies did not demonstrate different clinical outcomes when comparing provisional SB stenting with complex strategies. However, the majority reported higher use of contrast, longer procedural times, and consequently radiation exposure with two-stent approaches. In addition, having similar clinical outcomes, procedures requiring use of more materials (guidewires, balloons, stents) imply higher costs.

Target lesion revascularisation (TLR) rates are comparable between simple versus complex strategies, with a trend towards lower angiographic restenosis rates in the two-stent approach techniques when considering only true bifurcation lesions.[4,8] The general concept that in true bifurcations a provisional SB stent approach has worse outcomes than an upfront two-stent strategy was not seen in a post-hoc analysis of true bifurcations in the NORDIC Study, which demonstrated better clinical outcomes with the provisional approach (19.9 versus 30.1, p=0.044).[6] The primary outcome of the study also suggested a trend towards a lower incidence of major adverse cardiac events (MACE) in the provisional arm.

On the other hand, the DKCRUSH-II trial, enrolling mostly patients with true bifurcations, demonstrated significantly less TLR and a trend towards less MACE with the two-stent technique. However, this strategy had a numerically higher incidence of stent thrombosis.[4] In addition, Colombo and colleagues[8] failed to demonstrate a clinical benefit of the crush technique over provisional SB stenting in a study including only true bifurcation lesions. Provisional SB stenting and two-stent strategies using DES were tested in another two large randomised trials. Ferenc and colleagues[24] showed, in an elegant study, that routine T-stenting technique did not improve angiographic outcome when compared to stenting of the MV followed by KB angioplasty and

provisional SB stenting. Clinical outcomes, a secondary endpoint in this trial, revealed no difference between the two strategies.

Another large randomised study that compared simple versus complex strategies, the British Bifurcation Coronary Study trial showed higher rates of in-hospital and 9-month MACE with a systematic two-stent technique.[2] Nevertheless, this difference was largely driven by periprocedural myocardial infarction (MI), an endpoint of questionable significance not reported in other recent bifurcation trials.

Two contemporary randomised trials compared different complex strategies for the treatment of bifurcation lesions. The NORDIC Stent Technique Study compared crush versus culotte techniques and, at 36-month follow-up, found similar clinical outcomes.[7] It is important to accentuate that in this study only 10% of lesions were located in the left main and around 80% of all lesions were true bifurcations. Furthermore, Chen and colleagues[25] published in 2013 the DK Crush-III Study, a comparison of DK crush versus culotte stenting for unprotected distal left main bifurcations lesions. Besides only involving left main lesions, this trial enrolled basic medina 1,1,1 bifurcations. The major finding at 1-year follow-up was that culotte stenting was associated with significantly increased MACE (6.2 versus 16.3, p<0.05), mainly because of higher TLR rates (4.3 versus 11, p<0.05).

In two-stent techniques, such as culotte and crush, FKBI is considered mandatory.[26] The impact of FKBI in provisional SB stenting was assessed in the NORDIC-III Study, which demonstrated similar 6-month clinical outcomes with and without FKBI.[3] However, in a subgroup of patients that underwent quantitative coronary assessment at 8 months, FKBI reduced angiographic SB restenosis, 7.9% versus 15.4% (p=0.039), especially in patients with true bifurcation lesions, 7.6% versus 20.0% (p=0.024). Nevertheless, a small sample of these patients also had fractional flow reserve (FFR) performed immediately after the procedure and at follow-up.[27] FKBI improved acute functional outcome in the SB compared to leaving the SB jailed, but no significant difference was detected at follow-up.

New Stents and Platforms

The majority of randomised trials comparing simple versus two-stent strategies to date were conducted utilising first-generation DES. Data regarding the efficacy of second-generation DES are derived from registries and sub-group

Table 1: Randomised trials using DES that compared different bifurcation lesion treatment strategies.

Study	Year	Technique	N	Follow-up (months)	MACE (%)	TVR (%)	Definite ST (%)
Ferenc et al.[24]	2008	T stent vs. provisional	202	9	11.9 vs. 12.9	8.9 vs. 10.9	2 vs. 1
CACTUS[8]	2009	crush vs. provisional	350	6	15.8 vs. 15	7.9 vs. 7.5	1.7 vs. 1.1
BBC ONE[2]	2010	crush / culotte vs. provisional	500	9	15.2 vs. 8*	5.6 vs. 7.2	2.0 vs. 0.4
DKCRUSH-II[4]	2011	DK crush vs. provisional	370	12	10.3 vs. 17.3	6.5 vs. 14.6	2.2 vs. 0.5
NORDIC-III[3]	2011	FKBI vs. no FKBI	477	6	2.5 vs. 3	1.3 vs. 1.7	0.4 vs. 0.4
NORDIC[6]	2013	simple vs. complex	413	60	15.8 vs. 21.8	13.4 vs. 18.3	3 vs. 1.5
NORDIC-II[40]	2013	crush vs. culotte	424	36	22 vs. 19.1	11.5 vs. 6.5	1.4 vs. 4.7
DK-III[25]	2013	DK crush vs. culotte	419	12	6.2 vs. 16.3	4.3 vs. 11	0 vs. 1

TVR: target vessel revascularisation; ST: stent thrombosis; MACE: major adverse cardiac events (cardiac death, myocardial infarction, and TVR); DK: double-kiss; FKBI: final kissing balloon inflation; DES: drug-eluting stents.
*All-cause death, myocardial infarction, and TVR.

analyses of randomised trials. In a substudy of the RESOLUTE All Comers Trial, comparing the resolute zotarolimus-eluting stent (ZES, Santa Rosa, CA, USA) and the Xience V everolimus-eluting stent (Santa Clara, CA, USA), randomised patients undergoing bifurcation PCI had similar outcomes at 2 years compared to those undergoing non-bifurcation PCI only, with the exception of the occurrence of any MI, that tended to occur more frequently in the bifurcation group (7.3% versus 4.7%, p=0.068).[28] Similar results were reported by the SPIRIT V prospective registry.[29] In a retrospective comparison of patients treated with first-generation compared with second-generation DES with 2-year follow-up, Costopoulos et al.[30] reported a significantly lower MACE rate in the second-generation group (14.4% versus 23.1%, p=0.02). The comparison, of course compared different eras that differed not only in DES type and platform, but also in technical advances and concomitant medical therapy, that are likely also responsible for these observations.

Several recent reports have suggested the feasibility of treating bifurcation lesions with bioresorbable vascular scaffolds (BVS). To date these consist of isolated cases of complex stenting procedures (Figure 3) performed with the Absorb BVS (Santa Clara, CA, USA),[22,31,32] and small case series.[33] While treating bifurcation lesions with material that resorbs over time appears attractive, caution must be exercised as the poly-lactic acid material can fracture when dilated 0.5 mm or more beyond the rated diameter of the device.[34,35] This area is evolving rapidly.

Dedicated Bifurcation Stents

Alongside the evolution of bifurcation techniques there has been the development of several dedicated bifurcation stents. The most advanced of these in terms of evidence base is the Tryton Side Branch Stent, a bare-metal device utilising two guidewires and a bifurcating balloon that scaffolds the SB in the proximal aspect and allows for potential deployment of a second regular stent through the opening, resulting in complete coverage of the SB ostium, the use of which has in a pooled analysis of eight registries been shown to result in outcomes at 1 year similar to those reported in other contemporary trials and registries.[5] 3-year results were recently reported in the DIVERGE study, a prospective registry of 302 patients, 77% of whom had true bifurcation lesions, treated with the AXXESS, a nitinol self-expanding biolimus A9-eluting stent, showing a MACE rate of 16.1% and an ischaemia-driven TLR rate of 10.1%, again, comparing favourably with randomised trial results at shorter duration follow-up.[6]

ANATOMICAL AND FUNCTIONAL ASSESSMENT OF BIFURCATION LESIONS

Intra-Vascular Ultrasound Imaging (IVUS)

IVUS has been incorporated into clinical practice for the treatment of bifurcation lesions for many years, especially in left main lesions. It allows detailed assessment of plaque burden in the MV as well as in SB, helping decide the necessity of an upfront two-stent strategy.

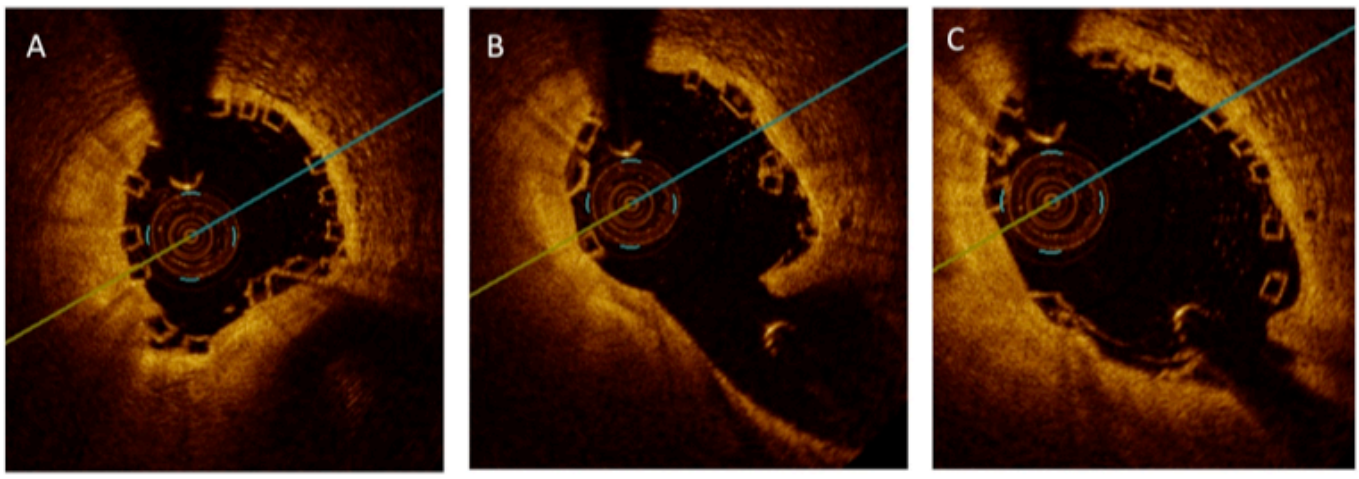

Figure 3: A) Left anterior descending-diagonal bifurcation just distal to the carina after deployment of a 3.0x28 mm Absorb BVS; B) at the carina; C) proximal to the carina after proximal optimisation and gentle kissing balloon inflation.

Stent apposition can also be assessed by this imaging modality. Two large Korean observational studies[36,37] demonstrated a significant advantage of IVUS-guided over angiographic guided PCI in bifurcations lesions. However, no randomised trials have tested this strategy in this scenario.

Optimal Coherence Tomography (OCT)

OCT's potential role for bifurcation lesions is very promising. Its ability of defining anatomical details of the bifurcation allows precise measurement of the angle, plaque burden, size of the vessel, and plaque characteristics. In addition, stent apposition and mechanical complications can easily be identified by OCT. It can also be used to create 3D reconstructions of implanted stent structures with excellent quality and at resolutions much higher than what is currently possible using IVUS.[38] Furthermore, the expected ability of OCT to assess the risk of carina shift or SB closure may influence the decision to protect a SB with a wire and whether or not to predilate it. To date, there is no systematic evaluation for its use in guiding the treatment of bifurcation lesions.

FFR

FFR has a defined role in the percutaneous treatment of bifurcation lesions. It has been used to assess the severity of residual stenosis in the SB after deployment of the MV stent, when using the provisional SB stent technique. Koo and colleagues[39] demonstrated in an elegant study that only 30% of lesions which appear >75% on quantitative coronary angiography are physiologically significant when assessed by FFR.

SUMMARY

Contemporary evidence from randomised clinical trials that compared different treatment strategies for bifurcation lesions using DES demonstrated similar clinical outcomes: less use of contrast, shorter procedural times, and consequently less radiation exposure with provisional SB stenting compared to complex strategies, even in true bifurcations. Also, most ostially narrow-jailed SBs are not functionally significant as assessed by FFR, and the operator should resist the temptation to improve the final angiographic appearance.

Among two-stent strategies, the DK crush technique has shown better results compared to the original crush and culotte techniques, and comparable results to provisional SB stent approach. The DK crush technique provides full coverage of the SB ostium as well as expansion of the SB stent. In addition, it allows the use of 6 Fr guides, permitting radial approach in virtually all patients. Newer DES platforms appear to confer better long-term safety compared to older generation stents. The BVS has been shown to be a feasible tool for bifurcation treatment; however, further studies are needed to ascertain its long-term safety and efficacy in this patient subset.

REFERENCES

1. Magro M et al. Acute procedural and six-month clinical outcome in patients treated with a dedicated bifurcation stent for left main stem disease: the TRYTON LM multicentre registry. EuroIntervention. 2013;8(11):1259-69.

2. Hildick-Smith D et al. Randomized trial of simple versus complex drug-eluting stenting for bifurcation lesions. The British Bifurcation Coronary Study: old, new, and evolving strategies. Circulation. 2010;121(10):1235-43.

3. Niemelä M et al. Randomized comparison of final kissing balloon dilatation versus no final kissing balloon dilatation in patients with coronary bifurcation lesions treated with main vessel stenting: the Nordic-Baltic Bifurcation Study III. Circulation. 2011;123(1):79-86.

4. Chen SL et al. A randomized clinical study comparing double kissing crush with provisional stenting for treatment of coronary bifurcation lesions results from the DKCRUSH-II (Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions) trial. J Am Coll Cardiol. 2011;57(8):914-20.

5. Grundeken MJ et al. Six-month and one-year clinical outcomes after placement of a dedicated coronary bifurcation stent: a patient-level pooled analysis of eight registry studies. EuroIntervention. 2013;9(2):195-203.

6. Buysschaert I et al. Three-year clinical results of the Axxess Biolimus A9 eluting bifurcation stent system: the DIVERGE study. EuroIntervention. 2013;9(5):573-81.

7. Verheye S et al. Six-month clinical and angiographic results of the STENTYS® self-apposing stent in bifurcation lesions. EuroIntervention. 2011;7(5):580-7.

8. Colombo A et al. Randomized study of the crush technique versus provisional side-branch stenting in true coronary bifurcations: the CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) Study. Circulation. 2009;119(1):71-8.

9. Louvard Y et al. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! Catheter Cardiovasc Interv. 2008;71(2):175-83.

10. Medina A et al. [A new classification of coronary bifurcation lesions]. Rev Esp Cardiol. 2006;59(2):183.

11. Behan MW et al. Simple or complex stenting for bifurcation coronary lesions: a patient-level pooled-analysis of the Nordic Bifurcation Study and the

British Bifurcation Coronary Study. Circ Cardiovasc Interv. 2011;4(1):57-64.

12. Kobayashi Y et al. Modified "T" stenting: a technique for kissing stents in bifurcational coronary lesion. Cathet Cardiovasc Diagn. 1998;43(3):323-6.

13. Chevalier B et al. Placement of coronary stents in bifurcation lesions by the "culotte" technique. Am J Cardiol. 1998;82(8):943-9.

14. Colombo A et al. Modified T-stenting technique with crushing for bifurcation lesions: immediate results and 30-day outcome. Catheter Cardiovasc Interv. 2003;60(2):145-51.

15. Colombo A, Giannini F. Improving the success to recross into the side branch after mini-crush technique for bifurcation lesions. J Invasive Cardiol. 2013;25(3): 123-4.

16. Lim PO, Dzavik V. Balloon crush: treatment of bifurcation lesions using the crush stenting technique as adapted for transradial approach of percutaneous coronary intervention. Catheter Cardiovasc Interv. 2004;63(4):412-6.

17. Chen SL et al. [DK crush technique: modified treatment of bifurcation lesions in coronary artery]. Chin Med J (Engl). 2005;118(20):1746-50.

18. Collins N, Dzavik V. A modified balloon crush approach improves side branch access and side branch stent apposition during crush stenting of coronary bifurcation lesions. Catheter Cardiovasc Interv. 2006;68(3):365-71.

19. Freixa X et al. Long-term outcomes using a two-stent technique for the treatment of coronary bifurcations. Int J Cardiol. 2013;168(1):446-51.

20. Burzotta F et al. Modified T-stenting with intentional protrusion of the side-branch stent within the main vessel stent to ensure ostial coverage and facilitate final kissing balloon: the T-stenting and small protrusion technique (TAP-stenting). Report of bench testing and first clinical Italian-Korean two-centre experience. Catheter Cardiovasc Interv. 2007;70(1):75-82.

21. Hoye A et al. Percutaneous therapy of bifurcation lesions with drug-eluting stent implantation: the culotte technique revisited. Int J Cardiovasc Intervent. 2005;7(1):36-40.

22. Costopoulos C et al. Optical coherence tomography of a bifurcation lesion treated with bioresorbable vascular scaffolds with the "mini-crush" technique. JACC Cardiovasc Interv. 2013;6(12):1326-7.

23. Stankovic G et al. Percutaneous coronary intervention for bifurcation lesions: 2008 consensus document from the fourth meeting of the European Bifurcation Club. EuroIntervention. 2009;5(1):39-49.

24. Ferenc M et al. Randomized trial on routine vs. provisional T-stenting in the treatment of de novo coronary bifurcation lesions. Eur Heart J. 2008;29(23):2859-67.

25. Chen et al. Comparison of double kissing crush versus Culotte stenting for unprotected distal left main bifurcation lesions: results from a multicenter, randomized, prospective DKCRUSH-III study, J Am Coll Cardiol. 2013;61(14): 1482-8.

26. Ge L et al. Clinical and angiographic outcome after implantation of drug-eluting stents in bifurcation lesions with the crush stent technique: importance of final kissing balloon post-dilation. J Am Coll Cardiol. 2005;46(4):613-20.

27. Kumsars I et al. Side branch fractional flow reserve measurements after main vessel stenting: a Nordic-Baltic Bifurcation Study III substudy. EuroIntervention. 2012;7(10):1155-61.

28. Diletti R et al. Clinical outcomes after zotarolimus and everolimus drug eluting stent implantation in coronary artery bifurcation lesions: insights from the RESOLUTE All Comers Trial. Heart. 2013;99(17):1267-74.

29. Dzavik V et al. Two-year outcomes after deployment of XIENCE V everolimus-eluting stents in patients undergoing percutaneous coronary intervention of bifurcation lesions: a report from the SPIRIT V single arm study. Catheter Cardiovasc Interv. 2013;82(3):E163-72.

30. Costopoulos C et al. First- versus second-generation drug-eluting stents for the treatment of coronary bifurcations. Cardiovasc Revasc Med. 2013;14(6):311-5.

31. Dzavik V et al. Complex bifurcation percutaneous coronary intervention with the Absorb bioresorbable vascular scaffold. EuroIntervention. 2013;9(7):888.

32. Ruzsa Z et al. Culotte stenting with bioabsorbable everolimus-eluting stents. Int J Cardiol. 2013;168(2):e35-7.

33. Chan W et al. Feasibility of everolimus-eluting bioresorbable vascular scaffold in the treatment of coronary bifurcations. Can J Cardiol. 2013;29(10):S337.

34. Dzavik V, Colombo A. The absorb bioresorbable vascular scaffold in coronary bifurcations: insights from bench testing. JACC Cardiovasc Interv. 2014;7(1):81-8.

35. Ormiston JA et al. Bioresorbable polymeric vascular scaffolds: a cautionary tale. Circ Cardiovasc Interv. 2011;4(5): 535-8.

36. Kim JS et al. Impact of intravascular ultrasound guidance on long-term clinical outcomes in patients treated with drug-eluting stent for bifurcation lesions: data from a Korean multicenter bifurcation registry. Am Heart J. 2011;161(1):180-7.

37. Kim SH et al. Long-term outcomes of intravascular ultrasound-guided stenting in coronary bifurcation lesions. Am J Cardiol. 2010;106(5):612-8.

38. Okamura T et al. High-speed intracoronary optical frequency domain imaging: implications for three-dimensional reconstruction and quantitative analysis. EuroIntervention. 2012;7(10):1216-26.

39. Koo BK et al. Physiologic assessment of jailed side branch lesions using fractional flow reserve. J Am Coll Cardiol. 2005;46(4):633-7.

40. Erglis A et al. Randomized comparison of coronary bifurcation stenting with the crush versus the Culotte technique using sirolimus eluting stents: the Nordic stent technique study. Circ Cardiovasc Interv. 2009;2:27-34.

CURRENT STATUS AND FUTURE PERSPECTIVES ON DRUG-ELUTING BIORESORBABLE CORONARY SCAFFOLDS: WILL THE PARADIGM OF PCI SHIFT?

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ABSTRACT

Despite improvements in stent platform, polymer, and drug elution, the permanent metallic stents have significant limitations as they distort vessel physiology, predispose to late thrombosis, and may preclude surgical revascularisation. Bioresorbable scaffold (BRS) technology has evolved over the last few years to overcome these drawbacks. Actually, different BRS are either available or under clinical and preclinical investigation. However, the use of BRS has largely been restricted to patients recruited into clinical trials with a relatively small number of 'real-world' patients treated with these devices. Here, we highlight the potentialities of these devices, describe the evidence from the recent clinical trials, and discuss the potential advantages as well as challenges that this novel technology may face in routine clinical practice.

Keywords: Bioresorbable scaffolds, drug-eluting stents, coronary angioplasty.

INTRODUCTION

The landscape of percutaneous coronary intervention (PCI) has evolved dramatically over the last 35 years. At the beginning, plain old balloon angioplasty (POBA) revolutionised the treatment of coronary artery disease (CAD). However, the outcomes following POBA were compromised by re-narrowing due to elastic recoil, abrupt coronary occlusion secondary to severe dissection, and neointimal hyperplasia.[1-3] Metallic stents were developed to overcome these issues and the two landmark trials, BENESTENT and STRESS, demonstrated the superiority of the bare-metal stents (BMS) over POBA and established BMS as second revolution in coronary intervention.[4,5] However, the medium and long-term results after BMS implantation showed a high incidence of in-stent restenosis.[6] The introduction of drug-eluting stents (DES) that were developed by coating BMS with anti-proliferative drugs (i.e. sirolimus or paclitaxel) significantly reduced in-stent restenosis and target lesion revascularisation (TLR) rates compared to BMS.[7,8] DES, considered the third revolution in interventional cardiology, broadened the applications of PCI, particularly in complex subsets of lesions and high-risk patients.[9,10]

However, first-generation DES were associated with an increased risk of stent thrombosis (ST),[11,12] but newer-generation DES, with thinner struts and biocompatible or biodegradable polymers, have a considerably improved safety profile.[13-15] Although DES technology seems to cover the needs of the interventional cardiologists, it cannot be considered the optimal solution as it leaves a permanent cage inside the vessel that could be associated with potential future problems.

The presence of a foreign body within the artery wall can be a source of chronic vessel wall inflammation and may interfere with the endothelial function, thus delaying the vessel wall healing that is associated with a higher risk of ST.[16-18] In addition, it has been demonstrated that stent implantation has an unfavourable effect on the geometry of curved arteries, increasing the risk for neointima hyperplasia.[19] Furthermore, the increased

rigidity of the stent may alter the pulsatile profile of the blood flow, affecting the shear stress within the stent.[20] Another important drawback of the metallic stents is the risk to preclude surgical revascularisation when implanted in a potential "anastomotic" segment of the coronary tree. Thus, the ideal solution would be a transient bioresorbable scaffold (BRS) that would initially maintain the vessel open and then it would disappear, allowing the vessel to return to its natural state whilst maintaining access for future surgical revascularisation, if required. The absence of a rigid permanent cage may result in restoration of endothelial function and shear stress, reducing the risk of late events and favouring positive remodelling of the vessel. These benefits may also result in reduced need for long-term dual anti-platelet therapy (DAT). Furthermore, BRS are an ideal device for allowing an eventual future non-invasive functional/morphological assessment (i.e. by the computed tomographic coronary angiography associated with myocardial perfusion scan or the non-invasive fractional flow-reserve) of the treated vessel as, in contrast to the traditional stents, they do not produce artifacts.[21]

Today, several BRS are available but only two devices have acquired Conformité Européenne (CE) mark approval and only one is currently used in clinical practice. Here, we provide a brief overview of the available (under development, under preclinical validation, or undergoing clinical trials) drug-eluting BRS and discuss the potential additional advantages and limitations that these devices may have in everyday clinical practice.

DRUG-ELUTING BRS

ABSORB Bioresorbable Vascular Scaffold (BVS)

The ABSORB® BVS (Abbott Vascular, Santa Clara, CA, USA) is comprised of semicrystalline poly L-lactic acid (PLLA) coated with amorphous poly-D,L-lactide (PDLA) polymer-eluting everolimus. Degradation of the bioresorbable components (PLLA and PDLA) of the scaffold is mainly through hydrolysis, followed by macrophage phagocytosis of the resulting degradation products, a process that is completed within 3 years.[22] Two versions of the BVS have been assessed in clinical trials. The safety and feasibility of the BVS 1.0 was tested in the open-label prospective 'A bioresorbable everolimus eluting coronary stent system for patients with single *de novo* coronary artery lesions (ABSORB) Cohort A' trial.[23] At 6 months, the angiographic in-stent late lumen loss (LLL) was 0.44 mm with evidence of scaffold shrinkage (-11.8%) as measured by intravascular ultrasound (IVUS). However, vasomotion appeared to be restored, with induced vasoconstriction and vasodilatation possible in the treated segment.[24] To prolong the mechanical BVS strength and reduce late recoil, a second-generation BVS (1.1) has been introduced. Of note, BVS 1.1 has a smaller maximum circular unsupported surface area,[25] a more uniform strut distribution, and improved stent retention. Importantly, these changes have not resulted in an increased amount of polymeric material or an increase in strut thickness. Proprietary process changes have been implemented to increase radial strength. In addition, these changes have reduced polymer degradation rates at early time points, and thus prolonged mechanical integrity of the scaffold throughout the first few months following implantation.[26]

The efficacy of the BVS 1.1 was assessed in the ABSORB Cohort B trial, which recruited 101 patients with single or two-vessel *de novo* disease all receiving a 3x18 mm BVS. At 6-month follow-up, there was only one TLR, while LLL was 0.19±0.18 mm; at 2-year follow-up, LLL was 0.27±0.20 mm. The scaffold area progressively increased during follow-up, although at 6-months there was significant reduction in minimal lumen area (MLA) on IVUS as compared with baseline (6.60±1.22 to 6.37±1.12 mm^2, $p<0.005$).[24] Furthermore, at 2-year angiographic follow-up no differences in LLL (0.29±0.16 versus 0.25±0.22 mm, p=0.439) were noted between small (reference vessel diameter [RVD] <2.5 mm) and large vessels (≥2.5 mm).[27] The recently published 3-year multimodality imaging observations of the ABSORB Cohort B trial showed interesting results. On IVUS, mean lumen and scaffold area remained stable between 2 and 3 years, whereas significant reduction in plaque behind the struts occurred with a trend toward adaptive restrictive remodelling of external elastic membrane. Hyperechogenicity of the vessel wall, a surrogate of the bioresorption process, decreased from 23.1% to 10.4% with a reduction of radiofrequency backscattering for dense calcium and necrotic core. The count of strut cores detected on optical coherence tomography (OCT) increased significantly, likely reflecting the dismantling of the scaffold, while 98% of struts were covered. At 3-year follow-up, there were seven (7%) ischaemia-driven TLR and three (3%) non-ST segment

elevation myocardial infarctions (MI). The major adverse cardiovascular event (MACE) rate was 10.0% without any scaffold thrombosis.[28]

Data regarding the use of ABSORB® in everyday practice are also becoming available. The prospective, single-centre, BVS Expand registry - examining the use of ABSORB® in routine clinical practice, with the exception of patients with ST-elevation MI (STEMI) and restenotic lesions - was associated with one (0.7%) MI and one (0.7%) non-target vessel revascularisation (TVR) at 30-day follow-up in a cohort of 131 patients.[29] Recently, Gori et al.[30] reported the outcome following ABSORB® implantation in 150 patients (194 lesions) with acute coronary syndromes compared with a control group composed of 103 consecutive patients (129 lesions) who underwent everolimus DES implantation in the same time period. In-hospital, 30-day, and 6-month MACE rates were similar between both groups (all p>0.5), while definite or probable in-stent/scaffold thrombosis occurred in two BVS patients (1.3%) and one (0.9%) DES patient during the index admission, and it occurred in another patient in each group in the first month after BVS/DES implantation.

The recently published BVS STEMI first study is a prospective, single-arm, single-centre study, reporting data following BVS implantation in 49 STEMI patients. The procedural success was 97.9%, while no patients had angiographically-visible residual thrombus at the end of the procedure. OCT analysis (performed in 31 patients) showed that mean percentage of malapposed struts per patient was 2.80±3.90%. At 30-day follow-up, target-lesion failure (TLF) rate was 0% and no death or scaffold thrombosis were reported.[31] Other interesting results in the STEMI subset come from the Prague-19 multicentre study where 40 patients undergoing primary PCI were evaluated. The 6-month survival free from death, MI or TVR was 95%, while an OCT substudy (performed on 21 patients) demonstrated only a 1.1% rate of scaffold struts malapposition.[32]

More, ongoing studies are currently evaluating the BVS 1.1. The ABSORB Extend study is recruiting 1,000 patients worldwide with *de novo* single or two-vessel disease. It allows the recruitment of patients with diseases in smaller vessels (>2.0 mm) as well as those with long lesions, thus giving the opportunity to evaluate the BVS performance in both these groups. An interim report on the 24-month clinical outcomes from the first 250 patients enrolled showed MACE and target vessel failure (TVF) rates of 4.4% and 4.8%, respectively.[33] Recently, the first 450 patients enrolled in this trial have completed a 12-month follow-up, and an interim report presented seven cases (1.5%) of device failure.[34] In particular, scaffold dislodgement occurred in three (0.67%) cases, while subacute or late scaffold thrombosis occurred in four (0.89%) cases.

The prospective, randomised ABSORB II study, on the other hand, will compare BVS 1.1 to the XIENCE® PRIME everolimus-eluting stent (Abbott Vascular) in patients with stable angina and single or two-vessel disease. The trial is expected to be completed in 2015. The multicentre randomised ABSORB III trial will aim to recruit over 2,000 patients with up to two *de novo* lesions in different epicardial vessels (vessel diameter 2.5–3.75 mm, length ≤24 mm) and randomise these to BVS 1.1 or XIENCE® PRIME. Finally, the ABSORB IV study will aim to add another 4,000 patients to ABSORB III in order to assess for BVS 1.1 superiority over XIENCE® PRIME with regards to TLF between 1 and 5 years.

The Amsterdam Investigator-initiateD Absorb strategy All-comers trial (AIDA trial) is a prospective, randomised (1:1), active-control, single-blinded, all-comer, non-inferiority study. About 2,690 all-comer subjects will be enrolled in order to evaluate the efficacy and performance of the ABSORB® BVS versus the Xience® family in the treatment of coronary lesions. The study population includes both simple and complex lesions, in patients with stable and acute coronary syndromes. The follow-up continues for 5 years and the primary end point of the trial is TVF, defined as the composite of cardiac death, MI, and TVR at 2-year follow-up.[35]

DESolve® BRS

The DESolve® BRS (Elixir Medical, Sunnyvale, CA, USA) is made from a PLLA-based polymer eluting novolimus, a major metabolite of sirolimus. The DESolve® is designed to be fully resorbed within 2 years. In the first-in-man (FIM) study, 15 patients with lesion length <10 mm and RVD 2.75–3.00 mm underwent DESolve® implantation with 14 patients completing 6-month follow-up angiography. Quantitative coronary angiography (QCA) analysis at 6-months showed reasonable in-scaffold LLL (0.19±0.19 mm) with OCT showing

low neointimal hyperplasia. At 1-year follow-up, one cardiac death, one target vessel MI, and one TLR occurred with no scaffold thrombosis. Multi-slice computed tomography (CT) at 12-months showed continued neointimal suppression and vessel patency.[36] The subsequent multicentre, prospective DESolve® Nx trial enrolled 126 patients worldwide. The principal imaging end point was in-scaffold LLL as assessed by QCA at 6-months. The main inclusion angiographic criteria were RVD 2.75–3.5 mm and lesion length ≤14 mm. At 6-month follow-up, MACE rate was 3.3%, with two cases of TLR and no cases of scaffold thrombosis. DESolve® BRS has recently achieved a CE mark.

Bioresorbable Magnesium BRS

Magnesium is the lightest structural metal. The strength-to-weight ratio of precipitation-hardened magnesium alloys is comparable with that of strong aluminium alloys and alloy steels.[37] Consequently, a magnesium BRS has the potential to provide a high radial strength for dilating atherosclerotic narrowing and, hence, higher acute gain of coronary lumen. Another virtue of magnesium as an endoprosthesis is its electrochemical properties. Magnesium is more electronegative than other metals used for implants and has shown anti-thrombogenic properties *in vivo*.[38-40] The bioresorbable magnesium scaffold is manufactured by BIOTRONIK (Berlin, Germany). The scaffold is balloon expandable, composed by magnesium (Mg) alloy, and has two radiopaque markers (proximal and distal end of the balloon) to facilitate positioning.

The first generation absorbable metallic stent (AMS I) was associated with a 40% TLR rate within the first 4 months and with an angiographically reported LLL (1.08±0.49mm) unacceptably high.[41,42] IVUS demonstrated that most of the AMS-I has been resorbed within 4 months, thus, the increased event rate and recoil were attributed to inappropriate support due to the fast resorption of the AMS. Second-generation devices, AMS-II and AMS-III, have since been designed with different Mg alloys and slower degradation times. The AMS-III DREAMS (DRug Eluting AMS) possessed a biodegradable matrix that eluted paclitaxel. The FIM, BIOSOLVE-I, enrolled 46 patients with *de novo* lesions ≤12 mm and RVD 3.0–3.5 mm. At 12-month follow-up, TLF was 7.0% and TLR rate was 4.7%; LLL was 0.52±0.39 mm. Vasomotion was shown to be restored by 6 months with no changes at 1 year. The 2-year clinical outcomes presented at EuroPCR 2013 showed that TLF and TLR remained stable between 12 and 24 months and no cardiac death or scaffold thrombosis were observed.[43] DREAMS has since been modified to DREAMS-II, which possesses tantalum radiopaque end-markers and elutes sirolimus instead of paclitaxel. The FIM study to assess DREAMS-II, BIOSOLVE-II, is currently recruiting patients to get the data needed to apply for CE mark.

IDEAL™ BRS

The IDEAL™ BRS (Xenogenics Corporation, Canton, MA, USA) is the only scaffold incorporating salicylate directly into the polymer chain. As the polymer degrades, salicylate and sirolimus are released, thereby reducing inflammation and platelet aggregation. The first-generation IDEAL™ BRS device required an 8-Fr guide catheter. It was associated with a larger-than-expected reduction in lumen area, likely due to insufficient neointimal suppression.[44] This was attributed to inadequate drug dosing and rapid drug release. The second-generation IDEAL™ BRS addressed these issues by incorporating a higher drug dose, a slower release pattern, and a 6-Fr compatible delivery system. The device is currently undergoing preclinical evaluation.[45]

ReZolve BRS

The ReZolve® BRS (REVA® Medical Inc., San Diego, CA, USA) consists of a tyrosine-based polymer, resorption of which takes 18–24 months to complete. The first-generation of this device was associated with a high rate of 1-year adverse clinical outcomes (66.6% TLR and 11.1% MI) that led to the redesign of the scaffold.[46] The current ReZolve® consists of a more resilient polymer that incorporates sirolimus. It also has a unique slide and spiral lock mechanism, which reduces acute recoil and provides better radial support. The ReZolve® BRS is undergoing clinical evaluation in the ReZolve® Sirolimus-Eluting Bioresorbable Coronary Scaffold (RESTORE) trial, which aims to recruit 50 patients with *de novo* CAD. A further CE Mark multicentre study with ReZolve®2 (a sheathless, lower profile device that can be delivered through a 6 Fr sheath), the RESTORE-II (Safety and Performance of the ReZolve®2 Sirolimus-Eluting Bioresorbable Coronary Scaffold) has recently completed the enrolment. The immediate and mid-term follow-up results of the patients enrolled in the trial will be presented in May at EuroPCR 2014.

Drug-Eluting BRS Under Preclinical Investigation

The ON-AVS (OrbusNeich Medical, Fort Lauderdale, FL, USA) differs from other drug-eluting BRS as it incorporates CD34+ antibodies for endothelial progenitor cell capture.[47] This aims to promote and achieve faster endothelialisation. The drug eluted is sirolimus. The Xinsorb BRS™ (Huaan Biotechnology Group, Laiwu, China) is made of PLLA and elutes sirolimus. Other BRS under development include: the Sahajanand BRS (Sahajanand Medical Technologies, Pvt, Ltd, India), the Avatar BRS (S3V; Vascular Technologies Pvt. Ltd., Bangalore, Karnataka, India), the FADES BRS (Zorion Medical Inc., USA), Stanza BRS (480 Biomedical, MA, USA), Arterius BRS (Arterius Ltd, Bradford, UK), and the MeRes BRS (Meril Life Science, Vapi, Gujarat, India).[48] Main characteristics of the most recent drug-eluting BRS under preclinical and clinical evaluation are summarised in Table 1.

From Clinical Trials to Clinical Practice

BRS may theoretically improve clinical outcomes in patients requiring revascularisation since the absence of a permanent metallic cage in the vessel wall may reduce chronic injury, predisposing to restenosis and ST. Currently available data have shown the complete biodegradation of the device at follow-up,[49,50] vessel remodelling with lumen gain over time,[49] and signs of physiological vasomotion of the 'scaffolded' coronary segment.[24,50] Furthermore, promising results have been shown in patients with simple lesions at different follow-up periods up to 5 years (Table 2).[36,49-51]

To date, the ABSORB is the only scaffold commercially available and the only one that has been used in everyday clinical practice. However, the experience with ABSORB was initially limited to younger patients with AHA/ACC Type A or B lesions in moderate-sized vessels.[52] Thus, there have been very limited data about the ABSORB

Table 1: Main characteristics of the most recent drug-eluting bioresorbable coronary scaffolds under preclinical and clinical evaluation.

Scaffold	Strut Material	Drug-Eluted	Strut Thickness (μm)	Radial Support Duration	Bioresorption Period (months)	Status
ABSORB® 1.1 (Abbott Vascular)	Poly-L-Lactide	Everolimus	150	3 months	24-48	CE mark approval acquired
AMS®-3 DREAMS (Biotronik SE)	Magnesium alloy	Paclitaxel	120	3-6 months	9	Under clinical evaluation
DREAMS® 2 (Biotronik SE)	Magnesium alloy	Sirolimus	120	3-6 months	9	Under development
DESolve® (Elixir)	Poly-L-Lactide	Novolimus	150	3-6 months	12-24	CE mark approval acquired
REVA® ReZolve (REVA medical)	Tyrosine-derived polycarbonate	Sirolimus	122	4-6 months	4-6	On clinical studies
IDEAL® Generation II (Xenogenics)	Polyanhydride ester with salicylate	Sirolimus, Salicylate	175	3 months	6-9	On clinical trials
Xinsorb™ (Huuan Biotech)	Poly-L-Lactid Acid	Sirolimus	160	-	-	On preclinical studies
ON-AVS (Orbus Neich)	3 x Lactide polymers	Sirolimus/ CD34+	150	6 months	>6	On preclinical studies

AMS: absorbable metallic stent; CE: Conformité Européenne.

Table 2: Main bioresorbable vascular scaffold clinical trials.

Scaffold	Clinical Study	Number of Patients	End Point	Late Loss (mm)	TLR (%)	MACE (%)
ABSORB® 1.0	ABSORB Cohort A	30	Procedural success, 5-year MACE	0.44 at 6 months	0 at 5 years	3.4 at 5 years
ABSORB® 1.1	ABSORB Cohort B	101	LLL, TLR, and MACE at 6 months, 1, 2, and 3 years	0.27 at 12 months	3.6% at 12 months	10% at 3 years
AMS®-3 DREAMS	BIOSOLVE-I	46	TLF at 6 and 12 months	0.64 at 6 month 0.52 at 12 months	4.3% at 6 months 6.5% at 12 months	4.3% at 6 months 6.5% at 12 months
DESolve®	DESolve 1	15	LLL at 6 months	0.19 at 6 months	6.7% at 12 months	20% at 12 months
	DESolve Nx	120	Procedural success, LLL at 6 months, and 5-year MACE	0.21 at months	1.6% at 6 months	3.25% at 6 months
REVA®	RESORB	27	MACE	1.81 at 6 months	66.7% at 6 months	-
REVA® ReZolve	RESTORE	50	TLR at 6 months, LLL at 12 months	0.20 at 12 months	2 of 12 at 6 months	2 of 12 at 6 months

LLL: late lumen loss; MACE: major adverse cardiac events; TLR: target lesion revascularisation; TLF: target lesion failure.

performance in complex lesions such as bifurcations, chronic total occlusions, calcified lesions, diffuse disease-requiring overlapping scaffolds, and restenosis, as well as in complex patients such as diabetics with or without multi-vessel disease.

Preliminary real-world data on the outcome following BVS implantation in coronary bifurcation lesions were presented at the Transcatheter Cardiovascular Therapeutics Congress 2013. Most of the lesions were true bifurcations while provisional approach was the default strategy (80-85% of the cases). Angiographic success was obtained in 98-99% of cases, TLR was about 3%, and no scaffold thrombosis was reported up to 6-months follow-up. Aggressive, intravascular-imaging (OCT or IVUS) guided post-dilatation (≥20 atm) was performed in all the BVS implanted in the main branch (MB), while final simultaneous balloon inflation was performed, only if required for clinical reasons, at low pressure with minimal protrusion of the side branch (SB) balloon (final 'snuggle'). No scaffold disruption was reported after simultaneous balloon inflation. The T and minimal protrusion (TAP) technique was the strategy for SB stenting as crossover from provisional, and it was usually performed with a conventional DES since a BVS may not pass through the MB struts. T-stenting was the preferred technique for elective double-stenting with BVS in order to avoid overlapping scaffolds (Figure 1).[53] Although complex double-stenting bifurcation techniques using the BVS platform in both MB and SB appear feasible, their use should be carefully evaluated and eventually limited to patients with large-calibre main vessels.[54,55]

The feasibility of BVS implantation in the setting of long, fibro-calcific lesions is limited to case reports.[56,57] Considering the relatively high BVS profile and the lower radial strength compared to a conventional DES, some points (i.e. an appropriate lesion evaluation with intravascular imaging, a

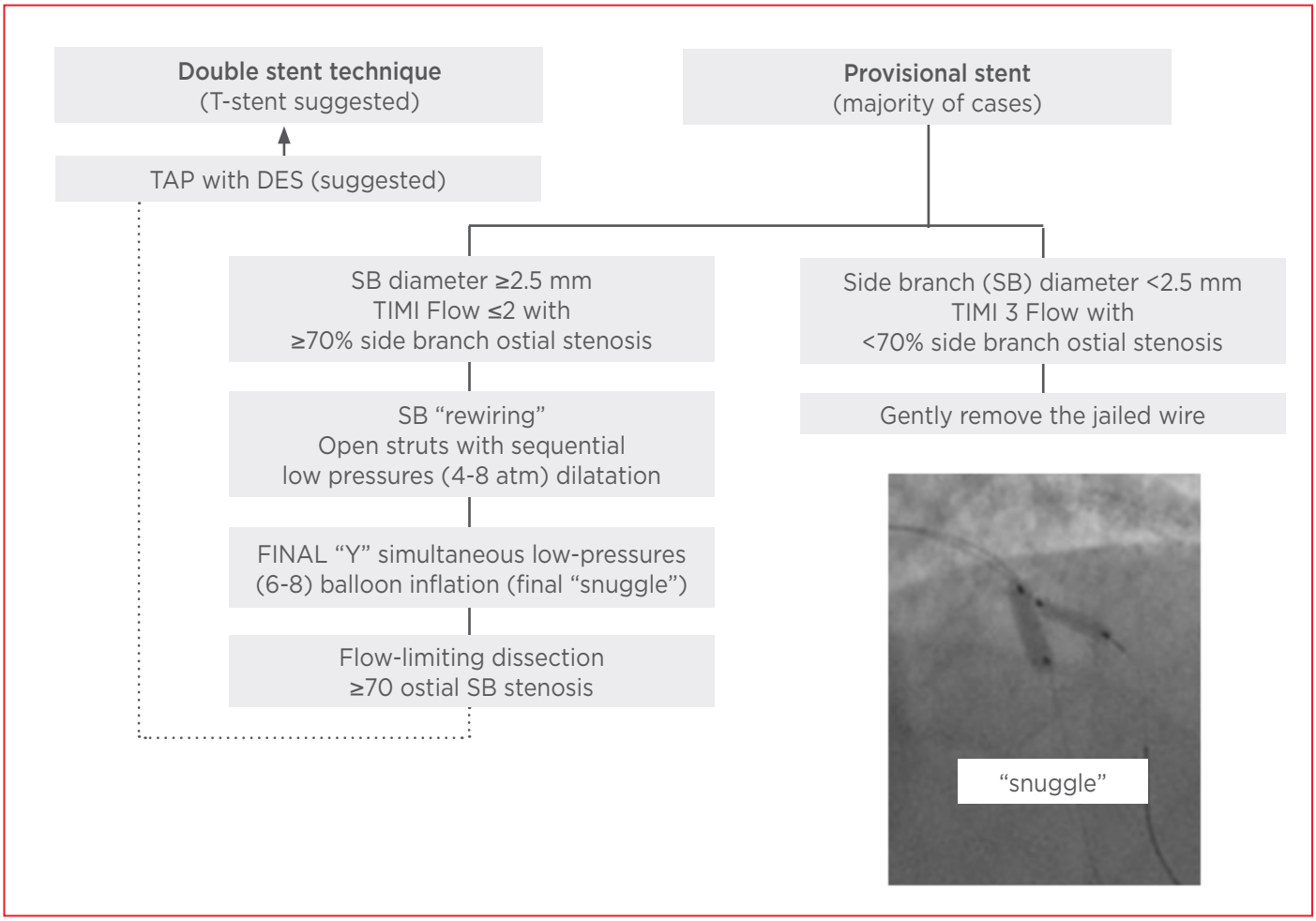

Figure 1: Algorithm for bifurcation lesion treatment with ABSORB.
TAP: T and minimal protrusion; DES: drug-eluting stents; SB: side branch; TIMI: thrombolysis in myocardial infarction.

7F guiding catheter, an extra support guidewire, an aggressive lesion preparation using scoring balloons or rotational atherectomy, or a bail-out enhanced back-up support using guide catheter extension systems) appear essential in order to successfully deploy and expand BVS in this complex subset of lesions. However, it is important to highlight that the friction that could be encountered between the thick (156 μm) polymeric BVS and a tortuous/calcified vessel or a daughter catheter (i.e. Guideliner) may result in BVS dislodgement when forcefully pushing the scaffold.[34]

Early, preliminary 'real-world' experience with ABSORB[34,58] may allow us to draw suggestions on which patients/lesions are best suited for these devices. Aside from simple lesions, patients with long diffuse left anterior descending disease and those requiring multi-vessel revascularisation are interesting candidates for ABSORB, as the eventual resorption of the BVS reduces stent length as well as sparing from a 'full metal jacket', both of which can predispose to ST and restenosis (Figure 2).[59] This is particularly important for younger patients since such an approach does not only maintain access for future bypass graft surgery if required, but also offers the possibility of further PCI treatment without the additional permanent metallic layers. However, it is important to remember that there are no published data regarding clinical outcomes in complex lesions treated with BVS.[58] The importance of intravascular imaging, pre and post-dilatation, in optimising scaffold implantation and expansion should not be underestimated, particularly in the case of complex lesions (i.e. bifurcations, long lesions, calcified plaques) where the scaffold under-expansion may be associated with sub-acute or late thrombotic events. However, the importance of meticulous procedural technique cannot be overemphasised;

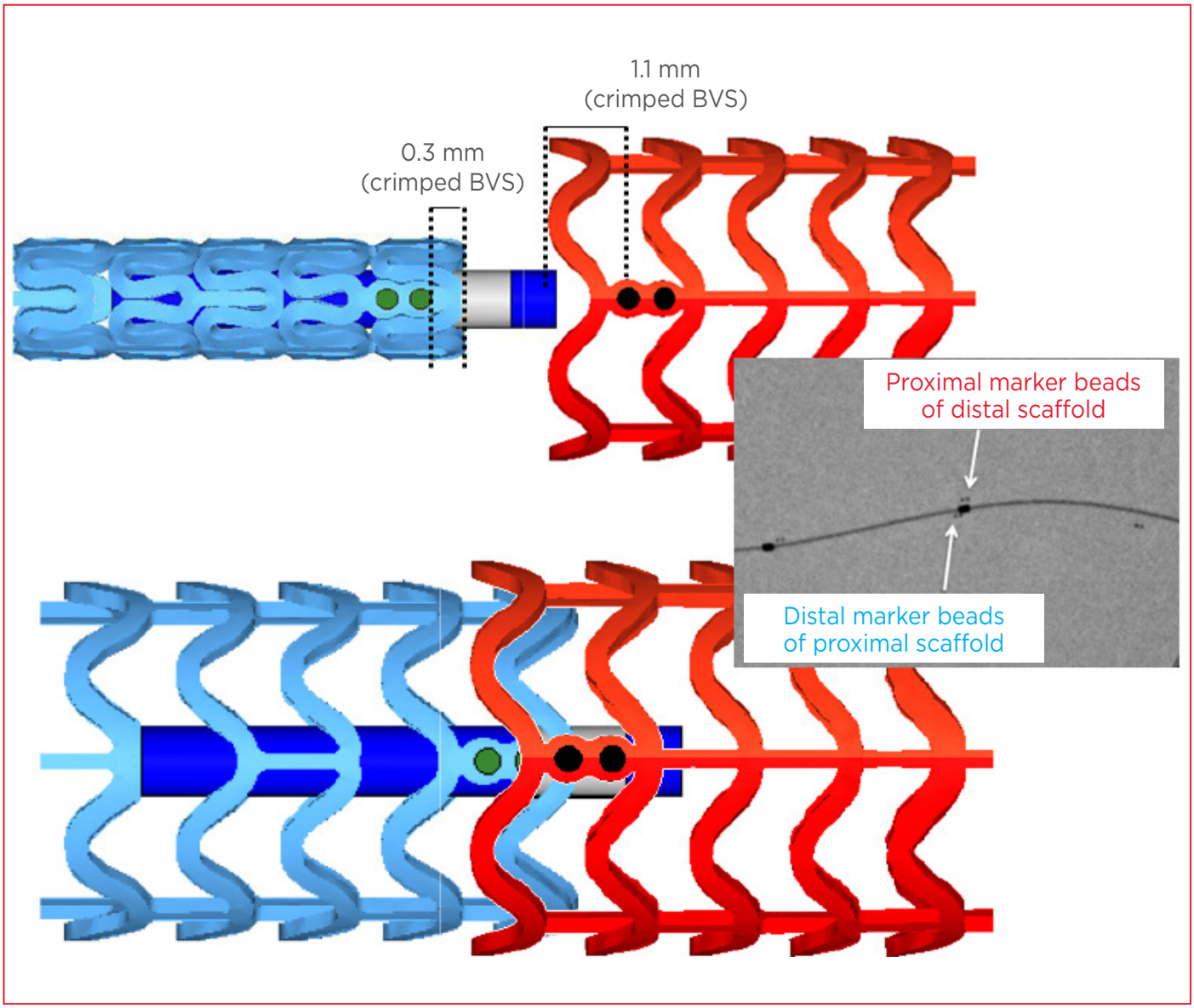

Figure 2: Consideration for overlapped ABSORB implantation.
To avoid 'geographical miss', without overlap or too much overlap, the following strategy is suggested: 1) advance the second scaffold system until the distal balloon marker lines up with the proximal marker beads of the implanted scaffold; 2) the markers of the second scaffold will be adjacent to the markers of the deployed scaffold (scaffold marker to scaffold marker); 3) the result will be about 1 mm of BVS overlap. BVS: bioresorbable vascular scaffold.

it should take longer to implant a BVS as compared to a conventional DES.

CONCLUSION

BRS have been heralded as the fourth revolution in interventional cardiology. This novel technology not only provides transient scaffolding and restores flow in the diseased segment but also restores vascular integrity and function. Over recent years, huge improvements have been made in the field of BRS, with encouraging data emerging from their use in clinical practice. The current results have provided promise for the future, although data regarding their use in complex lesions and long-term clinical outcomes in the 'real world' are lacking. The message that arises from their first applications is that BRS should not be considered as another type of stent but as a totally different device that has special strengths, weaknesses, and limitations, and also one that introduces a novel therapeutic potential. This field is an exciting area where further improvements will advance PCI practice.

REFERENCES

1. Grüntzig AR et al. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med. 1979;301(2): 61-8.

2. Sigwart U et al. Emergency stenting for acute occlusion after coronary balloon angioplasty. Circulation. 1988;78(5 Pt 1):1121-7.

3. Roubin GS et al. Influence of balloon size on initial success, acute complications, and restenosis after percutaneous transluminal coronary angioplasty. A prospective randomized study. Circulation. 1988;78(3):557-65.

4. Serruys PW et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med. 1994;331(8):489-95.

5. Fischman DL et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med. 1994;331(8):496-501.

6. Al Suwaidi J et al. Coronary artery stents. JAMA. 2000;284(14):1828-36.

7. Morice MC at al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002;346(23):1773-80.

8. Stone GW et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350(3):221-31.

9. Stone GW et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA. 2005;294(10):1215-23.

10. Sabaté M et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. Circulation. 2005;112(14):2175-83.

11. McFadden EP et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet. 2004;364(9444):1519-21.

12. Lagerqvist B et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. N Engl J Med. 2007;356(10):1009-19.

13. Stone GW et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med. 2010;362(18):1663-74.

14. Stefanini GG et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. Lancet. 2011;378(9807):1940-8.

15. Iqbal J et al. Incidence and predictors of stent thrombosis: a single-centre study of 5,833 consecutive patients undergoing coronary artery stenting. EuroIntervention. 2013;9(1):62-9.

16. König A et al. Influence of stent design and deployment technique on neointima formation and vascular remodeling. Z Kardiol. 2002;91 Suppl 3:98-102.

17. Joner M et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol. 2006;48(1):193-202.

18. Guo N et al. Incidence, mechanisms, predictors, and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial infarction. An intravascular ultrasound substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. Circulation. 2010;122(11):1077-84.

19. Wentzel JJ et al. Coronary stent implantation changes 3-D vessel geometry and 3-D shear stress distribution. J Biomech. 2000;33(10):1287-95.

20. Gijsen FJ et al. Usefulness of shear stress pattern in predicting neointima distribution in sirolimus-eluting stents in coronary arteries. Am J Cardiol. 2003;92(11):1325-8.

21. Bourantas CV et al. Bioresorbable scaffolds: current knowledge, potentialities and limitations experienced during their first clinical applications. Int J Cardiol. 2013;167(1):11-21.

22. Oberhauser JP et al. Design principles and performance of bioresorbable polymeric vascular scaffolds. EuroIntervention. 2009;5 Suppl F:F15-22.

23. Ormiston JA et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet. 2008;371(9616):899-907.

24. Serruys PW et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet. 2009;373(9667):897-910.

25. Okamura T et al. In vivo evaluation of stent strut distribution patterns in the bioabsorbable everolimus-eluting device: an OCT ad hoc analysis of the revision 1.0 and revision 1.1 stent design in the ABSORB clinical trial. EuroIntervention. 2010;5(8):932-8.

26. Brugaletta S et al. Comparison between the first and second generation bioresorbable vascular scaffolds: a six month virtual histology study. EuroIntervention. 2011;6(9):1110-6.

27. Diletti R et al. Clinical and intravascular imaging outcomes at 1 and 2 years after implantation of absorb everolimus eluting bioresorbable vascular scaffolds in small vessels. Late lumen enlargement: does bioresorption matter with small vessel size? Insight from the ABSORB cohort B trial. Heart. 2013;99(2):98-105.

28. Serruys PW et al. Dynamics of vessel wall changes following the implantation of the Absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study at 6, 12, 24 and 36 months. EuroIntervention. 2013.

29. Van Geuns R. BVS Expand: first result of wide clinical applications of bioresorbable vascular scaffold. Presented at: EuroPCR. Paris, France, 21–24 May 2013.

30. Gori T et al. Early outcome after implantation of absorb bioresorbable drug-eluting scaffolds in patients with acute coronary syndromes. EuroIntervention. 2013. [Epub ahead of print].

31. Diletti R et al. Everolimus-eluting bioresorbable vascular scaffolds for treatment of patients presenting with ST-segment elevation myocardial infarction: BVS STEMI first study. Eur Heart J. 2014. [Epub ahead of print].

32. Kocka V et al. Bioresorbable vascular scaffolds in acute ST-segment elevation myocardial infarction: a prospective multicentre study 'Prague 19'. Eur Heart J. 2014. [Epub ahead of print].

33. Whitbourn R. ABSORB EXTEND: an interim report on the 24-month clinical outcomes from the first 250 patients enrolled. J Am Coll Cardiol. 2013;62 (18 S1):B11.

34. Ishibashi Y et al. Lessons learned from acute and late scaffold failures in the ABSORB EXTEND trial. EuroIntervention. 2014. [Epub ahead of print].

35. Woudstra P et al. Amsterdam Investigator-initiateD Absorb strategy all-comers trial (AIDA trial): a clinical evaluation comparing the efficacy and performance of ABSORB everolimus-eluting bioresorbable vascular scaffold strategy vs the XIENCE family (XIENCE PRIME or XIENCE Xpedition) everolimus-eluting coronary stent strategy in the treatment of coronary lesions in

consecutive all-comers: Rationale and study design. Am Heart J. 2014;167(2): 133-40.

36. Verheye S et al. A next-generation bioresorbable coronary scaffold system-from bench to first clinical evaluation: six- and 12-month clinical and multimodality imaging results. JACC Cardiovasc Interv. 2013;doi:10.1016/j.jcin.2013.07.007. [Epub ahead of print].

37. Campos CM et al. Bioresorbable drug-eluting magnesium-alloy scaffold for treatment of coronary artery disease. Int J Mol Sci. 2013;14(12):24492-500.

38. Anstall HB et al. The effect of magnesium on blood coagulation in human subjects. Lancet. 1959;1(7077): 814-5.

39. Rukshin V et al. Comparative antithrombotic effects of magnesium sulfate and the platelet glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide in a canine model of stent thrombosis. Circulation. 2002;105(16):1970-5.

40. Moravej M, Mantovani D. Biodegradable metals for cardiovascular stent application: interests and new opportunities. Int J Mol Sci. 2011;12(7):4250-70.

41. Nishio S et al. Long-Term (>10 Years) clinical outcomes of first-in-human biodegradable poly-l-lactic acid coronary stents: Igaki-Tamai stents. Circulation. 2012;125(19):2343-53.

42. Ghimire G et al. Initial evidence for the return of coronary vasoreactivity following the absorption of bioabsorbable magnesium alloy coronary stents. EuroIntervention. 2009;4(4):481-4.

43. Haude M. Progress with Drug-eluting Magnesium Resorbing Stents (BIOTRONIK dreams program): DREAMS 2-Year Results. Presented at: Transcatheter Cardiovascular Therapeutics (TCT) Conference. Miami, FL, USA, 22–26 October 2012.

44. Jabara R et al. Novel fully bioabsorbable salicylate-based sirolimus-eluting stent. EuroIntervention. 2009;5 Suppl F:F58-64.

45. Jabara R. Bio-mechanical properties and ABC of bioresorption of adipic acid. Presented at: PCR Focus Group on Bioresorbable Vascular Scaffolds. Rotterdam, the Netherlands, 8–9 March 2012.

46. Grube E. Bioabsorbable Stent. The Boston Scientific and REVA Technology. Presented at: EuroPCR. Barcelona, Spain, 19–22 May 2009.

47. Cottone RJ et al. OrbusNeich fully absorbable coronary stent platform incorporating dual partitioned coatings. EuroIntervention. 2009;5 Suppl F:F65-71.

48. Costopoulos C et al. Looking into the future with bioresorbable vascular scaffolds. Expert Rev Cardiovasc Ther. 2013;11(10):1407-16.

49. Ormiston JA et al. First serial assessment at 6 months and 2 years of the second generation of absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study. Circ Cardiovasc Interv. 2012;5(5):620-32.

50. Haude M et al. Safety and performance of the drug-eluting absorbable metal scaffold (DREAMS) in patients with de-novo coronary lesions: 12 month results of the prospective, multicentre, first-in-man BIOSOLVE-I trial. Lancet. 2013;381(9869):836-44.

51. Onuma Y et al. Five-year clinical and functional multislice computed tomography angiographic results after coronary implantation of the fully resorbable polymeric everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB cohort A trial. JACC Cardiovasc Interv. 2013;6(10): 999-1009.

52. Liang M et al. Initial experience in the clinical use of everolimus-eluting bioresorbable vascular scaffold (BVS) in a single institution. Int J Cardiol. 2013;168(2):1536-7.

53. Naganuma T et al. Bioresorbable Vascular Scaffold Use in Coronary Bifurcation Lesions. Presented at: Transcatheter Cardiovascular Therapeutics. San Francisco, USA. 27 October – 1 November 2013.

54. Costopoulos C et al. Optical coherence tomography of a bifurcation lesion treated with bioresorbable vascular scaffolds with the "mini-crush" technique. JACC Cardiovasc Interv. 2013;6(12): 1326-7.

55. Dzavik V, Colombo A. The absorb bioresorbable vascular scaffold in coronary bifurcations: insights from bench testing. JACC Cardiovasc Interv. 2013;7(1):81-8.

56. Basavarajaiah S et al. Can bioabsorbable scaffolds be used in calcified lesions? Catheter Cardiovasc Interv. 2013;doi:10.1002/ccd.24939. [Epub ahead of print].

57. Ielasi A, Anzuini A. Guide-catheter extension system facilitated multiple bioresorbable vascular scaffolds (ABSORB®) delivery in a very long and resistant coronary artery lesion. Cardiovasc Revasc Med. 2013;doi:10.1016/j.carrev.2013.08.004. [Epub ahead of print].

58. Latib A et al. Which patients could benefit the most from bioresorbable vascular scaffold implant: from clinical trials to clinical practice. Minerva Cardioangiol. 2013;61(3):255-262.

59. Colombo A, Latib A. Can long-term results following balloon angioplasty be the "crystal ball" to predict outcome following bioresorbable vascular scaffolds? J Am Heart Assoc. 2012;1(5):e005272.

BIORESORBABLE SCAFFOLDS FOR CARDIOVASCULAR TISSUE ENGINEERING

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ABSTRACT

Cardiovascular disease is a major cause of morbidity and mortality, especially in developed countries. Currently, when suitable autologous tissue is lacking, mostly non-degradable synthetic material or fixated xenogeneic grafts (e.g. heart valves) are used to restore, repair, or replace the injured cardiovascular tissues. However, these materials are associated with several disadvantages, such as the significant risk of thromboembolism and calcification. Bioresorbable scaffolds for tissue-engineered solutions are proposed to overcome the limitations of the current replacement materials as they provide temporary scaffolding for the *in vitro*, *in situ*, or *in vivo* formation of autologous tissue. Thereby, it is pursued that the engineered tissue mimics the composition and structure of the original tissue and has the capacity of regeneration and growth. The initial scaffold should possess strong material properties as the cardiovascular system requires an enormous strength, flexibility, and durability of the engineered structures, while on the other hand complete resorption of the scaffold material is aimed for. This review discusses the diversity of natural and synthetic bioresorbable materials that are currently investigated for their suitability as a scaffold for cardiovascular tissue engineering.

Keywords: Bioresorbable, biodegradable, tissue-engineered vascular grafts and heart valves, scaffold, starter matrix, polymers.

INTRODUCTION

Cardiovascular disease is the number one cause of death worldwide, globally claiming 17 million lives each year and accounting for 29% of all deaths. Due to an ever-ageing population and an increase of comorbidities, mortality numbers are expected to rise to about 23 million per year within the coming decades.[1] However, successful treatment of cardiovascular disease is limited in many situations by the lack of suitable autologous tissue for restoring injured cardiac muscle or serving as vascular conduits to replace or bypass diseased or occluded vessels. Despite positively influencing the field of reconstructive arterial surgery, the preparation of autologous vascular grafts increases time, cost, and the potential for morbidity to the surgical procedure.[2,3] Tissue-engineered solutions are suggested to overcome these problems with the intention to repair, replace, or regenerate injured tissues and organs (for example, the heart, lungs, liver, or bones) by engineered biological substitutes, based on cells, biocompatible scaffolds, and suitable biochemical (e.g. growth factors) and physical (e.g. cyclic mechanical loading) factors. While the engineered living substitute develops, the scaffold should degrade without leaving remnants in the body, requiring a so-called bioresorbable starter material (according to the definitions formulated by Vert et al.,[4,5] as listed in Table 1). During the last decades, tissue engineering has gained popularity also in the field of cardiovascular research, and research groups have used a variety of different approaches and methods to develop tissue-engineered heart valves (TEHVs) and tissue-engineered vascular grafts (TEVGs) that are at various stages of clinical development.

Table 1: Definitions of biodegradable, bioabsorbable, and bioresorbable materials according to Vert et al.[4,5]

Terms	Definitions	Examples
Biodegradable	Polymeric materials and solid devices that undergo dispersion as a consequence of macromolecular degradation. Although degradation products can be removed from the site of action, their degradation products will not completely be eliminated, remaining inside the human body.	Polyurethane
Bioabsorbable	Solid polymeric materials or devices that can dissolve into body fluids without breakdown of the macromolecular chain or reduction in molecular mass.	Polyethylene glycol
Bioresorbable	Solid polymers and devices that degrade into non-toxic products (low–molecular weight compounds), which will be eliminated via metabolic pathways (i.e. the citric acid cycle) or directly via renal excretion without residual side-effects.	Poly-D,L-lactide

Here we review the available bioresorbable scaffold materials that are used to develop cardiovascular substitutes with growth and regeneration capacity.

TISSUE ENGINEERING AND SCAFFOLD REQUIREMENTS

Generally speaking, there are three distinct tissue engineering approaches, namely *in vitro*, *in vivo*, and *in situ* tissue engineering. The traditional tissue engineering approach generates constructs *in vitro* by seeding autologous cells onto 3D starter materials, so-called scaffolds. Thereafter, tissue formation is stimulated under controlled conditions in a bioreactor. For this approach, autologous cells are preferred to prevent immunogenic reaction and rejection. However, when relying on the regenerative capacity of the body in the case of *in situ* tissue engineering, long *in vitro* cell expansion and tissue culture times could be eliminated when an acellular scaffold is directly implanted to recruit endogenous cells.

In vivo tissue engineering describes the fabrication of an autologous substitute by making use of the body (e.g. peritoneal cavity) as a bioreactor.[6] In all cases the key processes during tissue formation and maturation are cell proliferation and migration, extracellular matrix (ECM) production and organisation, and scaffold degradation. Finally, the capacities of these engineered tissues to enable repair of structural injury, remodelling of the ECM, and potential growth are crucial for their long-term success. Therefore it is of utmost importance to understand the specific demands of the cardiovascular system that, due to the cyclic mechanical loading of the blood with every heart contraction, requires an enormous strength, flexibility, and durability of the tissue-engineered cardiovascular replacements.

Consequently, the scaffolds need appropriate mechanical properties to endure the cyclic stresses and strains exerted upon implantation. More specifically, scaffolds for TEHVs should contain stiffness at around 0.5 MPa, while being elastic without any tendency to deform permanently under the influence of stresses.[7] For TEVGs, the scaffold should be compliant and able to withstand the burst pressure requirements during degradation and neotissue formation.[8] These requirements to the overall mechanical behaviour are determined by the intrinsic material properties (e.g. stiffness), scaffold architecture (e.g. fibre thickness and direction), and degradation rate. Moreover, due to intense contact with blood in cardiovascular applications, it is desirable to use a thromboresistance material or provide an endothelial surface layer.[9,10]

In general, the scaffold microstructure (i.e. pore size and fibre thickness) primarily determines cell infiltration, which is one of the prerequisites for successful tissue regeneration.[11] Additionally, it can affect cell phenotype and influence the behaviour of the infiltrating cells regarding cell adhesion, spreading, and proliferation.[12] The microstructure is also used to attach different bioactive molecules and signals that improve specific cell function, such as pro-angiogenic signals,[13] or to promote

recruitment of specific cell types via chemotaxis. The mechanical properties of the scaffold provide an important stimulus to the cells for ECM production and remodelling, as the cells experience different local stresses and strains depending on the scaffold stiffness. On the other hand, these mechanical cues, as a result of scaffold stiffness, can modulate the differentiation of cells into pathological phenotypes, e.g. osteoblastic or myofibroblastic differentiation.[14] Although the optimal cell type for preseeding the scaffold (or to attract *in vivo*) is not yet defined, an elaborative amount of information is available in literature[15,16] but is considered beyond the scope of this review.

To conclude, the initial scaffold for cardiovascular tissue engineering should ideally meet the following requirements: (1) be biocompatible and thromboresistant; (2) be able to support cell infiltration, growth, and cell-to-cell interaction; (3) start with sufficient mechanical properties and degrade at a rate in relation to new tissue formation; (4) have optimum architectural properties of pore size, porosity, and permeability in order to allow diffusion of nutrients and metabolic waste products; and last, but not least, (5) be bioresorbable.[15]

BIORESORBABLE SCAFFOLD MATERIALS

Roughly, the bioresorbable materials can be divided into natural-based and synthetic polymers. For natural polymers, no toxic degradation or sustained inflammatory reactions are expected as they can be produced from biological sources, such as collagen, gelatin, fibrin, hyaluronic acid, alginate, and decellularised matrices.[17] In contrast, the bulk degradation of several synthetic polymers, such as polyglycolic acid (PGA), polylactic acid (PLA), polyhydroxyalkanoate, and copolymers, leads to a decrease in the pH within the polymeric matrix and might result in local inflammation.[18] The degradation of implants is of special interest for the medical industry as no further surgical procedure is required to remove the implant. Such biomaterials should have degradation and resorption rates which are compatible with the formation of the neotissue; there must be a balance between scaffold degradation and ECM production.[19,20] The bioresorbable polymers should maintain mechanical features and secure their function during tissue formation as unexpected faster material degradation can result in mechanical instability and vessel rupture or valve failure. However, after healing of tissue, the implanted scaffold must be completely degraded and resorbed in order to avoid side-effects.[19,20] Prolonged macrophage activity due to the presence of synthetic scaffold remnants may lead to excessive chronic inflammation resulting in fibrosis, calcification, and/or degeneration of the cardiovascular implants.[18] Different factors influence the degradation kinetics, including hydrophobicity, crystallinity, configurational structure, molar mass, stress and strain, polydispersity, chain orientation, and site of implantation.[21-24]

There are four main degradation mechanisms for polymers: (1) hydrolysis; (2) oxidation (due to oxidants produced by tissues); (3) enzymatic degradation; and (4) physical degradation.[25] Degradation via hydrolysis has been studied intensively, in particular for bioresorbable polymers. The chemical properties enable hydrolytic degradation as a consequence of ester bond hydrolysis. After degradation, the monomeric components are removed by the natural (metabolic) pathways of the human body. Table 2 displays the degradation time and products of the most important natural-based and synthetic polymers, such as PLA and poly-ε-caprolactone (PCL), which have been used in several cardiovascular tissue engineering applications.[27-29]

SYNTHETIC POLYMERS

Synthetic bioresorbable polymers have found extensive applications in tissue engineering, mainly due to their variety of advantages compared to natural scaffold materials, including: more predictable mechanical and physical properties such as durability, degradation rate, strength, and elastic modulus. Furthermore, these materials are less expensive, better to reproduce, and may be stored over longer time periods, which make them interesting raw materials for scaffold fabrication.

Aliphatic Polyesters

Aliphatic polyesters have been known and studied since the 1930s[30] and their success in tissue engineering relies mainly on their degradability, biocompatibility, good processability, and mechanical features. Currently, the most widely investigated and most commonly used biomedical aliphatic polyesters are PGA, PLA, and PCL.

PGA is a rigid thermoplastic material with high crystallinity and is not soluble in most organic solvents. PGA is usually synthesised by ring-

Table 2: Bioresorbable polymers and their degradation time and degradation products.

Polymer	Abbreviation	Approximate Degradation Time	Degradation Products	Reference
Polyglycolic acid	PGA	6-12 months	Glycolic acid	107
Poly-L-lactic acid	PLLA	>24 months	L-lactic acid	107
Poly-D,L-lactic acid	PDLLA	12-16 months	D,L-lactic acid	107
Poly-D,L-lactide-co-glycolide 50:50	PDLGA 50:50	2 months	D,L-lactic acid Glycolic acid	107
Poly-D,L-lactide-co-glycolide 15:85	PDLGA 15:85	5 months	D,L-lactic acid Glycolic acid	107
Polycaprolactone	PCL	>24 months	Caproic acid	107
Poly-4-hydroxybutyrate	P4HB	2-12 months	4-hydroxbutyrate	108
Collagen		~2 weeks	Amino acids	109
Fibrin		few days	Fibrin degradation products (FDP)	110

opening polymerisation of glycolide, the cyclic dimer of glycolic acid.[31] Similarly, lactic acid is polymerised to synthesise PLA. Lactic acid, which is normally produced by muscular contraction, can be eliminated through the citric acid cycle, whereas glycolic acid may be eliminated directly in urine or may be converted to enter the citric acid cycle via pyruvic acid.[32] Due to the chiral nature of PLA, distinct forms exist, namely poly-L-lactide (PLLA), poly-D-lactide (PDLA), and racemic polylactide (PDLLA). The characteristics of PLA are highly affected by the stereo-isomeric L/D ratio of lactate units. Generally, an increased stereo-isomeric ratio decreases the crystallinity, whereby the degradation is enhanced. For example, degradation of PLA is faster than PDLA due to the lower crystallinity of PLA.

PCL is a semicrystalline, aliphatic polyester which is synthesised by ring-opening polymerisation of ε-caprolactone.[33,34] It displays good mechanical characteristics, such as high elongation and strength. PCL degrades very slowly *in vivo* by enzymatic action and by hydrolysis (Table 2).[33] All three polyesters are FDA approved polymers for clinical use.[35]

The feasibility of creating autologous TEVGs was first demonstrated in 1998 by seeding vascular cells onto PGA scaffolds.[36,37] After *in vitro* culture and biomimetic perfusion, these grafts were implanted into the right saphenous artery of miniature swine and demonstrated to stay patent up to 24 days.[36] However, the relatively stiff nature of the PGA fibres was not optimal and resulted in poor compliance match and poor surgical handling qualities.[37] Despite PGA being bioresorbable, breakdown products are acidic, which could induce an inflammatory response. Furthermore, PGA degrades faster than PLA, resulting in lower mechanical properties of TEVGs.[36] Other studies used PGA-PLLA scaffolds for microvessels in mice[38] or investigated TEVG scaffolds composed of polyglycolide knitted fibre and an L-lactide and ε-caprolactone copolymer sponge in a canine inferior vena cava model.[39] Surgical handling characteristics were improved after the introduction of a more elastic hybrid polymeric scaffold, fabricated from either PGA or PLA fibre-based mesh coated with a 50:50 copolymer of L-lactide and ε-caprolactone (PCLA/PGA or PCLA/PLA), due to an improved compliance match between vessel and conduit.[40] In 1998, Shinòka et al.[37] reported surgical implantation of TEVGs in lambs, based on autologous myofibroblasts and endothelial cells seeded onto PGA scaffolds. This study demonstrated the first vascular graft using autologous cells that yielded a viable structure.[37]

Polyhydroxyalkanoates (PHA)

Another group of polyesters that appeared to be convenient for tissue engineering is the PHA family, which is built from hydroxyacids produced by microorganisms under unbalanced growth conditions.[41,42] This group is generally bioresorbable and thermoprocessable and includes

poly-3-hydroxybutyrate (P3HB), copolymers of 3-hydroxybutyrate and 3-hydroxyvalerate (PHBV), poly-4-hydroxybutyrate (P4HB), copolymers of 3-hydroxybutyrate and 3-hydroxyhexanoate (PHBHHx), and poly-3-hydroxyoctanoate (PHO). A disadvantage of some PHA polymers, however, is their limited availability and the time-consuming production by bacteria. In order to adjust mechanical features or biocompatibility PHA polymers can be either blended, surface modified, or composed with other polymers, enzymes, or inorganic materials.[43] Additionally, their degradation rate can be tailored by varying their copolymer ratio. For example in 1999, TEVGs based on PGA-PHA scaffolds were implanted in the abdominal aorta of lambs and successfully followed up to 5 months *in vivo*. Overtime, the mechanical properties of these preseeded TEVGs changed towards those of native blood vessels.[44] For both heart valve and vascular tissue engineering the use of PGA coated with P4HB, meaning the combination of the thermoplastic characteristic of P4HB and high porosity of PGA, has been investigated intensively, presenting promising results in *in vitro* and preclinical studies.[45-50] Hoerstrup et al.[51] provided, in 2006, the first evidence of growth of living, functional pulmonary arteries engineered from vascular cells seeded on PGA/P4HB scaffolds in a growing lamb model. The evidence of the growth and remodelling capacity of these implants proved their potential also for use in paediatric applications.

NATURAL POLYMERS

Whereas synthetic materials have performed better in durability and strength, they pale in comparison with the functional capabilities of natural tissues. A good alternative to the synthetic polymers are natural polymers which possess biologically recognisable side groups. The category of natural-based materials for scaffolds includes polysaccharides (aliginate, chitin/chitosan, and hyaluronic acid derivate), proteins (soy, collagen, fibrin, gels, and silk), or decellularised ECM. Natural polymers are used as pure materials or in combination with synthetic polymers or inorganic substances to produce scaffolds.[52-54] The natural polymers mostly used for cardiovascular tissue engineering are collagen, fibrin, and decellularised ECM.

Collagen

Collagen molecules have a triple-helical structure and provide high tensile strength due to the arrangement of triple helices in fibrils. This biopolymer is the major protein component of the ECM and plays a dominant role in maintaining the biologic and structural integrity. There are four main collagen Types (I, II, III, and V) that make up the essential part of collagen in bone, cartilage, tendon, skin, and muscle.[55,56] The most explored collagen for biomedical applications is collagen Type I. Collagen scaffolds have been investigated for blood vessels, heart valves, and ligaments[57] in a variety of formats including porous sponges,[60] gels, sheets,[61,62] and foams.[63] The possible degradation by human collagenases makes collagen an ideal scaffold for tissue engineering and could potentially lead to the restoration of tissue structure and functionality.[58] The degradation rate often needs to be regulated using diverse methods such as crosslinking techniques.[59] The feasibility of TEVGs made of collagen and cells was first demonstrated in 1986 by Weinberg and Bell.[64] They generated cultures of bovine endothelial cells, smooth muscle cells (SMCs), and fibroblasts in layers of collagen gel. Later, a polyethylene terephthalate (PET) mesh was added to enhance the burst pressure.[64] Since, several studies have been conducted to improve the strength of collagen-based constructs by incorporating cells, matrix components, undegradable or degradable meshes,[69-71] and intracellular biomolecules by glycation[65-68] or dynamic mechanical stimulation.[72] Furthermore, cross-linking with chemicals makes collagen stronger and modifies its degradation rate.[73] A distinctive drawback, however, is the low availability of homologous (human) collagen.

Fibrin

Fibrin is a biopolymer of the monomer fibrinogen, i.e. the end-product of the coagulation cascade following the conversion of fibrinogen in the presence of thrombin and calcium.[74] Fibrinogen is a soluble plasma glycoprotein, which is produced by the liver. Fibrin and fibrinogen play essential roles in blood clotting, fibrinolysis, cellular and matrix interactions, the inflammatory response, wound healing, and neoplasia.[74] Fibrin is used as a naturally-occurring, autologous scaffold without the potential risk of a foreign body reaction.[75] Based on the autologous and bioresorbable properties, many applications for tissue engineering have been established in combination with cells,

growth factors, or drugs.[76-78] The most broadly used forms of fibrin scaffolds are fibrin hydrogels, fibrin glue, and fibrin microbeads.[79] Interestingly, fibrin gels can stimulate SMCs to synthesise elastin, which is an important component of arteries.[81] Fibrin vascular constructs are weaker and more extensible than collagen-based constructs. Therefore mechanical properties can be improved by fibrin-collagen composites presenting higher strength than collagen alone, but also more gel compaction.[80] Next to the shrinkage of the gel and low mechanical stiffness, its rapid degradation before proper tissue formation is another major disadvantage of fibrin hydrogels.[76,82] On the other hand, degradation within several days by cell-associated enzymatic activities can be utilised for the controlled release of growth factors.[83] Moreover, by adding aprotinin (for example), which restricts or even stops fibrinolyse, the degradation can be controlled.[82] Aprotinin is a monomeric serine protease inhibitor found to effectively inhibit the activity of several proteases, including plasmin, trypsin, chymotrypsin, and kallikrein.[84]

Decellularised ECM

Besides using proteins, such as fibrin or collagen, the complete natural ECM, i.e. decellularised xeno or homo-grafts, has also been discovered as an appropriate scaffold for tissue engineering. The ECM works as a supporting material and regulator of cellular functions including cell survival, proliferation, morphogenesis, and differentiation.[85] However, xenografts are associated with the risk of immunogenic reactions or disease transmission, and the availability of homografts is limited.[86] To eliminate immune reactions the xenogenic tissues can be decellularised, which is generally performed by perfusion of the tissue with various detergents or enzymatically, aiming at the removal of all cellular and nuclear matter while reducing any effects on the integrity and structure of the remaining ECM.[87-89] For this purpose, many organs and tissues, such as vessel, heart valves, and pericardium from humans and animals (e.g. sheep, pigs, and rabbits) have been studied.[90-93] Moreover, *in vivo* complete cellular ingrowth was proved in animal models.[94,95]

CLINICAL APPLICATIONS

Next to the elimination of possible immune rejection and the requirement of lifelong anticoagulation therapy, the major advantage of autologous tissue-engineered vessels or valves compared to current replacements is their ability to grow, repair, and remodel. However, despite the variety of accepted biomaterials for clinical applications and successful *in vitro* studies, just a few reports describe the effective transplantation of cardiovascular tissue engineering into clinics. In 2001, Shinòka's group[96] performed the first clinical study using vascular cell-seeded biodegradable polymer scaffolds (PGA or PLLA 50:50 copolymer ε-caprolactone) in the high-flow low-pressure pulmonary venous system of paediatric and young patients. 7 months after implantation, TEVGs were still functional, without complications or aneurysm.[96] Nevertheless, few patients showed TEVG stenosis, which was successfully treated with angioplasty.[97] L`Heureux`s group[98] treated haemodialysis patients with end-stage renal disease and haemodialysis failure with complete autologous *in vitro* grown TEVGs.[98] However, three out of ten TEVGs failed due to thrombosis or aneurysm, attributed to a low postoperative flow rate and diffuse dilatation. The clinical translation of autologous living valves, created according to the classical tissue-engineering paradigm, is, among others, limited by cell-mediated contraction of the valve leaflets caused by traction forces exerted by the cells. Decellularisation of the TEHVs before implantation can prevent this retraction, meanwhile enabling off-the-shelf availability.[50,99] Although preclinical trials have been performed for this promising approach,[49,50,100] more sophisticated studies should be performed to support future clinical studies.

The first clinical implementation of valves was performed with decellularised pulmonary allografts, reseeded with autologous endothelial progenitor cells, showing improved freedom from reintervention in contrast to conventional homografts and xenografts.[100] Additionally, decellularised allografts, reseeded with autologous vascular endothelial cells, demonstrated uncompromised follow-up of 10 years with excellent haemodynamic performance.[101] Nevertheless, the need for valve replacements exceeds the supply of donor valves. Therefore, also the largely available decellularised xenogenic pulmonary valves, reseeded with autologous vascular endothelial cells, have been introduced for right ventricular outflow tract reconstruction, with excellent early and midterm results.[101] Moreover, the short and mid-term performance of non-seeded decellularised xenograft valves in children and patients with congenital heart disease were recently reported to meet the performance of other currently available

implants.[102] However, cellular infiltration is sparse in humans.[102-104,106]

CONCLUSION

This review displays the significant progress of the applications of bioresorbable materials in the field of cardiovascular tissue engineering. As the scaffold plays a crucial role in the successful design of tissue-engineered constructs, the choice of material directly influences the outcome. Natural-based polymers display no toxic degradation or sustained inflammatory reactions and can be produced from biological sources. On the other hand, synthetic polymers present a higher strength and durability compared to natural polymers, but the bulk degradation might result in local inflammation. Composite biomaterials have the potential to overcome the current predicament of having to choose between either synthetics or natural tissues. Therefore, despite a variety of materials having been validated, future effort should focus on perfecting composite materials to take full advantage of the best properties. Moreover, optimising methods to extract natural polymers from human (cell) sources will enable the production of non-genoxenic (composite) grafts. In the coming decades research will most likely focus on intelligent, off-the-shelf scaffolds that make use of the regenerative capacity of the human body by attracting endogenous cells. Obviously, long-term (pre-clinical) studies are compulsory to evaluate the remodelling of these optimised materials towards native-like tissues. Nevertheless, bioresorbable scaffolds have large potential to eventually replace the use of the current synthetic and fixed-biological grafts in clinical practice.

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REFERENCES

1. World Health Organization (WHO). Cardiovascular diseases (CVDs). 2009: Fact sheet N°317.

2. Verma S et al. Should radial arteries be used routinely for coronary artery bypass grafting? Circulation. 2004;110(5):e40-6.

3. McKee JA et al. Human arteries engineered in vitro. EMBO Rep. 2003;4(6):633-8.

4. Vert M. Bioresorbable polymers for temporary therapeutic applications. Die Angewandte Makromolekulare Chemie. 1989;166(1):155-68.

5. Vert M et al. Bioresorbability and biocompatibility of aliphatic polyesters. J Mater Sci – Mater Med. 1992;3(6):432-46.

6. Hoenig MR et al. Tissue-engineered blood vessels: alternative to autologous grafts? Arterioscler Thromb Vasc Biol. 2005;25(6):1128-34.

7. Driessen NJ et al. Modeling the mechanics of tissue-engineered human heart valve leaflets. J Biomech. 2007;40(2):325-34.

8. Institute ANS. ANSI 2000 cardiovascular implants—vascular graft prostheses. 1994.

9. Patterson JT et al. Tissue-engineered vascular grafts for use in the treatment of congenital heart disease: from the bench to the clinic and back again. Regen Med. 2012;7(3):409-19.

10. Li S et al. Vascular tissue engineering: from in vitro to in situ. Wiley Interdiscip Rev Syst Biol Med. 2013;6(1):61-76.

11. Balguid A et al. Tailoring fiber diameter in electrospun poly(epsilon-caprolactone) scaffolds for optimal cellular infiltration in cardiovascular tissue engineering. Tissue Eng Part A. 2009;15(2):437-44.

12. Li WJ et al. Fabrication and characterization of six electrospun poly(alpha-hydroxy ester)-based fibrous scaffolds for tissue engineering applications. Acta Biomater. 2006;2(4):377-85.

13. Singh S. The enhancement of VEGF-mediated angiogenesis by polycaprolactone scaffolds with surface cross-linked heparin. Biomaterials. 2011;32(8):2059-69.

14. Schoen FJ. Heart valve tissue engineering: quo vadis? Curr Opin Biotechnol. 2011;22(5):698-705.

15. Weber B, Hoerstrup SP, "Regenerating Heart Valves," Cohen IS, Gaudette GR (eds.), Regenerating the Heart: Stem Cells and the Cardiovascular System (2011), Totowa: Humanam, pp.403-42.

16. Leor J et al. Cells, scaffolds, and molecules for myocardial tissue engineering. Pharmacol Ther. 2005;105(2):151-63.

17. Kong HJ et al. Controlling degradation of hydrogels via the size of cross-linked junctions. Advanced Materials. 2004. 16(21):1917-21.

18. Mendelson K, Schoen FJ. Heart valve tissue engineering: concepts, approaches, progress, and challenges. Ann Biomed Eng. 2006;34(12):1799-819.

19. Middleton IP et al. Professor Bamford's research in the field of biomaterials. J Biomater Sci Polym Ed. 2000;11(12): 1287-306.

20. James K, Kohn J. New biomaterials for tissue engineering. MRS Bulletin. 1996;21(11):22-6.

21. Dunn AS et al. The influence of polymer blend composition on the degradation of polymer/hydroxyapatite biomaterials. J Mater Sci Mater Med. 2001;12(8):673-7.

22. Heidemann W et al. Degradation of poly(D,L)lactide implants with or without addition of calciumphosphates in vivo. Biomaterials. 2001;22(17):2371-81.

23. Li S. Hydrolytic degradation characteristics of aliphatic polyesters derived from lactic and glycolic acids. J Biomed Mater Res. 1999;48(3):342-53.

24. Vert M et al. Complexity of the hydrolytic

degradation of aliphatic polyesters. Die Angewandte Makromolekulare Chemie. 1997;247(1):239-53.

25. Lyu S, Untereker D. Degradability of polymers for implantable biomedical devices. Int J Mol Sci. 2009;10(9): 4033-65.

26. Chan BP, Leong KW. Scaffolding in tissue engineering: general approaches and tissue-specific considerations. Eur Spine J. 2008;17(Suppl 4):467-79.

27. François S et al. A poly(L-lactic acid) nanofibre mesh scaffold for endothelial cells on vascular prostheses. Acta Biomater. 2009;5(7):2418-28.

28. Heydarkhan-Hagvall S et al. Three-dimensional electrospun ECM-based hybrid scaffolds for cardiovascular tissue engineering. Biomaterials. 2008;29(19):2907-14.

29. Ulery BD et al. Biomedical applications of biodegradable polymers. J Polym Sci Part B: Polym Phys. 2011;49(12):832-64.

30. Carothers WH, Coffman DD. The thermal decomposition of sodium ethyl. J Am Chem Soc. 1929;51(2):588-93.

31. Athanasiou KA et al. Orthopaedic applications for PLA-PGA biodegradable polymers. Arthroscopy. 1998;14(7):726-37.

32. Engelberg I, Kohn J. Physico-mechanical properties of degradable polymers used in medical applications - a comparative-study. Biomaterials. 1991;12(3):292-304.

33. Couet F et al. Macromolecular biomaterials for scaffold-based vascular tissue engineering. Macromol Biosci. 2007;7(5):701-18.

34. Pankajakshan D, Agrawal DK. Scaffolds in tissue engineering of blood vessels. Can J Physiol Pharmacol. 2010;88(9):855-73.

35. Thomas LV et al. Tissue engineered vascular grafts--preclinical aspects. Int J Cardiol. 2013;167(4):1091-100.

36. Niklason LE et al. Functional arteries grown in vitro. Science. 1999;284(5413):489-93.

37. Shinoka T et al. Creation of viable pulmonary artery autografts through tissue engineering. J Thorac Cardiovasc Surg. 1998;115(3):536-45.

38. Wu X et al. Tissue-engineered microvessels on three-dimensional biodegradable scaffolds using human endothelial progenitor cells. Am J Physiol Heart Circ Physiol. 2004;287(2):H480-7.

39. Matsumura G et al. Long-term results of cell-free biodegradable scaffolds for in situ tissue-engineering vasculature: in a canine inferior vena cava model. PloS One. 2012;7(4):e35760.

40. Watanabe M et al. Tissue-engineered vascular autograft: inferior vena cava replacement in a dog model. Tissue Eng. 2001;7(4):429-39.

41. Li H et al. Fabrication, characterization, and in vitro degradation of composite scaffolds based on PHBV and bioactive glass. J Biomater Appl. 2005;20(2): 137-55.

42. Chen GQ, Wu Q. The application of polyhydroxyalkanoates as tissue engineering materials. Biomaterials. 2005;26(33):6565-78.

43. Rezwan K et al. Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering. Biomaterials. 2006;27(18):3413-31.

44. Shum-Tim D et al. Tissue engineering of autologous aorta using a new biodegradable polymer. Ann Thorac Surg. 1999;68(6):2298-304.

45. Schmidt D et al. Tissue engineering of heart valves using decellularized xenogeneic or polymeric starter matrices. Philos Trans R Soc Lond B Biol Sci. 2007;362(1484):1505-12.

46. Hoerstrup SP et al. Functional living trileaflet heart valves grown in vitro. Circulation. 2000;102(19 Suppl 3):III44-9.

47. Rabkin E et al. Evolution of cell phenotype and extracellular matrix in tissue-engineered heart valves during in-vitro maturation and in-vivo remodeling. J Heart Valve Dis. 2002;11(3):308-14.

48. Stekelenburg M et al. Dynamic straining combined with fibrin gel cell seeding improves strength of tissue-engineered small-diameter vascular grafts. Tissue Eng Part A. 2009;15(5): 1081-9.

49. Weber B et al. Off-the-shelf human decellularized tissue-engineered heart valves in a non-human primate model. Biomaterials. 2013;34(30):7269-80.

50. Dijkman PE et al. Decellularized homologous tissue-engineered heart valves as off-the-shelf alternatives to xeno- and homografts. Biomaterials. 2012;33(18):4545-54.

51. Mol A et al. Autologous human tissue-engineered heart valves: prospects for systemic application. Circulation. 2006;114(1 Suppl):I152-8.

52. Chen GP et al. The use of a novel PLGA fiber/collagen composite web as a scaffold for engineering of articular cartilage tissue with adjustable thickness. J Biom Mater Res A. 2003;67(4):1170-80.

53. Zhang Y, Zhang M. Synthesis and characterization of macroporous chitosan/calcium phosphate composite scaffolds for tissue engineering. J Biom Mater Res. 2001;55(3):304-12.

54. Kim HW et al. Stimulation of osteoblast responses to biomimetic nanocomposites of gelatin-hydroxyapatite for tissue engineering scaffolds. Biomaterials. 2005;26(25):5221-30.

55. Grant ME. From collagen chemistry towards cell therapy - a personal journey. Int J Exp Pathol. 2007;88(4):203-14.

56. Smith K, Rennie MJ. New approaches and recent results concerning human-tissue collagen synthesis. Curr Opin Clin Nutr Metab Care. 2007;10(5):582-90.

57. Auger FA et al. Tissue-engineered human skin substitutes developed from collagen-populated hydrated gels: clinical and fundamental applications. Med Biol Eng Comput. 1998;36(6):801-12.

58. Yannas IV et al. Wound tissue can utilize a polymeric template to synthesize a functional extension of skin. Science. 1982;215(4529):174-6.

59. Weadock KS et al. Effect of physical crosslinking methods on collagen-fiber durability in proteolytic solutions. J Biomed Mater Res. 1996;32(2):221-6.

60. Taylor PM et al. Human cardiac valve interstitial cells in collagen sponge: a biological three-dimensional matrix for tissue engineering. J Heart Valve Dis. 2002;11(3):298-306.

61. Butcher JT, Nerem RM. Porcine aortic valve interstitial cells in three-dimensional culture: comparison of phenotype with aortic smooth muscle cells. J Heart Valve Dis. 2004;13(3):478-85.

62. Tedder ME et al. Stabilized collagen scaffolds for heart valve tissue engineering. Tissue Eng Part A. 2009;15(6):1257-68.

63. Rothenburger M et al. Ultrastructure of proteoglycans in tissue-engineered cardiovascular structures. Tissue Eng. 2002;8(6):1049-56.

64. Weinberg CB, Bell E. A blood vessel model constructed from collagen and cultured vascular cells. Science. 1986;231(4736):397-400.

65. Qi J et al. Modulation of collagen gel compaction by extracellular ATP is MAPK and NF-kappaB pathways dependent. Exp Cell Res. 2009;315(11):1990-2000.

66. Fernandez P, Bausch AR. The compaction of gels by cells: a case of collective mechanical activity. Integr Biol (Camb). 2009;1(3):252-9.

67. Zhou M et al. [Constructing a small-diameter decellularized vascular graft pre-loaded with bFGF]. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2008;22(3):370-5.

68. Girton TS et al. Mechanisms of stiffening and strengthening in media-equivalents fabricated using glycation. J Biomech Eng. 2000;122(3):216-23.

69. Miwa H et al. Development of a hierarchically structured hybrid vascular graft biomimicking natural arteries. ASAIO J. 1993;39(3):M273-7.

70. Berglund JD et al. Incorporation of intact elastin scaffolds in tissue-engineered collagen-based vascular grafts. Tissue Eng. 2004;10(9-10):1526-35.

71. Berglund JD et al. A biological

hybrid model for collagen-based tissue engineered vascular constructs. Biomaterials. 2003;24(7):1241-54.

72. Seliktar D et al. Dynamic mechanical conditioning of collagen-gel blood vessel constructs induces remodeling in vitro. Ann Biomed Eng. 2000;28(4):351-62.

73. Barnes CP et al. Cross-linking electrospun type II collagen tissue engineering scaffolds with carbodiimide in ethanol. Tissue Eng. 2007;13(7): 1593-605.

74. Mosesson MW et al. The structure and biological features of fibrinogen and fibrin. Ann N Y Acad Sci. 2001;936:11-30.

75. Dietrich M et al. Fibrin-based tissue engineering: comparison of different methods of autologous fibrinogen isolation. Tissue Eng Part C Methods. 2013;19(3):216-26.

76. Mol A et al. Fibrin as a cell carrier in cardiovascular tissue engineering applications. Biomaterials. 2005;26(16):3113-21.

77. Cho SW et al. Enhancement of adipose tissue formation by implantation of adipogenic-differentiated preadipocytes. Biochem Biophys Res Commun. 2006;345(2):588-94.

78. Eyrich D et al. Long-term stable fibrin gels for cartilage engineering. Biomaterials. 2007;28(1):55-65.

79. Ahmed TA et al. Fibrin: a versatile scaffold for tissue engineering applications. Tissue Eng Part B Rev. 2008;14(2):199-215.

80. Cummings CL et al. Properties of engineered vascular constructs made from collagen, fibrin, and collagen-fibrin mixtures. Biomaterials. 2004;25(17): 3699-706.

81. Long JL, Tranquillo RT. Elastic fiber production in cardiovascular tissue-equivalents. Matrix Biol. 2003;22(4): 339-50.

82. Jockenhoevel S et al. Fibrin gel -- advantages of a new scaffold in cardiovascular tissue engineering. Eur J Cardiothorac Surg. 2001;19(4):424-30.

83. Chiu LL, Radisic M. Scaffolds with covalently immobilized VEGF and Angiopoietin-1 for vascularization of engineered tissues. Biomaterials. 2010;31(2):226-41.

84. Kang HM et al. The kinetics of plasmin inhibition by aprotinin in vivo. Thromb Res. 2005;115(4):327-40.

85. Adachi E et al. Basement-membrane stromal relationships: interactions between collagen fibrils and the lamina densa. Int Rev Cytol. 1997;173:73-156.

86. Badylak SF, Gilbert TW. Immune response to biologic scaffold materials. Semin Immunol. 2008;20(2):109-16.

87. Byrne GW, McGregor CG. Cardiac xenotransplantation: progress and challenges. Curr Opin Organ Transplant. 2012;17(2):148-54.

88. Badylak SF et al. Extracellular matrix as a biological scaffold material: structure and function. Acta Biomater. 2009;5(1): 1-13.

89. Piterina AV et al. ECM-based materials in cardiovascular applications: inherent healing potential and augmentation of native regenerative processes. Int J Mol Sci. 2009;10(10):4375-417.

90. Schmidt CE, Baier JM. Acellular vascular tissues: natural biomaterials for tissue repair and tissue engineering. Biomaterials. 2000;21(22):2215-31.

91. Gilbert TW et al. Decellularization of tissues and organs. Biomaterials. 2006;27(19):3675-83.

92. Mirsadraee S et al. Development and characterization of an acellular human pericardial matrix for tissue engineering. Tissue Eng. 2006;12(4):763-73.

93. Mirsadraee S et al. Biocompatibility of acellular human pericardium. J Surg Res. 2007;143(2): 407-14.

94. Elkins RC et al. Decellularized human valve allografts. Ann Thorac Surg. 2001;71(5 Suppl):S428-32.

95. Hopkins RA et al. Decellularization reduces calcification while improving both durability and 1-year functional results of pulmonary homograft valves in juvenile sheep. J Thorac Cardiovasc Surg. 2009;137(4):907-13.

96. Shinòka T et al. Transplantation of a tissue-engineered pulmonary artery. N Engl J Med. 2001;344(7):532-3.

97. Shinòka T, Breuer C. Tissue-engineered blood vessels in pediatric cardiac surgery. Yale J Biol Med. 2008;81(4):161-6.

98. L'Heureux N et al. Tissue-engineered blood vessel for adult arterial revascularization. N Engl J Med. 2007;357(14):1451-3.

99. Dahl SL et al. Decellularized native and engineered arterial scaffolds for transplantation. Cell Transplant. 2003;12(6):659-66.

100. Cebotari S et al. Use of fresh decellularized allografts for pulmonary valve replacement may reduce the reoperation rate in children and young adults: early report. Circulation. 2011;124(11 Suppl):S115-23.

101. Dohmen PM et al. Ten years of clinical results with a tissue-engineered pulmonary valve. Ann Thorac Surg. 2011;92(4):1308-14.

102. Konertz W et al. Right ventricular outflow tract reconstruction with decellularized porcine xenografts in patients with congenital heart disease. J Heart Valve Dis. 2011;20(3):341-7.

103. Sayk F et al. Histopathologic findings in a novel decellularized pulmonary homograft: an autopsy study. Ann Thorac Surg. 2005;79(5):1755-8.

104. Miller DV et al. Endothelial and smooth muscle cell populations in a decellularized cryopreserved aortic homograft (SynerGraft) 2 years after implantation. J Thorac Cardiovasc Surg. 2006;132(1):175-6.

105. Simon P et al. Early failure of the tissue engineered porcine heart valve SYNERGRAFT in pediatric patients. Eur J Cardiothorac Surg. 2003;23(6):1002-6.

106. Hiemann NE et al. Complete destruction of a tissue-engineered porcine xenograft in pulmonary valve position after the Ross procedure. J Thorac Cardiovasc Surg. 2010;139(4): e67-8.

107. Gunatillake PA, Adhikari R. Biodegradable synthetic polymers for tissue engineering. Eur Cell Mater. 2003;5:1-16.

108. Martin DP, Williams SF. Medical applications of poly-4-hydroxybutyrate: a strong flexible absorbable biomaterial. Biochemical Engineering Journal. 2003;16(2):97-105.

109. Meyer U et al. Fundamentals of tissue engineering and regenerative medicine. Springer. 2009.

110. Han B et al. A fibrin-based bioengineered ocular surface with human corneal epithelial stem cells. Cornea. 2002;21(5):505-10.

NEW GENERATIONS OF DRUG-ELUTING STENTS - A BRIEF REVIEW

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ABSTRACT

This review focuses on describing new generations of drug-eluting stents (DES) based on the use of novel stent platforms, coatings, and carrier systems, developed to enhance DES safety. Examples of various DES classes among the most clinically-used DES are briefly discussed.

Keywords: Drug-eluting stents (DES), biodegradable polymer DES, durable polymer DES, polymer-free DES, bioabsorbable vascular scaffolds.

BACKGROUND

Drug-eluting stents (DES) were designed to reduce in-stent neointimal proliferation, and thus, minimise in-stent restenosis (ISR), which is the major disadvantage of percutaneous coronary interventions with bare-metal stents (BMS). DES have revolutionised the treatment of coronary artery disease by reducing the rate of ISR from 20-40% with BMS to 6-8% with DES.

In recent years, however, concern has been raised regarding the long-term safety of DES and the risk of stent thrombosis (ST) and late restenosis due to neoatherosclerosis. This potential increased risk remains an area of uncertainty in the field of interventional cardiology. DES consist of a standard metallic stent, a polymer coating, and an antiproliferative drug that is embedded within a durable or biodegradable (bioabsorbable) polymer and released over time. Although the common basic concept of DES remains constant, all DES are not made equal and each type may vary significantly with respect to deliverability, efficacy, and safety (Table 1).

FIRST-GENERATION DES

First-generation DES include sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES). Since their introduction into worldwide clinical practice in the years 2003 and 2004, first-generation DES - Cypher (SES; Cordis Corporation, Johnson & Johnson, Warren, NJ, USA) and Taxus (PES; Boston Scientific Corporation, Natick, MA, USA) - have dramatically reduced ISR and target vessel revascularisation (TVR) across virtually all lesion and patient subsets compared with BMS. However, their safety has been questioned because of suboptimal polymer biocompatibility leading to their propensity for late and very late ST,[1] and local drug toxicity. Concerns were based on human autopsy studies, which identified the durable polymers (DP) of these first-generation DES as possible triggers of chronic vessel wall inflammation, delayed hypersensitivity reactions, delayed arterial healing, incomplete stent strut re-endothelialisation due to inhibition of endothelial cell proliferation, stent malapposition, accelerated neoatherosclerosis, and polymer-induced increased risk of very late ST.[2–8] Also, DP used in first-generation DES have been associated with mechanical complications (polymer delamination and 'webbed' polymer surface leading to stent expansion issues) and nonuniform coating, resulting in unpredictable drug distribution and release.[9]

Table 1: Overview of first, second, and third-generation drug-eluting stents.

Series	Platform	Coating and Drug	Trials
Cypher®	316L stainless steel Bx Velocity stent (140 μm struts, 1.1176 mm crimped profile).	12.6 μm 3-layer coating (2 μm parylene C base coat, 10 μm main coat of PEVA, PBMA, and sirolimus, 0.6 μm top coat of PBMA). 80% of sirolimus elutes over ~30 days; remainder released by end of 90 days.	RAVEL, SAPPHIRE, SIRIUS
Taxus®	316L stainless steel Express2 stent (132 μm struts).	16 μm single-layer SIBS copolymer (nonresorbable elastomeric) coating containing paclitaxel, which elutes over ~90 days.	ELUTES, TAXUS II, ASPECT
Ion®	316L stainless steel PtCr alloy (81 μm struts for diameters 2.25–3.50 mm, 86-μm struts for 4.00 mm).	Triblock copolymer (composed of polystyrene and polyisobutylene units) coating containing paclitaxel.	PERSEUS
Promus®	L605 CoCr alloy ML Vision stent (81 μm struts, 1.0668 mm stent profile).	Durable PBMA, PVDF-HFP, and everolimus; 100% drug elution over 120 days.	SPIRIT I SPIRIT II
PROMUS Element™ Plus	PtCr alloy (minimum strut thickness 81 μm), open-cell stent design, short serpentine rings, helically distributed links, diameters of 2.25–4.0 mm, and lengths of 8–38 mm.	7 μm everolimus-eluting durable fluoropolymer coating.	DUTCH PEERS
Synergy®	Thin strut (74 μm) PtCr stent.	Ultrathin (4 μm) PLGA bioabsorbable polymer applied only to the abluminal surface, everolimus 38-179 μg, depending on stent length.	EVOLVE EVOLVE II
JACTAX®	Liberté (316 L) stainless steel stent, strut thickness of 96.5 μm.	Paclitaxel (0.6 μg/mm of stent length), bioabsorbable polymer DLPLA applied to the abluminal surface on premounted stent.	JACTAX Trial Drug Eluting Stent Trial
Xience V®	L605 CoCr ML Vision stent (81 μm struts).	7.6 μm fluoropolymer multilayer coating with 100 mcg/cm^2 everolimus.	SPIRIT III SPIRIT V EXCELLENT
Endeavor®	Cobalt chrome Driver stent (91 μm struts).	4.3 μm phosphorylcholine coating includes zotarolimus on 1 μm base coat.	ENDEAVOR I ENDEAVOR II
Resolute®	CoCr, open-cell stent design in a continuous, sinusoidal-helical pattern.	Biolinx polymer coating includes zotarolimus with extended release of 85% of zotarolimus within 60 days and almost 100% by 180 days.	TWENTE RESOLUTE All-Comers RESOLUTE International
Resolute Integrity®	CoCr, open-cell stent design, single, sinusoidal-formed, helically wrapped, locally laser-fused wire (strut thickness 91 μm), stent diameters of 2.25–4.0 mm, and lengths of 8–38 mm.	6 μm layer of coating that consists of zotarolimus and the BioLinx polymer system.	DUTCH PEERS

Table 1 continued.

Series	Platform	Coating and Drug	Trials
Nobori®	Stainless steel, S-Stent™ strut thickness of 120 μm.	Bioabsorbable PLA, polymer thickness of 20 μm, biolimus A9, 15.6 μg/mm length.	NOBORI I, NOBORI I- 2nd Phase, NOBORI-JAPAN, COMPARE II NEXT
BioMatrix®	S-Stent platform, a thin, stainless steel, laser-cut, tubular stent, strut thickness of 137 μm.	Bioabsorbable PLA polymer applied to the abluminal surface, Biolimus A9 (15.6 μg/mm of stent length).	LEADERS
Yukon® Choice PC	Stainless steel, 316 LVM, modified microporous stent surface, strut thickness of 87 μm.	Abluminal coating with biodegradable PLA and shellac, polymer thickness of 5 μm, sirolimus.	ISAR-TEST 3 ISAR-TEST 4
Absorb BVS	Semicrystalline PLLA, strut thickness of 150 μm.	PDLA polymer, 8.2 μm/mm length, antiproliferative drug everolimus.	ABSORB Cohort A ABSORB Cohort B ABSORB II ABSORB Extend (ongoing)

PEVA: polyethylene vinyl acetate; PBMA: poly(n-butyl methacrylate); SIBS: styrene isoprene butadiene; PtCr: platinum chromium; CoCr: cobalt chromium; ML: multi-link; PVDF-HFP: poly(vinylidene fluoride-co-hexafluoropropylene); PLGA: poly(lactide-co-glycolide); DLPLA: D-lactic poly(lactic acid); PLA: poly(lactic acid); LVM: left ventricular mass; PLLA: poly-L-lactic acid; PDLA: poly(d-lactic acid).

SECOND-GENERATION DES

As a consequence, the extensive incentive towards the development of novel durable and absorbable (biodegradable) polymeric drug carrier systems and non-polymeric stent surfaces, and also the development of more modern stent platforms (ensuring better deliverability, radiopacity, flexibility, and radial strength), as well as the use of novel antiproliferative agents, resulted in the successful accomplishment of numerous second and third-generation DES.

The second-generation DES include the Endeavor (Medtronic, Minneapolis, MN, USA), Resolute (Medtronic), Xience V (Abbot Vascular, Santa Clara, CA, USA), and Promus (Boston Scientific, USA) stents, and utilise a more biocompatible DP. The Endeavor second-generation stents utilise a cobalt-chromium (CoCr) platform and a permanent phorylcholine polymer that facilitates the release of the sirolimus analogue, zotarolimus. The main representative of second-generation absorbable-polymer family of DES is the BioMatrix stent (Biosensors International, Singapore), which utilises a sirolimus analogue (Biolimus A9) and a biodegradable polylactic acid (PLA) polymer that completely dissolves over a 6-9 month period. CoCr, and later platinum chromium (PtCr), platforms used in second-generation DES permitted similar radial strength, enabling a thinner strut design and subsequently significantly improved deliverability.

To improve DES safety, second-generation DES have more biocompatible DPs, or bioabsorbable polymers, which are eventually bioresorbed, rendering the stent surface similar to BMS free of a chronic inflammatory stimulation. Some studies have shown that bioabsorbable polymer-based DES are more effective than BMS[10] and, by reducing the risk of very late ST, perhaps safer than first-generation DES.[11] However, second-generation fluorinated DP-based CoCr everolimus-eluting stents (Xience V, Abbott Vascular, and Promus, Boston Scientific) and PtCr everolimus-eluting stents (Promus Element, Boston Scientific) have been associated with lower rates of early, late, and very late ST compared with first-generation DES and BMS,[12] challenging the widespread belief that bioabsorbable polymers are necessary to minimise the risk of ST.

A recent meta-analysis[13] compared the short-term (1 month) and mid-term (1 year) performance of sirolimus, biolimus A9, and paclitaxel biodegradable-polymer DES, as well as the 1-year performance of biodegradable polymer DES with DP DES. The incidence of target lesion revascularisation (TLR) at 30 days was 0.4% in the biodegradable polymer SES, 0.7% in the biodegradable polymer PES, and 1.4% in the biodegradable polymer biolimus-eluting stents (BES). These incidences were statistically significantly different (overall p=0.01). At 1-year follow-up clinical endpoints were assessed in seven randomised controlled studies comparing biodegradable polymer DES with DP DES. It was observed that the risk of developing TLR at 1-year follow-up was not significantly different in DP DES compared to biodegradable polymer DES (OR=0.8, 95% CI=0.5-1.4, p=0.5). Similarly, the 1-year risk of definite ST was not significantly different in DP DES compared to biodegradable polymer DES (OR=0.7, 95% CI=-0.2-2.4, p=0.5). These results suggest that biodegradable, polymer DES do not necessarily perform better than DP DES, and that short, mid, and long-term results should be carefully judged for newly emerging biodegradable polymer DES before they become a new clinical standard.

Another, more recent, large-scale network meta-analysis[14] documented bioabsorbable polymer BES to be associated with superior clinical outcomes compared with BMS and first-generation DES, and similar rates of cardiac death/myocardial infarction (MI), and TVR compared with second-generation DP DES. The same paper from Palmerini et al.[14] highlighted, however, higher rates of definite ST with bioabsorbable polymer BES than with CoCr everolimus-eluting stents. The increased risk for definite ST with bioabsorbable polymer BES compared with CoCr everolimus-eluting stents was apparent both in the early period (before 30 days) and the late period (between 30 days and 1 year). These data demonstrate that the use of currently available bioabsorbable polymers is not associated with the lowest risk of ST, especially within the first year after stent implantation.

Polymers requiring active bioresorption have historically been associated with greater rates of inflammation than DPs.[15] Among all new generation DES the concept of non-polymeric or polymer-free DES deserves to be mentioned. A good example is Yukon Choice DES (Translumina, Germany), the first stent especially designed for nonpolymeric application of antiproliferative, anti-inflammatory, and/or antithrombotic drugs. The surface of the YUKON Choice DES contains micropores to enable the adsorption of different organic substances. The coating solution (biodegradable polylactide and shellac) fills the pores completely and creates a uniform layer. After the drug (sirolimus) is fully released, the microporous PEARL surface favours the adhesion of endothelial cells.

THIRD-GENERATION DES

Bioabsorbable Drug-Eluting Vascular Scaffolds (BVS)

Dramatic advances in bioabsorbable materials and technology have delivered the potential for a fully absorbable scaffold, which is able to mechanically support the coronary artery for a predetermined time period. BVS represent a new concept of providing transient vessel support with drug delivery capability but theoretically without the long-term limitations of metallic DES, such as permanent vessel caging and possible malapposition, risk of late ST, neoatherosclerosis, and local inflammation.[16-21] Also, permanent metallic stenting precludes the possibility of later surgical revascularisation, prevents late lumen enlargement, results in jailing of side-branches, and inhibits non-invasive imaging of coronary arteries using computed tomography (CT) and magnetic resonance imaging (MRI).[22-26] On the contrary, BVS have the unique ability of restoration of vascular physiology and anatomical integrity, such as native tortuosity and angulation, as they provide only a temporary scaffold necessary to maintain the patency of the vessel after intervention.

Currently, there are four materials used in BVS, of which lactide polymers, particularly poly-levo-lactic acid (PLLA), form the basis of several devices and are the most extensively investigated. Other materials include magnesium, polyanhydrides (salicylic acid and adipic acid), and polycarbonates (amino acids, e.g. tyrosine).

The absorbable metallic stent (Biotronik, Berlin, Germany) is composed of magnesium and some other rare metals, and is the only bioresorbable metallic stent implanted in humans. The device has a high mechanical strength and similar properties to the other metallic stents. The stent resorption is completed within 4 months, producing inorganic salts without causing a

significant inflammatory response.[27-31] The efficacy of the first-generation of magnesium stents was examined in the PROGRESS AMS trial, revealing a high incidence of TLR (45%) at 12 months and an increased late luminal loss (LLL) on angiograms at 4 months follow-up (1.08±0.49 mm). Intravascular ultrasound (IVUS) at 4 months follow-up revealed almost complete resorption of the device and a significant reduction in luminal dimensions due to neointima formation (45%), negative remodelling (42%), and to an increase in the plaque area outside the stent (13%). The negative remodelling was attributed to an early reduction of the scaffold radial force caused by too fast a resorption of the device. Thus, significant modifications using a different magnesium alloy, with increased radial strength and prolonged duration of the resorption, as well as the incorporation of paclitaxel elution within a biodegradable matrix to control the release of the antiproliferative drug, were necessary. The drug-eluting absorbable metallic stent (DREAMS) was tested in a clinical setting in the BIOSOLVE-I study, which showed TLR rate at 6 months of 4.3%, and LLL of 0.64±0.50 mm.[32] DREAMS was further modified to create the next generation DREAMS 2 with radiopaque markers at both ends and sirolimus elution instead of paclitaxel.[33] Further progress of this exciting project is eagerly awaited.

One of the most clinically widely used - and, to date, most widely investigated - BVS is ABSORB (Abbott Vascular). This fully resorbable BVS has been tested in the ABSORB cohort A study, and demonstrated excellent long-term clinical results up to 3 years with a major adverse cardiac event rate (MACE) of 3.4%.[34-36]

The scaffold consisted of a backbone of PLLA coated with poly-DL-lactide (PDLLA), which contained and controlled the release of the antiproliferative drug everolimus. The first-generation of BVS showed slightly higher acute recoil than conventional metallic platform stents, and at 6 months, an 11.8% reduction in scaffold area and a 24.3% decrease in minimal luminal area (late recoil).[37]

Although the short and long-term results of the ABSORB cohort A trial were favourable, reinforcement of the mechanical performance of the device and prolongation of its mechanical integrity up to 6 months were necessary. To enhance the mechanical strength of the struts and to reduce immediate and late recoil, the strut design and the manufacturing process of the polymer were modified in the revised version, BVS 1.1., with more uniform strut distribution, reduced maximum circular unsupported surface area, more uniform vessel wall support, and drug transfer. Also, the modified manufacturing has resulted in a lower hydrolysis rate of the polymer, thus preserving its mechanical integrity for a longer period of time. Clinical outcomes in Cohort B demonstrate a MACE rate of 8.9% at 2 years follow-up.[38]

CONCLUSION

In summary, based on available data at the time this review was written, the newer biocompatible DP everolimus-eluting stents and Resolute zotarolimus-eluting stents, and the biodegradable polymer biolimus-eluting stents, maintain the efficacy of gold standard SES. However, and disappointingly, with respect to safety endpoints, second-generation biodegradable polymer-based DES fell short of high expectations, and differences when compared with second-generation DP DES become obvious, with everolimus-eluting stents and Resolute zotarolimus-eluting stents emerging as the safest stents to date.[39] Moreover, second-generation DES, particularly the everolimus-eluting stent (Xience V, Abbot; Promus, Boston Scientific), significantly reduced the risk of TVR in patients with ST-segment-elevation MI (STEMI) without increasing the risk of adverse safety outcomes, including rates of ST, when compared with BMS.[40] BVS is a relatively new technology introduced to address the limitations of the traditional metallic stents.

However, these devices still have limited applications, and to date they do not outperform the current generation of high performance metallic drug-eluting devices. Evidence from the validation of the second-generation BVS indicates that they have overcome the drawbacks of the first-generation (e.g. rapid bioresorption and device shrinkage) and that they are able to compete with the metallic stents in terms of safety and efficacy. However, it remains to be demonstrated from the ongoing and upcoming clinical studies whether BVS can truly restore vascular integrity and function.

Finally, when assessing the efficacy and safety of any DES, obviously everything matters; biodegradability of polymer, the optimal combination of stent alloy, design, strut thickness,

polymer, and the drug. Nonetheless, however important the quality and performance of DES may seem, stents are only one of numerous, often underestimated but complex and critically relevant, interplaying factors influencing the individual clinical outcome (e.g. lesion complexity, coronary anatomy, comorbidities, operator technical skill, and experience etc.). Thus, effective management of patients undergoing percutaneous coronary intervention requires focus on clinical and angiographic data to guide optimal device choice in the continuously expanding scenario of coronary stents.

REFERENCES

1. Stettler C et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet. 2007;370:937-48.

2. Bertrand OF et al. Biocompatibility aspects of new stent technology. J Am Coll Cardiol. 1998;32(3):562–71.

3. Nakazawa G et al. Drug-eluting stent safety: findings from preclinical studies. Expert Rev Cardiovasc Ther. 2008;6(10):1379–91.

4. Nakazawa G et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation. 2008;118(11):1138–45.

5. Cook S et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation. 2007;115(18):2426–34.

6. Siqueira DA et al. Late incomplete apposition after drug-eluting stent implantation: incidence and potential for adverse clinical outcomes. Eur Heart J. 2007;28(11):1304 –9.

7. Joner M et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol. 2006;48(1):193-202.

8. Kounis NG et al. Coronary stents, hypersensitivity reactions, and the Kounis syndrome. J Interv Cardiol. 2007;20(5):314–23.

9. Hossainy S, Prabhu S. A mathematical model for predicting drug release from a biodurable drug-eluting stent coating. J Biomed Mater Res A. 2008;87(2):487–93.

10. Raber L et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. JAMA. 2012;308(8):777-87.

11. Stefanini GG et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J. 2012;33(10):1214-22.

12. Palmerini T et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet. 2012;379(9824):1393-402.

13. Ahmed TA et al. Clinical performance of drug-eluting stents with biodegradable polymeric coating: a meta-analysis and systematic review. EuroIntervention. 2011;7(4):505-16.

14. Palmerini T et al. Clinical outcomes with bioabsorbable polymer versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol. 2014;63(4):299-307.

15. De Scheerder IK et al. Biocompatibility of biodegradable and nonbiodegradable polymer-coated stents implanted in porcine peripheral arteries. Cardiovasc Intervent Radiol. 1995;18(4):227-32.

16. Ormiston JA and Serruys PWS. Bioabsorbable coronary stents. Circ Cardiovasc Interv. 2009;2(3):255–60.

17. Waksman R. Biodegradable stents: they do their job and disappear. J Invasive Cardiol. 2006;18(2):70–4.

18. Finn AV et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation. 2007;115(18):2435–41.

19. Hoffmann R et al. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. Circulation. 1996;94(6):1247–54.

20. Togni M et al. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. J Am Coll Cardiol. 2005;46(2):231–6.

21. Barlis P et al. Coronary bioabsorbable magnesium stent: 15-month intravascular ultrasound and optical coherence tomography findings. Eur Heart J. 2007;28(19):2319.

22. Cademartiri F et al. Usefulness of 64-slice multislice computed tomography coronary angiography to assess in-stent restenosis. J Am Coll Cardiol. 2007;49(22):2204–10.

23. Erbel R et al. Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. Lancet. 2007;369(9576):1869–75.

24. Eggebrecht H et al. Images in cardiovascular medicine. Novel magnetic resonance-compatible coronary stent: the absorbable magnesium-alloy stent. Circulation. 2005;112(18):e303–4.

25. Okamura T et al. 3-Dimensional optical coherence tomography assessment of jailed side branches by bioresorbable vascular scaffolds: a proposal for classification. JACC Cardiovasc Interv. 2010;3(8):836–44.

26. Serruys PW et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet. 2009;373(9667):897–910.

27. Serruys PW et al. From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade? Eur Heart J. 2012;33(1):16–25b.

28. Waksman R. Biodegradable stents: they do their job and disappear.

J Invasive Cardiol. 2006;18(2):70–4.

29. Waksman R et al. Safety and efficacy of bioabsorbable magnesium alloy stents in porcine coronary arteries. Catheter and Cardiovasc Interv. 2006;68(4):607-17.

30. Waksman R. Current state of the absorbable metallic (magnesium)

stent. EuroIntervention. 2009;5(Suppl F):F94–7.

31. Waksman R et al. Early- and long-term intravascular ultrasound and angiographic findings after bioabsorbable magnesium stent implantation in human coronary arteries. JACC: Cardiovasc Interv. 2009;2(4):312–20.

32. Haude M. From PROGRESS to DREAMS. PCR focus group on bioresorbable vascular scaffolds. Session 6: CLINICAL DATA: Current status – Part I. Presented at EuroPCR, March 2012, Rotterdam, the Netherlands.

33. Waksman R. Lessons learned from preclinical studies of magnesium scaffolds (Biotronik's DREAMS program). PCR focus group on bioresorbable vascular scaffolds. Session 3: Understanding the basics of polymer bioresorption in vivo – Part II. EuroPCR, March 2012, Rotterdam,

the Netherlands.

34. Ormiston JA et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet. 2008;371(9616):899–907.

35. Onuma Y et al. Three-year results of clinical follow-up after a bioresorbable everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention. 2010;6(4):447–53.

36. Tanimoto S et al. Late stent recoil of the bioabsorbable everolimus-eluting coronary stent and its relationship with plaque morphology. J Am Coll Cardiol. 2008;52(20):1616–20.

37. Okamura T et al. In vivo evaluation of stent strut distribution patterns in the bioabsorbable everolimus-eluting device: an OCT ad hoc analysis of the revision 1.0 and revision 1.1 stent design in the ABSORB clinical trial. EuroIntervention. 2010;5(8):932–8.

38. Dudek D. Evaluation of the absorb everolimus eluting bioresorbable vascular scaffold (ABSORB BVS) in the treatment of patients with de novo native coronary artery lesions: 2 year clinical results of ABSORB cohort B trial. J Am Coll Cardio. 2012;59(13s1):E319.

39. Navarese EP et al. Safety and efficacy outcomes of first and second generation durable polymer drug eluting and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. BMJ. 2013;347:f6530.

40. Bangalore S et al. Outcomes with various drug-eluting or bare-metal stents in patients with ST-segment elevation myocardial infarction: a mixed treatment comparison analysis of trial level data from 34 068 patient-years of follow-up from randomized trials. Circ Cardiovasc Interv. 2013;6(4):378-90.

CORONARY STENT EVOLUTION – FROM PATHOLOGY TO CLINIC

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ABSTRACT

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. The pathogenesis of CAD relates to the presence of atherosclerotic plaques in coronary arteries, which are today most frequently treated by percutaneous coronary intervention. Initially, plain old balloon angioplasty demonstrated feasibility of dilating atherosclerotic coronary lesions; however, the high rate of acute-vessel recoil, restenosis, and dissection resulted in high acute closure rates and restenosis, which lead to the introduction of coronary stents, improving clinical outcome. However, in-stent restenosis (ISR) became the Achilles heel of bare metal stents owing to sustained neointimal (NI) growth. Drug-eluting stents (DES) were developed to reduce ISR, improving clinical outcomes and reducing the need for target vessel revascularisation. However, late and very late stent thrombosis emerged as a new problem compromising long-term results of DES, along with late catch-up of NI growth. Better materials, especially more biocompatible polymers, contributed to the refinement of DES technology, which substantially reduced stent thrombosis rates in second-generation DES. The idea of eliminating the foreign material after temporary scaffolding using fully bioresorbable scaffolds may hold great potential to revisit the interventional approach of treating CAD. This article will review the evolution of coronary artery intervention from clinical application to pathology, and will discuss current status and potential future directions of the newer therapeutic approaches.

Keywords: Plain old balloon angioplasty (POBA), bare metal stent, drug-eluting stent, bioresorbable stent, late stent thrombosis, very late stent thrombosis.

INTRODUCTION

Coronary balloon angioplasty, described by Dotter and Judkins (1964), was primarily performed by Andreas Gruntzig in 1977,[1] which led to the initial revolution in the treatment of coronary artery disease (CAD). Plain old balloon angioplasty (POBA) often resulted in acute vessel recoil owing to the inherent elasticity of coronary arteries, and along with the occurrence of dissection resulted in the frequent need of urgent revascularisation, which was solved by the implantation of metal scaffolds called stents. While stents helped to avoid acute vessel closure, persistent vascular injury of a metallic foreign body led to a new disease termed in-stent restenosis (ISR), which is the result of an exaggerated proliferation and migration of smooth muscle cells (SMCs) from the media into the nascent neointimal (NI) tissue. Consequently, the idea to disrupt NI growth by the use of anti-proliferative drugs delivered via coating the metal surface with non-erodible polymers was born.

To this end, drug-eluting stents (DES) are composed of a metallic platform with polymers releasing anti-proliferative compounds for days to weeks, which resulted in a significant reduction of NI growth in major clinical trials. However, this undoubted clinical success was acquired at the expense of a substantial delay in vascular healing,[2] which manifested in an increased risk of late thrombotic events. With these major drawbacks

in mind, newer alloys, thinner struts, better radial strength, and conformability were implemented in second-generation DES. Owing to the permanent irritation of metallic stents in the coronary arteries with all its consequences on vascular biology, bioresorbable scaffolds (BRS) have recently been introduced as a novel therapeutic option to temporarily scaffold dilated atherosclerotic plaques with eventual resorption of the scaffold that leads to the restoration of vascular function in the long-term. This review article discusses the clinical evidence of the different interventional coronary approaches and provides important pathological insights into the underlying vascular reactions of the different endovascular therapies, with a focus on coronary stents.

BARE METAL STENT (BMS)

Clinical Data

Sigwart et al.[3] implanted the first WALLSTENT® (Schneider AG, Bülach, Switzerland), a self-expanding Nitinol stent in 1986. The Palmaz-Schatz® (Johnson & Johnson, New Brunswick, NJ, USA) stent was developed thereafter (1987); it was the first balloon-expandable stainless steel stent. In the 1990s, concerns were first raised referring to high metallic density, frequent deployment failure, embolisation, complete occlusion, and significant risk of ISR.[4] However, at later stages of developmental efforts, two studies related to BMS changed the existing treatment paradigm, the BENESTENT and STRESS clinical trials; both established the superiority of BMS over POBA, making implantation of BMS a standard for the treatment of CAD.[5,6] However, the major issue with the use of BMS was the high incidence of ISR.[7] The clinical predictors of ISR included: lesion length,[8,9] stenting of small vessels,[10] use of multiple stents,[11,12] proximal left anterior descending (LAD) coronary stenting,[13] smaller final lumen diameter,[14] and use in diabetic patients.[15]

Pathology Findings

A systematic examination of BMS pathology was performed by Farb et al.,[14] who evaluated data from 35 coronary arteries (55 BMS). Fibrin, platelets, and acute inflammatory cells were predominantly observed ≤11 days after stenting, chronic inflammatory cells surrounded the struts after 12 days, and granulation tissue with SMC infiltration appeared after 14 days, which was only complete after 6 months.

Based on the recognition of restenosis as a clinical problem,[16] Farb et al.[14] determined that media injury induced greater arterial inflammation, and penetration of stent struts into a necrotic core was associated with increased NI growth (Figure 1).[15] Furthermore, the presence of neovascularisation as a consequence of persistent inflammation was another source for growth factor release, and this process turns into a vicious circle of sustained NI growth. Also, arterial medial fracture was associated with a 29% increase in NI thickness compared to an intact media wall ($p<0.01$).[15]

There have been significant changes in the material and design of BMS over the past decade.[17] New alloys such as cobalt chromium and platinum chromium have outdated stainless steel as the material of choice for stents. The newer materials permit manufacture of stents with lower profile, pushability and trackability, higher radiopacity, and thinner struts without compromising radial strength.

FIRST-GENERATION DES

Clinical Data

The need for repeat revascularisation secondary to restenosis was the main limitation of BMS implantation. The introduction of DES has resulted in a dramatic reduction of restenosis with a decrease in revascularisation procedures in a wide variety of patient and lesion subsets in large randomised clinical trials (RCTs).

Landmark studies such as RAVEL,[18] SIRUS,[19] and TAXUS IV[20] clearly demonstrated a reduction of angiographic restenosis and the need for target lesion revascularisation (TLR) or target vessel revascularisation (TVR), angiographic restenosis, and NI proliferation. Subsequently, the efficacy of DES in reducing ISR was confirmed in a number of larger clinical studies for different indications.[21,22]

However, the undoubted efficacy of first-generation DES came at the expense of substantially delayed arterial healing, and McFadden et al.[23] were the first to publish four confirmed cases of late stent thrombosis/very late stent thrombosis (LST/VLST) with sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES). After that, various meta-analyses were published reporting an LST/VLST incidence ranging from 0.2-0.7% and from 0.15-0.5%, respectively.[24-26] The risk of VLST was reported to increase at 0.5% per year for up to 4

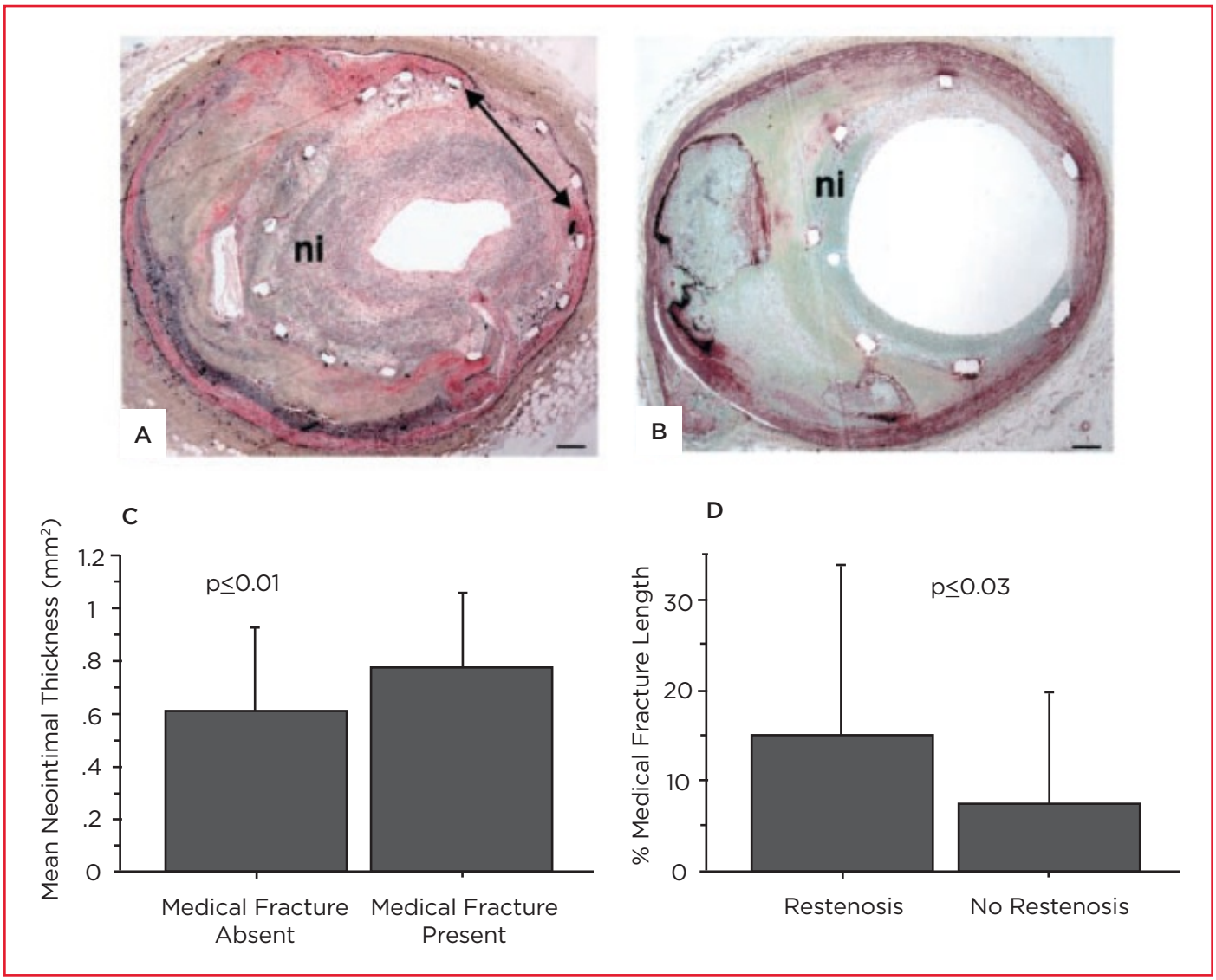

Figure 1: Photomicrographs (A and B) and bar graph (C) showing the association of arterial injury (medial fracture, arrow in A) with increased neointimal (ni) thickness versus stents in which the arterial media was intact (B). Medial fracture length as a percentage of the circumference of the internal elastic lamina was greater in restenotic stents compared with stents without restenosis (D). A and B have a Movat pentachrome stain. Scale bars 0.23 mm in A and 0.30 mm in B.
Reproduced from Farb et al.[15]

years of follow-up with first-generation DES.[27-29] Higher rates of LST and VLST were related to 'off-label' indication and anatomic factors such as: long lesions, calcification, vessel diameter (<3.0 mm), renal disease, or prior brachytherapy.[30,31]

Pathology Findings

Delayed arterial healing

Fundamental histopathologic insights of human DES implants were derived from a number of pathology studies that reported differences between DES and BMS cases. Joner et al.[2] evaluated 32 DES and 36 BMS to determine the long-term effects of DES on arterial healing, and identified pathologic mechanisms underlying LST. In ≥30 days duration, stent thrombosis (ST) was observed in 61% of DES versus 8% in BMS (p=0.0001). DES had significantly less in-stent NI growth compared with BMS (NI 2.9±1.1 mm^2 versus 4.9±3.0 mm^2, p=0.005). Regardless of implant duration, the percentage of covered (endothelialised) stent struts was significantly higher in BMS compared to DES.[2] At 60 days, the SES showed greater inflammatory reaction including eosinophils and giant cells, whereas PES predominantly showed

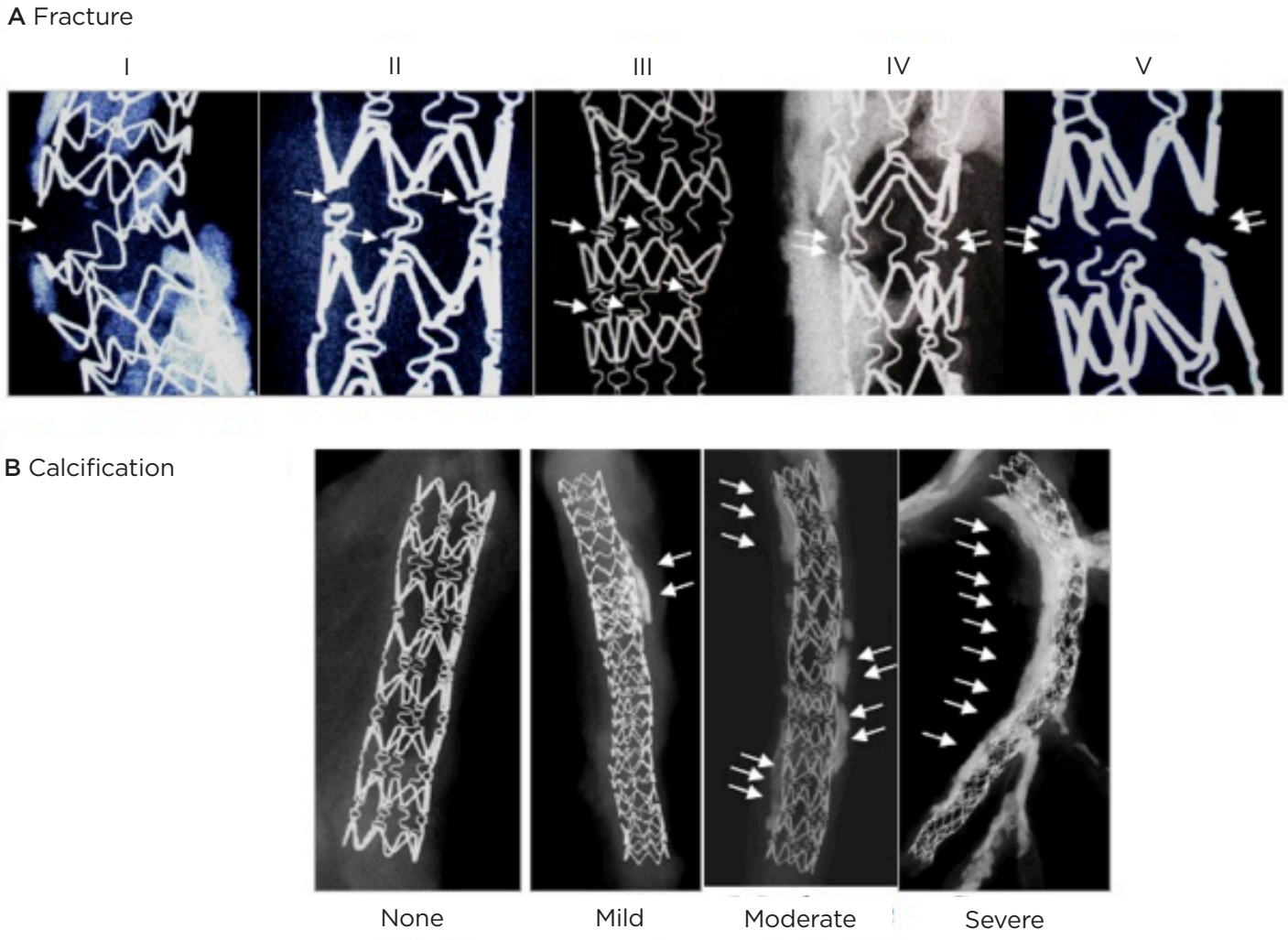

Figure 2: Representative images of stent fracture and calcification.
(A) Grade 1 fracture of paclitaxel-eluting stent (single-strut fracture), Grade 2 fracture of sirolimus-eluting stent (SES) (multiple breaks but alignment is preserved), Grade 3 fracture of SES (multiple breaks with deformation), Grade 4 fracture of SES (multiple breaks with transection but without gap), and Grade 5 fracture of SES (total separation). Arrows indicate fractured stents.
(B) Classification of calcification (mild: focal calcification; moderate: multiple sites of calcification; severe: >75% of stent length is associated with calcification). Arrows indicate areas of calcification.
Reproduced from Nakazawa et al.[37]

greater fibrin deposition. At 120 days, there was focal fibrin deposition and giant cell reaction around SES, whereas PES showed increased inflammation. At 60 days, BMS did not show fibrin deposition, but relatively greater NI coverage of stent struts was observed, which was complete at 120 days.[2]

In another study, Finn et al.[32] demonstrated that the pathologic determinant of LST/VLST following DES implantation was the presence of uncovered struts. A total of 46 human autopsy cases (62 coronary lesions) with DES implanted for >30 days were investigated. 28 ST lesions were compared with 34 lesions without ST of similar implant duration. The ratio of uncovered to total stent struts per section (RUTTSS) was greater in thrombosed compared to the patent lesions (0.50±0.23 versus 0.19±0.25, p<0.0001). Moreover, while some struts showed NI growth (healing), other struts remained bare and served as a nidus for thrombus (Thr) formation. RUTTSS was best correlated with endothelialisation among other morphometric parameters.

The heterogeneity in vascular healing was especially pronounced in the clinical setting of acute myocardial infarction (AMI) and bifurcation stenting. Nakazawa et al.[33] compared 25 AMI patients with 46 stable angina patients treated

by DES. In patients within 30 days after DES implantation, ST was similar in both groups (50%). However, in those implanted for >30 days, ST was more frequent (41%) in AMI compared to those with stable angina (11%). AMI culprit sites had significantly less NI thickness, greater fibrin deposition, higher inflammation, and greater incidence of uncovered struts compared with culprit sites from patients with stable angina.

A total 40 cases of bifurcation lesions with DES (n=19) and BMS (n=21) with implant duration >30 days were compared in a separate study.[33] Plaque formation in native coronary bifurcations and NI growth after DES implantation was significantly less at the flow divider versus the lateral wall. A higher incidence of LST in DES compared with BMS was associated with greater uncovered struts at flow divider sites, which is likely due to flow disturbances.[33]

The impact of stent fractures

Clinical incidence of DES fracture is reported as 1-2%.[34-36] Our group investigated the incidence of stent fracture by using high-contrast film-base radiography to determine the impact on histopathologic outcomes.[37] Stent fracture and the amount of calcification were defined as shown in Figure 2. The prevalence of stent fracture was observed in 29% of cases of first-generation DES cases. In single-stented lesions, the majority of stent fractures were localised in the middle portion of the stent body. On the other hand, in overlapping stents, most fractures were observed within a 5 mm distance from the overlapping zone, with similar frequency in proximal and distal regions.[37]

Lesions with stent fracture showed a higher rate of SES usage, longer stent length, greater number of stents, and a higher rate of overlapping stents. Six adverse pathologic findings (five thrombosis and one restenosis) were associated with Grade 5 fracture (67%).[37]

The pathology of restenosis

Nakano et al.[38] evaluated the histomorphological predictors and NI characteristics of DES restenosis. From our autopsy registry, 65 patients with 82 stented lesions were analysed and categorised to four groups: (i) patent (<50% stenosis); (ii) intermediate (50-74% stenosis); (iii) restenosis (≥75% but with residual lumen); or (iv) total occlusion (in-stent area occupied by organised Thr, proteoglycan matrix with microcapillaries) (Figure 3). The neointima of patent, intermediate, and restenotic DES stents consisted mainly of SMCs in a proteoglycan-collagen matrix, while the neointima of total occlusions consisted of an organised Thr showing a low smooth muscle cellularity within the proteoglycan matrix with micro-capillaries in the presence or absence of inflammation.[38]

Medial disruption was more frequently observed in the occluded group (80%) when compared with the patent (25%), intermediate (52%), and restenosis groups (53%) (p=0.016). Medial tears were associated with a higher incidence of inflammation, angiogenesis, and haemorrhage around struts. Furthermore, NI thickness correlated with maximum inter-strut distance more robustly in the presence of medial disruption (r=0.678, p<0.001) than in the absence of medial disruption (r=0.332, p=0.11), suggesting that the combination of medial disruption and irregular strut distribution resulted in uneven drug distribution that may lead to greater NI growth.[38] When NI composition was examined, DES showed significantly lower cellularity and collagen content than BMS. Conversely, the percentage of proteoglycan-rich extracellular matrix was greater in DES when compared to BMS.[38]

Pathology of malapposition

Malapposition or incomplete stent apposition (ISA) had been described as one of the risk factors for ST or restenosis.[39] ISA, defined as the lack of contact between at least one stent strut and the vessel intimal surface, not overlying a side-branch, was evaluated by Attizzani et al.[40] The author mentioned our group, which initially described the complex pro-inflammatory events after an ISA, with thick fibrin Thr between struts and vessels,[41] also relating the ISA with ST due to healing delay.[2] Another element to consider was the vessel positive remodelling, mentioning that Cook et al.[42] found a correlation between positive remodelling and eosinophils infiltrate, suggesting a hypersensitivity reaction on patient with ISA.

Pathology of neoatherosclerosis

Neoatherosclerosis has recently gained attention as a novel disease entity, representing a further manifestation of atherosclerotic lesion formation, which typically forms as an aftermath of stent implantation. Such atherosclerotic changes within the intra-stent NI tissue represent an accelerated

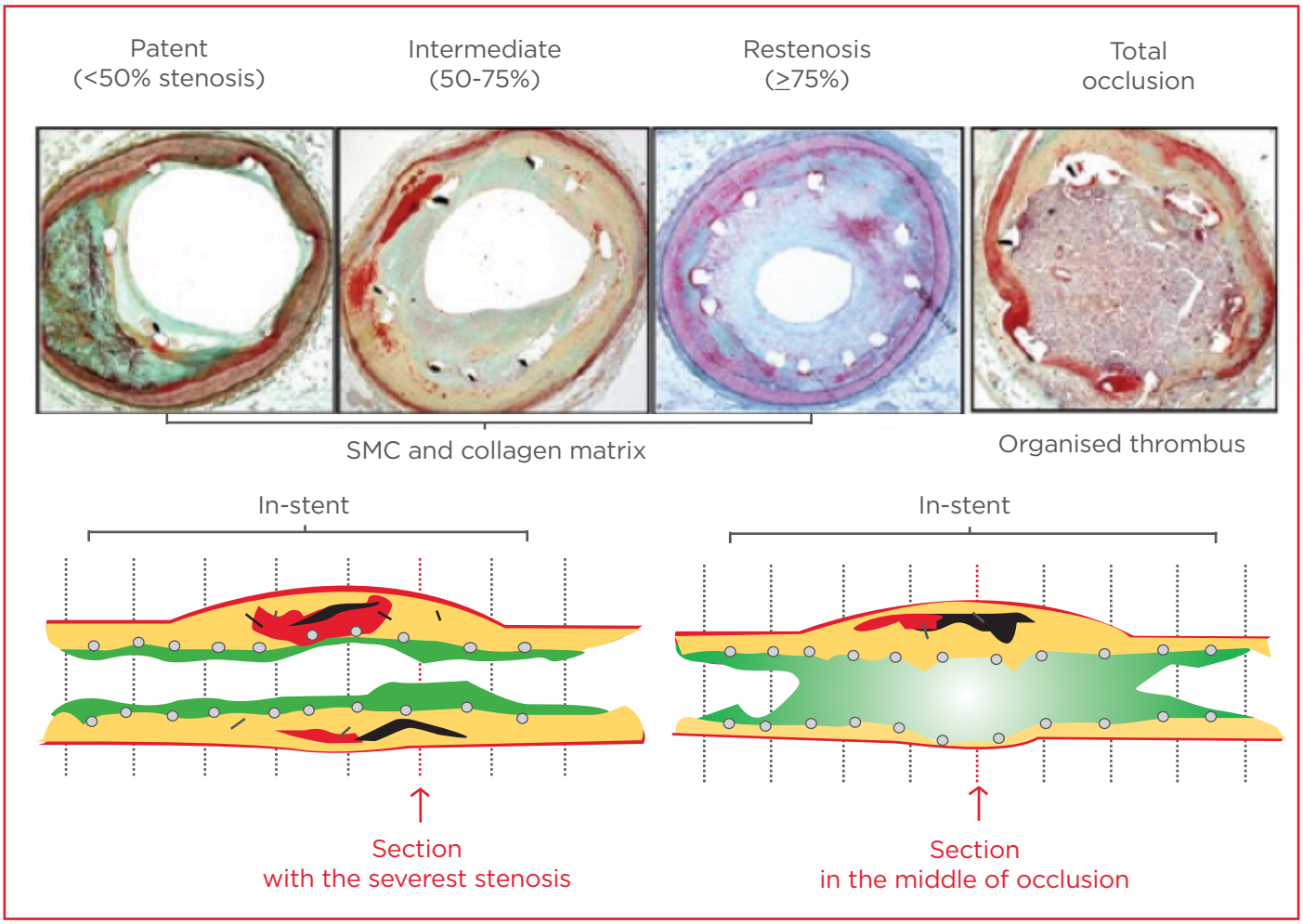

Figure 3: Representative histology and morphometry.
Photomicrographs in the upper row are representative cross-sectional histology of coronary lesions with drug-eluting stents implantation. Morphometry was performed at the site of the severest stenosis for patent, intermediate, and restenosis groups (left bottom). The section in the middle of the occlusion was used for measurements in arteries with total occlusion (right bottom).
Key: Yellow: underlying plaque; red: necrotic core; black: calcification; green: neointimal tissue.
Reproduced from Nakano et al.[38]

manifestation of atherosclerotic disease and are likely to have a substantial impact on clinical outcomes. Nakazawa et al.[43] evaluated 299 autopsy cases (142 BMS and 157 DES) with 406 lesions from our registry. The incidence of any neoatherosclerosis was greater in DES than BMS (31% versus 16%; p<0.001). Nearly one-half of the DES lesions with neoatherosclerosis (48%) contained peristrut foamy macrophage clusters, and the other half showed fibroatheromas. The implant duration was significantly shortened in DES with neoatherosclerotic change compared to BMS neoatherosclerotic change (DES 1.5±0.4years compared to BMS 6.1±1.5 years).[43] Neoatherosclerotic changes were greater in SES than in PES for implant durations of <2 years, while there was no significant difference for implant durations between 2 and 6 years.[43]

SECOND-GENERATION DES

Clinical Data

Second-generation DES were designed to overcome the limitations of the first-generation DES, and consisted of thinner stent struts and more biocompatible polymeric coatings with reductions in drug load. Data from 13 RCTs demonstrated that cobalt-chromium everolimus-eluting stent (CoCr-EES) had significantly reduced ST, TVR, and myocardial infarction (MI) (p=0.001; p=0.004; p=0.02, respectively) compared to other stents.[44]

In a network meta-analysis by Palmerini et al.,[45] CoCr-EES showed significantly lower rates of definite ST compared to BMS, as well as first and second-generation DES at 1 and 2-years.

In the RESOLUTE trial,[46] Resolute-Zotarolimus-eluting stent (Re-ZES) was non-inferior to the CoCr-EES with respect to cardiac death, MI, or revascularisation. No differences in ST were observed between Re-ZES and EES[46] at 13-months. These findings were also confirmed in the TWENTE trial,[47] which demonstrated no differences in target vessel failure (TVF) between Re-ZES and CoCr-EES. Also, definite and probable ST were similar among groups (p=0.59).[47]

Recently, in a further attempt to refine DES technology, biodegradable polymer-based DES and polymer-free DES were introduced. Koppara et al.[48] compared the histopathology of biodegradable polylactic acid (PLLA) versus permanent polymer polyethylene-co-vinyl acetate/poly-n-butyl methacrylate (PEVA/PBMA) based DES with uncoated BMS, demonstrating significant reductions in inflammation and NI growth with biodegradable polymer PLLA among others groups. A recent meta-analysis by Stefanini et al.[49] comparing biodegradable polymer-based DES to permanent polymer-based DES (ISAR-TEST, ISAR-TEST 4, and LEADERS) at 4-years showed a significant reduction in TLR and ST, driven by lower LST[49] for biodegradable polymer-based DES group; also the incidence of MI was lower on the same group. Navarese et al.[50] recently published a network meta-analysis comparing polymer-free versus durable polymer DES. From 8 studies and 6,178 patients, the polymer-free DES was as safe and as effective as durable polymer DES, in terms of mortality, MI, ST, TVR, and TLR.[50] Also Bangalore et al.[51] evaluated efficacy and safety of biodegradable polymer compare to BMS and durable polymer DES. In terms of TVR and LST, biodegradable polymer was better than paclitaxel and ZES, but inferior to CoCr-EES.[51] Those findings suggest a tendency for a better outcome on biodegradable polymer; however, in the near future, more RCTs with specific head-to-head comparison should be addressed.

The Pathology Findings

Recently, Otsuka et al.[52] published a pathologic study comparing second-generation to first-generation DES (Figure 4). A total of 204 lesions (SES=73; PES=85; CoCr-EES=46) from 149 autopsy cases with duration of implantation >30 days and ≤3 years were pathologically analysed. The observed frequency of LST and VLST was lower in CoCr-EES (4%) compared with SES (21%; p=0.029) and PES (26%; p=0.008). The prevalence of restenosis for CoCr-EES (17%) did not differ significantly from that observed for SES (14%) and PES (12%). The frequency of uncovered struts was markedly lower in CoCr-EES (2.6%) compared to SES (18.0%; p<0.0005) and PES (18.7%; p<0.0005). The prevalence of DES lesions with >30% uncovered struts was also significantly lower in CoCr-EES (20%) than in SES (60%; p<0.0005) and PES (67%; p<0.0005) (Figure 4). Strut coverage was also evaluated in the setting of off-label clinical indications versus on-label indications. CoCr-EES compared with SES and PES showed greater strut coverage for both on and off-label indications. In terms of inflammation, CoCr-EES showed significantly lower inflammation scores compared with SES. The overall prevalence of neoatherosclerosis after CoCr-EES implantation in native coronary arteries was 29%, which did not differ significantly from SES (35%, p=0.62) and PES (19%, p=0.47).[52]

BRS

Clinical Data

The concept of BRS to support vascular integrity during the acute phase of percutaneous coronary intervention after dilatation procedures, followed by antiproliferative drug release and finally with a controlled scaffold degradation to restore vasoreactivity and function,[53] has emerged as a potential solution to resolve the drawbacks of current metallic stents. Although results of large clinical trials are not available to date, several small clinical studies in selected populations have been published.

The ABSORB everolimus-eluting bioresorbable vascular scaffold (BVS) (Abbott Vascular, Santa Clara, CA,USA) was evaluated in the ABSORB cohort A study, a multicentre single-arm study that enrolled 30 patients. The ABSORB BVS was found to be safe and had a low ischaemia-driven major adverse cardiovascular events (id-MACE) rate at 4-year follow-up.[54] There was only a single non-Q-wave MI, and no new id-MACE events were reported between 6 months and 4 years; also there was no occurrence of ST according to Academic Research Consortium (ARC) definitions.[54] The second-

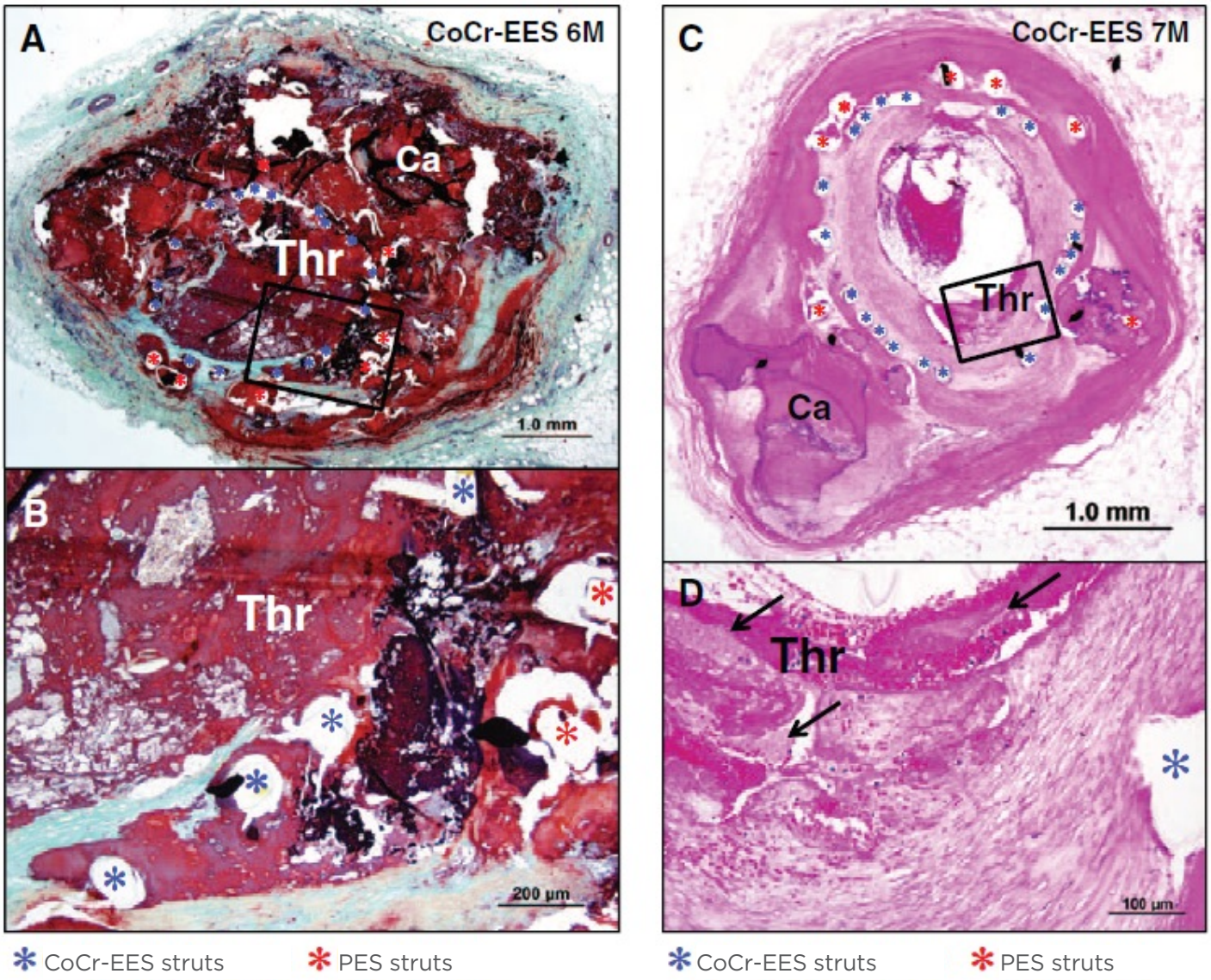

Figure 4: Late stent thrombosis in two cases with cobalt-chromium everolimus-eluting stent (CoCr-EES). A and B: Histological sections from a 55-year-old man with CoCr-EES implanted over an underlying paclitaxel-eluting stent (PES) in the proximal right coronary artery 6 months antemortem, who died suddenly of stent thrombosis (ST). A low-power image (A) shows occlusive luminal thrombus (Thr) within the stents with underlying calcified plaque; Ca indicates calcification. A few struts of CoCr-EES are covered with thin neointima, but the majority of the struts are uncovered, which is highlighted in a high-power image in B.

C and D: Histological sections from a 72-year-old woman with CoCr-EES implanted over an underlying PES in the proximal left anterior descending (LAD) coronary artery 7 months antemortem. The patient presented with acute myocardial infarction from ST and underwent balloon angioplasty, which resulted in rupture of the LAD coronary artery. A low-power image (C) shows in-stent restenosis with luminal Thr; the neointima is focally dissected because of the balloon angioplasty with overlying nonocclusive Thr. A high-power image (D) shows erosive neointima with overlying fibrin and platelet Thr. A and B are stained with Movat pentachrome, and C and D are stained with haematoxylin and eosin. *Reproduced from Otsuka et al.*[52]

generation, Absorb BVS 1.1, has improved radial strength, mechanical integrity, and release kinetics. In the ABSORB Cohort B long-term follow-up trial, there were 6 cases of in-segment restenosis in a total of 101 patients. Of six restenosis cases, two occurred early (<6 months), one occurred late (6-12 months), and three occurred very late (>12 months) by angiography.[55] More clinical studies are needed to determine the true safety and efficacy of BRS in complex lesion settings.

Pathologic Finding

Preclinical experience

Preclinical studies are very important in the assessment of BRS since details of degradation and absorption can only be confirmed by histopathology. Onuma et al.[56] correlated the histopathologic findings after implantation of the ABSORB BVS with optical coherence tomography (OCT). They described four degradation levels based on morphological appearance of stent struts: i) Perserved Box, an open acellular region with well-defined borders; ii) Open Box, a region of hyaline material (proteinaceous) separated by extracellular matrix (proteoglycans) and cells; iii) Dissolved Black Box, a region without hyaline material but with low to moderately cellular connective tissue; and iv) Dissolved Bright Box, a poorly circumscribed region of dense connective tissue with moderate-to-low cellularity in which cells were not regularly arranged.[56] The chronological histopathology findings, found in the early phase as stent struts, are covered by NI tissue composed of SMCs and proteoglycans, while stent struts remain intact. In the intermediate phase, struts are partially substituted by proteoglycan matrix, followed by infiltration of connective tissue and cellular components. In the final phase, stent strut resorption sites become completely integrated into the arterial wall in the absence of polymer residues.[56]

CONCLUSION

While DES contributed to the global success in improving outcomes of patients suffering from CAD, this benefit is partly counterbalanced by reports of delayed arterial healing associated with increased rates of ST in DES compared to BMS. While second-generation DES substantially improved upon the shortcomings of first-generation DES, there remain important issues such as increased inflammation, especially with the use of permanent polymers, which was clearly improved in second-generation DES as demonstrated by Otsuka et al.[52] DES with biodegradable polymer technology will likely help to further improve outcomes. Complete BRS likely hold great value to eliminating some of the remaining hazards of current DES technology but this needs confirmation in large clinical trials. Histopathologic assessment of coronary stents provides valuable insights for the identification of relevant obstacles with contemporary endovascular approaches, and will likely play an important role for the improvement of future interventional strategies.

REFERENCES

1. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet. 1978;1(8058):263.

2. Joner M et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol. 2006;48(1):193-202.

3. Sigwart U et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med. 1987;316(12):701-6.

4. Serruys PW et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med. 1991;324(1):13-7.

5. Serruys PW et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med. 1994;331(8):489-95.

6. Fischman DL et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med. 1994;331(8):496-501.

7. Hoffmann R et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. Circulation. 1996;94(6):1247-54.

8. Linnemeier TJ. The illusive ostial and proximal LAD. Catheter Cardiovasc Interv. 2000;49(3):272-3.

9. de Feyter PJ et al. Reference chart derived from post-stent-implantation intravascular ultrasound predictors of 6-month expected restenosis on quantitative coronary angiography. Circulation. 1999;100(17):1777-83.

10. Lee SG et al. Predictors of diffuse-type in-stent restenosis after coronary stent implantation. Catheter Cardiovasc Interv. 1999;47(4):406-9.

11. Mercado N et al. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. J Am Coll Cardiol. 2001;38(3):645-52.

12. Schwartz RS et al. Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model. J Am Coll Cardiol. 1992;19(2): 267-74.

13. Rogers C, Edelman ER. Endovascular stent design dictates experimental restenosis and thrombosis. Circulation. 1995;91(12):2995-3001.

14. Farb A et al. Pathology of acute and chronic coronary stenting in humans. Circulation. 1999;99(1):44-52.

15. Farb A et al. Morphological predictors of restenosis after coronary stenting in humans. Circulation. 2002;105(25): 2974-80.

16. Antoniucci D et al. Restenosis after coronary stenting in current clinical practice. Am Heart J. 1998;135(3):510-8.

17. Morton AC et al. The influence of physical stent parameters upon restenosis. Pathol Biol (Paris). 2004;52(4):196-205.

18. Morice MC et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002;346(23):1773-80.

19. Moses JW et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery.

N Engl J Med. 2003;349(14):1315-23.

20. Stone GW et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350(3):221-31.

21. Spaulding C et al. Four-year follow-up of TYPHOON (trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with BallOON angioplasty). JACC Cardiovasc Interv. 2011;4(1):14-23.

22. Meier B et al. Sirolimus-eluting coronary stents in small vessels. Am Heart J. 2006;151(5):1019.e1-7.

23. McFadden EP et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet. 2004;364(9444):1519-21.

24. Ong AT et al. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol. 2005;45(12):2088-92.

25. Moreno R et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol. 2005;45(6):954-9.

26. Urban P et al. Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. Circulation. 2006;113(11):1434-41.

27. Stone GW et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med. 2007;356(10): 998-1008.

28. Kastrati A et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007;356(10):1030-9.

29. Mauri L et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med. 2007;356(10): 1020-9.

30. Lasala JM et al. Drug-eluting stent thrombosis in routine clinical practice: two-year outcomes and predictors from the TAXUS ARRIVE registries. Circ Cardiovasc Interv. 2009;2(4):285-93.

31. Mishkel GJ et al. Correlates of late and very late thrombosis of drug eluting stents. Am Heart J. 2008;156(1):141-7.

32. Finn AV et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. Circulation. 2007;115(18):2435-41.

33. Nakazawa G et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation. 2008;118(11):1138-45.

34. Aoki J et al. Incidence and clinical impact of coronary stent fracture after sirolimus-eluting stent implantation. Catheter Cardiovasc Interv. 2007;69(3):380-6.

35. Lee MS et al. Stent fracture associated with drug-eluting stents: clinical characteristics and implications. Catheter Cardiovasc Interv. 2007;69(3):387-94.

36. Shaikh F et al. Stent fracture, an incidental finding or a significant marker of clinical in-stent restenosis? Catheter Cardiovasc Interv. 2008;71(5):614-8.

37. Nakazawa G et al. Incidence and predictors of drug-eluting stent fracture in human coronary artery a pathologic analysis. J Am Coll Cardiol. 2009;54(21):1924-31.

38. Nakano M et al. Human autopsy study of drug-eluting stents restenosis: histomorphological predictors and neointimal characteristics. Eur Heart J. 2013;34:3304-13.

39. Lee CW et al. Intravascular ultrasound findings in patients with very late stent thrombosis after either drug-eluting or bare-metal stent implantation. J Am Coll Cardio. 2010;55:1936-42.

40. Attizzani GF et al. Mechanisms, pathophysiology, and clinical aspects of incomplete stent apposition. J Am Coll Cardio. 2014;63:1355-67.

41. Virmani R et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: Should we be cautious? Circulation. 2004;109:701-5.

42. Cook S et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation. 2009;120:391-9.

43. Nakazawa G et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol. 2011;57(11): 1314-22.

44. Baber U et al. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. J Am Coll Cardiol. 2011;58(15):1569-77.

45. Palmerini T et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet. 2012;379(9824):1393-402.

46. Serruys PW et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med. 2010;363(2):136-46.

47. von Birgelen C et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol. 2012;59(15):1350-61.

48. Koppara T et al. Histopathological comparison of biodegradable polymer and permanent polymer based sirolimus eluting stents in a porcine model of coronary stent implantation. Thromb Haemost. 2012;107:1161-71.

49. Stefanini GG et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J. 2012;33(10):1214-22.

50. Navarese EP et al. Short and long-term safety and efficacy of polymer-free vs. durable polymer drug-eluting stents. A comprehensive meta-analysis of randomized trials including 6178 patients. Atherosclerosis. 2014;233:224-31.

51. Bangalore S et al. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. BMJ. 2013;347:f6625.

52. Otsuka F et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. Circulation. 2014;129(2):211-23.

53. Waksman R. Biodegradable stents: they do their job and disappear. J Invasive Cardiol. 2006;18(2):70-4.

54. Dudek D et al. Four-year clinical follow-up of the ABSORB everolimus-eluting bioresorbable vascular scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention. 2012;7(9):1060-1.

55. Nakatani S et al. Early (before 6 months), late (6-12 months) and very late (after 12 months) angiographic scaffold restenosis in the ABSORB Cohort B trial. EuroIntervention. 2014;pii:20130829-09. [Epub ahead of print].

56. Onuma Y et al. Intracoronary optical coherence tomography and histology at 1 month and 2, 3, and 4 years after implantation of everolimus-eluting bioresorbable vascular scaffolds in a porcine coronary artery model: an attempt to decipher the human optical coherence tomography images in the ABSORB trial. Circulation. 2010;122(22):2288-300.

REVIEW: TRANSCATHETER AORTIC VALVE IMPLANTATION

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) has evolved as a routine therapeutic option to treat elderly and high-risk patients with symptomatic aortic stenosis over recent years. Different prostheses with self-expandable nitinol frames or balloon expandable cobalt-chromium frames are available to be inserted by means of a retrograde transfemoral, retrograde transaortic, or an antegrade transapical approach. Current risks of TAVI include: malpositioning, particulate embolisation with subsequent stroke, vascular diseases, annular injury, or coronary obstruction, as well as the need for new onset pacemaker implantation; procedural complication rates for these remain at 5%. Second-generation valves, together with further technical developments, are expected to lead to easier and safer implantation techniques, translating into optimised outcomes for individual patients. The key to successful TAVI therapy is: joint pre-procedural indication, peri-procedural conduct, and post-procedural care of the patients by an experienced heart team.

Keywords: Transcatheter aortic valve implantation, aortic valve, high-risk, aortic stenosis, heart team.

INTRODUCTION

The aim of this review is to give an overview on transcatheter aortic valve implantation (TAVI), technical aspects, results, and perspectives. TAVI has evolved as a standardised and routine procedure to treat elderly and high-risk patients with aortic stenosis (AS) over the past years. Following initial implants using retrograde transfemoral (TF) access (2002 onwards) and antegrade transapical (TA) access (2004 onwards), different valve systems have received Conformité Européenne (CE) approval in 2007 and 2008. Since then, the numbers of TAVI procedures have seen a steep increase; in part due to referrals of elderly and high-risk patients who had not received treatment before. In Germany, the country with the largest number of implants in Europe, approximately 9,000 patients received TAVI in 2012, whereas a slightly larger and more stable number have received conventional aortic valve surgery (AVS) recently.[1] According to current guidelines there is an indication to perform TAVI in elderly and high-risk patients with relevant comorbidities as diagnosed by the heart team.[2,3]

TECHNICAL ASPECTS OF THE PROCEDURES

TAVI consists of two parts: 1) access to the cardiovascular system by means of a sheath or a sheathless application system; and 2) positioning and implantation of a prosthetic heart valve at the site of the native aortic valve. The usually calcified native aortic valve leaflets remain in place and are squeezed aside. The implanted prosthesis consists of a self-expandable or a balloon expandable stent with an integrated xenograft consisting of pericardial or porcine leaflets. Access for TAVI is gained using a retrograde TF, a retrograde transaortic (TAo), a retrograde trans-subclavian (TS) or an antegrade TA approach.

Access sheath size ranges from 14 F up to 24 F for the currently used TF devices and from 18 F to 26 F for TA devices, with some larger ones being sheathless. There are specific advantages and disadvantages of the antegrade versus retrograde approaches. Important factors influencing the approach include: the size and invasiveness of the respective incisions, the distances to the targeted aortic valve, potential manipulations on the aortic arch, coaxial versus oblique access with direct or remote control, and the feasibility of commissural alignment during valve implantation. Potential advantages and disadvantages of performing TAVI under conscious sedation versus fast track general anaesthesia must also be considered.

Optimal imaging is required to safely perform TAVI; this includes a fluoroscopic system with 3D visualisation, transoesophageal echocardiography with 3D visualisation, and a hybrid operative theatre if available. Additional software tools allow for specific evaluations of the dimensions as well as the morphology of the aortic root, including the amount of calcifications, etc.

Due to its inherent complexity and potential complications, TAVI has to be considered equivalent to an operative procedure. This is especially true when considering the specific challenges of some procedures as well as the complexities of underlying diseases of high-risk patients. Therefore it should be performed under circumstances quite comparable to conventional AVS. Utmost technical quality is paramount for procedural success. This includes: 1) an established heart team with a cardiologist and a cardiac surgeon, experienced experts in the field of TAVI, working together in the procedure; 2) standardised procedural workflows; and 3) a well-equipped hybrid operative theatre with optimal imaging modalities including 3D visualisation. All three aspects lead to high quality and, thus, maximum safety for the patients.

PATIENTS

Patients with relevant aortic valve disease, mostly AS, suffer relevant clinical symptoms such as dyspnoea on exertion, angina, or even syncope. Under these conditions, full physical functionality can only be regained by a new valve due to the fact that there is no effective medical treatment for AS. Conventional surgery, e.g. resection of the diseased native valve cusps and insertion of an artificial valve (mechanical, xenograft, or homograft) by means of standard suturing techniques, has been the only therapeutic option for decades. Conventional AVS has evolved as a standardised and low-risk procedure (risks of approximately 1% in experienced centres) with excellent long-term outcomes. Elderly and higher-risk patients, however, have frequently neither been referred for, nor accepted for, conventional surgery. Therefore, TAVI offers an appealing additional therapeutic option. According to the current guidelines, old age and increased risk profiles are factors required to select a patient for TAVI. Many patients who may not have been referred several years ago are now being treated. According to current guidelines, TAVI is indicated in high-risk elderly patients with AS according to the treating heart team's decision. In addition to high-risk elderly patients, some intermediate-risk patients may receive TAVI as well. In order to perform best practice, clear interdisciplinary heart team decisions should be performed taking individual patient-related factors into account.

Exact patient screening is important before performing TAVI. This includes specific imaging delineating the morphology of aortic valve disease and the respective dimensions of the aortic root. Due to the fact that TAVI is performed by means of valve implantation without resection of native calcified cusps and without direct measurement of the annular dimensions, annular sizing by transoesophageal echocardiography in a 2D and 3D view as well as computed tomography (CT) is important. For CT assessment there are specific software tools allowing for precise and automated measurement of the aortic root, including the effective aortic annulus based on its area and/or perimeter. Over the past years, these specific assessments have been an important contributing factor to the further improvement of the results of TAVI procedures throughout. The slightly decreasing incidence of severe paravalvular regurgitation after TAVI may be clearly related to improved preoperative patient assessment by improved imaging.

Regarding outcomes, there are several studies showing good outcomes with TAVI. Selected studies, however, may be at risk of reflecting a 'selected reality', whereas larger scale 'all-comers' registries may reflect the effective therapeutic outcomes in a better way. Therefore, the currently ongoing German Aortic Valve Registry (GARY), for example, is of utmost importance to build

further evidence of which therapeutic option is best for the respective patients.[4]

A prospectively randomised all-comers trial comparing TAVI to conventional surgery in intermediate-risk patients would be ideal; however, such a trial is neither available nor in view. The currently performed Placement of Aortic Transcatheter Valve (PARTNER) 2 and Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trials target an intermediate-risk population while having selective inclusion criteria, and thus, do not reflect everyday all-comers practice. The US PARTNER trial has been a prospectively randomised trial with quite selective patient inclusion, showing comparable outcomes of TAVI in comparison to conventional surgery in high-risk patients.[5] The initial results from the GARY registry indicate higher-risk profiles for TAVI patients in comparison to those receiving conventional surgery. Although this registry reflects all-comers clinical practice from Germany, the choice of procedure being performed was made by the physicians. Therefore, further comparison of outcomes may only, in part, be justified statistically.

Up to 1 year follow-up, conventional valve surgery led to the lowest mortality rates in patients with low and intermediate-risk profiles, as discriminated by the logistic EUROscore and the German Aortic Valve Score (AKL score). In very high-risk patients, however, TAVI was as good as conventional surgery in relation to 1-year outcomes.[4] The recently published randomised clinical trial on a self-expanding TF device led to superior results as compared to high-risk surgical patients; patients had a mean age of 83 years and mean Society Thoracic Surgeons (STS) score of 7.5%.[6] In the 'Transcatheter Valve Therapy' registry in the USA, 7,710 patients were included from November 2011 until May 2013. A total of 2.6% of cases were technically unsuccessful and 4.1% of patients had to be supported with cardiopulmonary bypass, while conversion to conventional surgery was required in 1.2%. Overall 30-day mortality was 7.6% and 30-day stroke was 2.8%, with data completeness at this time of 41%.[7]

TAVI DEVICES

Current devices to perform TAVI mostly are first or second-generation valves that have been used clinically for several years. Newer systems are being developed, aiming at offering additional solutions for improved patient outcomes and enhanced safety. This includes specific features to minimise paravalvular leakage, further reduction in crimped sheath diameter in order to allow for an easy insertion, options to retrieve the device in part or completely (if possible after it is already fully functional), possible commissural orientation with exact anatomical positioning, potential features to further ease perfect positioning, and eventually, automated functionality. Some of these features may be available for clinical practice soon whereas others warrant significant further developments.

TAVI devices consist of a specifically designed valve and an application system, which is usually inserted over a guidewire by means of a sheath or in a sheathless manner. The valve consists of a thin stent, which is balloon expandable (stainless steel or cobalt-chromium) or self-expandable (usually nitinol). Valve leaflets consist of bovine pericardium, porcine pericardium, or of porcine leaflets. Some of these valves have an additional anticalcification treatment similar to conventional surgical xenografts in order to protect against tissue degeneration, and thus achieve optimal valve durability. Examples of common TAVI valves are shown in Figure 1. An overview on the sizes of the different devices and on treatable annulus diameters is given in Table 1. The different features of current and future TAVI valves are summarised in Table 2.

In the early years, the Edwards SAPIEN™ balloon expandable valve and the Medtronic COREVALVE™ self-expandable valve were available. These are the two devices with the largest clinical experience worldwide. Whereas the SAPIEN™ valve is available for retrograde (TF, TAo, TS) and antegrade (TA) insertion, the COREVALVE™ is available for retrograde implantation only. The SAPIEN™ is a rather short device (16-22 mm), designed for subcoronary implantation whereas the COREVALVE™ stent has a length of almost 50 mm, thus requiring an implantation that surpasses the coronary ostia while obtaining additional aortic stabilisation. After implantation, the leaflets are in a rather intra-annular position with the SAPIEN™, whereas, they are slightly supra-annular with the COREVALVE™. Available valve sizes are 23 mm, 26 mm, and 29 mm for both, and an additional 31 mm for the COREVALVE™.

Figure 1: Common valves for transcatheter aortic valve implantation.

Table 1: Valve diameters and treatable annulus sizes of different currently available transcatheter heart valves.

Device	Sizes (mm)	Oversizing in relation to nominal size (mm)	Treatable annulus diameter (mm)
Sapien XT™	20, 23, 26, 29	1-3	18-27
Sapien 3™	20, 23, 26, 29	1-3	18-28
CoreValve™	23, 26, 29, 31	3	18–29
CoreValve Evolut™	23, 26, 29, 31	3	18-29
Portico™	23, 25, 27*, 29*	2-3	18-27
Direct Flow™	23, 25, 27, 29	2-3	19-27
Lotus™	23, 27	0-3	20-27
Accurate™	23, 25, 27	0-3	20-27
Jenavalve™	23, 25, 27	0-3	20-27
Engager™	23, 26, 29	1-3	20-27

** No CE approval yet, currently in clinical trial.*

Table 2: Current and new devices and their respective features.

Device	Access (TF, TA, TAo)	SE (self-expandable), BE (balloon expandable)	Re-positioning	Commissural alignment	Paravalvular leak prevention
Sapien XT™	TF, TA, TAo	BE	no	no	no
Sapien 3™	TF, TA, TAo	BE	no	no	yes
CoreValve™	TF, TAo	SE	no	no	no
CoreValve Evolut™	TF, TAo	SE	partially	no	no
Portico™	TF, TA*	SE	partially	no	no
Direct Flow™	TF	Inflatable	yes	no	no
Lotus™	TF	SE	yes	no	yes
Accurate™	TA, TF*	SE	partially	yes	no
Jenavalve™	TA, TF*	SE	partially	yes	no
Engager™	TA	SE	partially	yes	no

** Under development.*

The initial SAPIEN™ prosthesis was replaced by the SAPIEN XT™ prosthesis from 2009 onwards.

Recent developments of these two devices are the SAPIEN 3™ valve, which just received CE approval, and the COREVALVE EVOLUT™ prosthesis. The SAPIEN 3™ offers smaller sheath diameters (14-18 F) and an additional outer skirt to minimise the risk of post-implant paravalvular leakage.[8] The COREVALVE EVOLUT™ offers improved stability during positioning and some retrieval options.[9]

Besides these large players in the field, several other devices have been developed in the past years.

For retrograde TF access the PORTICO™ (St. Jude Medical), DIRECT FLOW™ (Direct Flow Medical Inc.), and SADRA™ Lotus valve (Boston Scientific Inc.) have received CE approval, with further devices being studied (ACCURATE TF™, Symetis Inc.) or being developed (JENAVALVE TF™). The PORTICO™ device consists of a nitinol stent of approximately 50 mm length, which looks slightly similar to the previously mentioned Corevalve™. It allows for retrieval after up to 80% of implantation, a position where valve functionality can already be assessed. At present, the 23 mm and the 25 mm PORTICO™ valves have received CE approval whereas the 27 mm and 29 mm versions will undergo further clinical evaluation.[10] A transapical version is being further developed in parallel.

The DIRECT FLOW™ valve is unique in design, as it avoids any metal and is made from two inflatable circular structures that are connected by cloth. It has a unique implantation and fixation technique, which leads to good outcomes with TF implantation in experienced hands.[11] The SADRA LOTUS™ valve consists of a nitinol mesh, which is quite long in the crimped position and foreshortens during TF implantation; it allows for complete retrieval of the device.[12]

The ACCURATE TF™ valve (Symetis Inc.) has recently entered clinical trials to reach CE approval.[13] For TA access, the ACCURATE™ system has gained relatively large clinical expertise with more than 1,000 implants at the end of 2013. The ACCURATE™ valve has a self-expanding nitinol stent that can be placed in an anatomically correct position, matching the commissures to the native ones quite easily. Furthermore, it allows for partial repositioning. The overall implantation procedure is strikingly easy. Future developments will include larger application system diameters down to 18 F and an active mechanism to seal against paravalvular leaks.

Clinical results with the first generation ACCURATE™ valve are promising.[13,14]

The JENAVALVE™ (Jenavalve Inc.) TA system received CE approval in parallel to the previously mentioned device and has seen several hundred implantations since. The JENAVALVE™ has a unique self-expandable stent with additional 'feelers' to guide positioning at the annular level together with commissural alignment and safe anchoring.[15] The ENGAGER™ (Medtronic Inc.) system has some comparable functionality as the previously mentioned JENAVALVE™ in terms of three 'arms' that are being placed at the three nadirs during implantation. The ENGAGER™ consists of a self-expanding frame, and has been implanted into several hundred patients.[16]

FUTURE DEVELOPMENTS

Over the past 10 years, TAVI has gained widespread acceptance in many countries for treating elderly and high-risk patients. At present, there are different ongoing discussions upon the future of TAVI; the assessment of risk profiles using currently available scoring systems versus the development of a TAVI-specific risk scoring system is of clinical interest. Morphological factors, especially the amount, extent, and eccentricity of aortic valve calcifications, together with specific aortic root anatomy, should be taken into account. In the future there may be specific patient-related factors that lead to a certain indication for one or another of the currently available TAVI valve systems. Imaging in general will further evolve towards an increasing use of 3D visualisation, coupled with online overlay of relevant structures. This will certainly lead to improved implantation procedures with better outcomes for patients.

The extension of indications for TAVI, extending from high-risk patients to intermediate-risk patients, is being frequently discussed. By means of all-comers clinical trials only, in the future we will be able to decide the best therapeutic option for these patients. Different access routes will be further discussed in the future. At present it remains clear that there is no clinical evidence to support a retrograde versus antegrade access route, or vice versa. For the patient, any access performed by an experienced heart team leading to a minimal complication rate is ideal.

TAVI is still associated with some severe complications, which may occur in up to 5% of procedures. Some of these complications have a significant and immediate, severe impact upon the patient, which could put their future at risk. Avoidance of complications, therefore, is of utmost interest for all physicians. Excellent quality of TAVI procedures, being performed by a heart team in a hybrid operative theatre, together with trained conduct of the procedures, is important. The goal of TAVI for the coming years - besides further standardisation - is the reduction of technical risks, including less malpositioning, the avoidance of post-implant renal failure, avoidance of other organ failures, and the minimisation of stroke. Further developments of TAVI devices, as outlined previously, will certainly contribute to an improved functionality during the procedures as well as even better patient outcomes for the future.

CONCLUSION

In summary, TAVI - after only 10 years of clinical practice - has already evolved towards a highly standardised and relatively safe procedure for minimally invasive treatment of severe symptomatic AS in elderly and high-risk patients. By means of a heart team approach, indications for selection of TAVI versus other therapeutic strategies will be set for the utmost benefit of our patients.

REFERENCES

1. Beckmann A et al. Cardiac surgery in Germany during 2012: a report on behalf of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg. 2014;62(1):5-17.

2. Vahanian A et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012;33(19):2451-96.

3. Vahanian A et al. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2008;29(11):1463-70.

4. Hamm CW et al. The German Aortic Valve Registry (GARY): in-hospital outcome. Eur Heart J. 2013;doi:10.1093/eurheartj/eht381. [Epub ahead of print].

5. Smith CR et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364(23):2187-98.

6. Adams DH et al. Transcatheter aortic valve replacement with a self-expanding prosthesis. N Engl J Med. 2014. [Epub

ahead of print].

7. Mack MJ et al. Outcomes following transcatheter aortic valve replacement in the United States. JAMA. 2013;310(19):2069-77.

8. SAPIEN 3. Available at: http://www.edwards.com/eu/Products/TranscatheterValves/Pages/sapien3.aspx.

9. Sinning JM et al. Medtronic CoreValve Evolut valve. EuroIntervention. 2012;Suppl Q:Q94-6.

10. Willson AB et al. Transcatheter aortic valve replacement with the St. Jude Medical Portico valve: first-in-human experience. J Am Coll Cardiol. 2012;60(7):581-6.

11. Schofer J et al. Prospective multicenter evaluation of the direct flow medical transcatheter aortic valve. J Am Coll Cardiol. 2014;63:763-8.

12. Gooley R et al. The SADRA Lotus Valve System: a fully repositionable, retrievable prosthesis. Minerva Cardioangiol. 2013;61:45-52.

13 Möllmann H et al. Symetis ACURATE TF™ aortic bioprosthesis. EuroIntervention. 2013;9 Suppl:S107-10.

14. Kempfert J et al. Trans-apical aortic valve implantation using a new self-expandable bioprosthesis: initial outcomes. Eur J Cardiothorac Surg. 2011;40(5):1114-9.

15. Kempfert J et al. A new self-expanding transcatheter aortic valve for transapical implantation - first in man implantation of the JenaValve™. Eur J Cardiothorac Surg. 2011;40(3):761-3.

16. Falk V et al. Transapical aortic valve implantation with a self-expanding anatomically oriented valve. Eur Heart J. 2011;32(7):878-87.

Closed heart surgery: a proven success

TRANSAORTIC valve replacement (TAVR) has been performed for the first time by merely puncturing the chest or femoral artery with a needle. Surgeons no longer need to displace chest bones to repair the aortic valves of patients with narrowing valves or symptomatic aortic stenosis.

Upon entry, the surgeon can repair – rather than replace – the damaged valve by inserting a new, collapsible valve into the aortic valve site through a catheter. To begin to regulate the blood flow the new valve expands, its tissue pushing the old valve leaflets out of the way, and out of use.

The procedure does not expose any organs, making it optimal for high-risk valve replacement therapy. Not having to overcome the effects of major surgery and anaesthesia also means that many patients can return home within 24 hours.

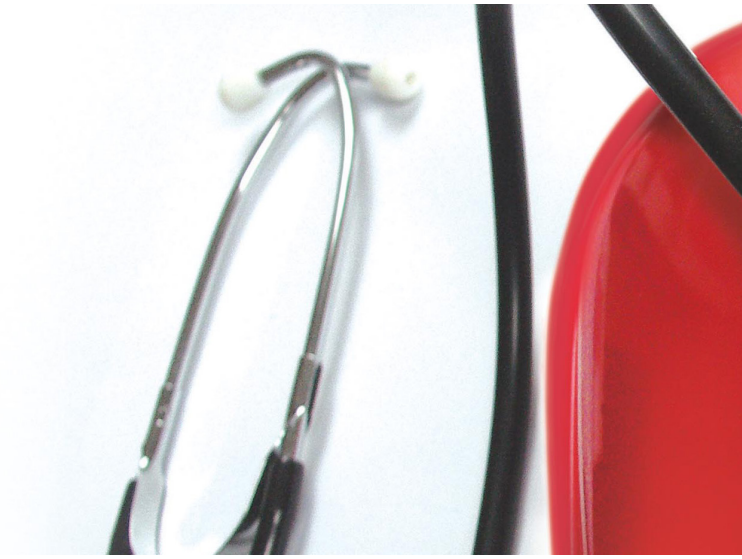
"Given the current healthcare landscape of unknown costs and insurance, as doctors we needed to evolve and provide patients with an option that doesn't involve lengthy time in a hospital bed."

Dr Marco Costa,
Case Western Reserve University
School of Medicine,
Cleveland, USA

TAVR therefore denotes a significant improvement in the quality of life of patients as a result of the improved infection rates, reduced recovery time, and lower associated medical costs.

Approved by the Food and Drug Administration, there is little doubt that the procedure is a superior choice for patients with otherwise limited options for the repair of symptomatic aortic stenosis. These usually include those who are 70 or 80 years old, and/or those with other medical conditions, which make surgery, and its side-effects, a dangerous option.

"The TAVR procedure's success has already been proven," said Dr Marco Costa, Director, Interventional Cardiovascular Center, The Harrington Heart & Vascular Institute at UH Case Medical Center and Professor of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA. "Given the current healthcare landscape of unknown costs and insurance, as doctors we needed to evolve and provide patients with an option that doesn't involve lengthy time in a hospital bed. This allows us to solve many problems at one time," Dr Costa continued.



Non-invasive surgery a heartbeat away

A BEATING heart has been directly operated on for the first time in the world during a new, minimally invasive procedure, which facilitates the replacement of the heart's mitral valve for patients who are considered high-risk with conventional procedures.

"Being able to replace the mitral heart valve without open heart surgery will give our sickest patients a chance of survival and a better quality of life," said Mr Vinayak Bapat, Consultant Cardiothoracic Surgeon, Guy's and St. Thomas' Hospital NHS Trust, London, UK.

The keyhole surgery was performed under general anaesthetic, where a tiny opening in the chest was made directly over the heart. With the assistance of ultrasound and X-ray guidance technology to visualise the inside of the heart, surgeons replaced the damaged mitral valve with an artificial valve. Overall, the duration of this procedure is just over 30 minutes.

Located between the left atrium and the left ventricle, the mitral valve separates the dual functions of collecting and pumping chambers to prevent the backflow of blood. If the mitral valve does not close properly, this leads to a flooding of the lungs and heart failure. If the condition worsens, there is irreversible damage to the heart and premature death.

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> "Being able to replace the mitral heart valve without open heart surgery will give our sickest patients a chance of survival and a better quality of life."
>
> *Mr Vinayak Bapat, Guy's and St. Thomas' Hospital NHS Trust, London, UK*

Conventionally, the valve can only be replaced through invasive heart surgery, which involves stopping the heart and placing the patient on a heart machine.

Mr Bapat commented: "We've demonstrated that this procedure is feasible and in future can save the lives of similar patients in the UK and around the world."

Dr Ian Abbs, Medical Director, Guy's and St Thomas' NHS Foundation Trust, London, UK added: "This development in cardiac surgery is a huge step forward for the UK, proving our position at the forefront of medical research and development to improve the care and save the lives of patients."

Mini-VADs to replace LVADs in heart failure therapy

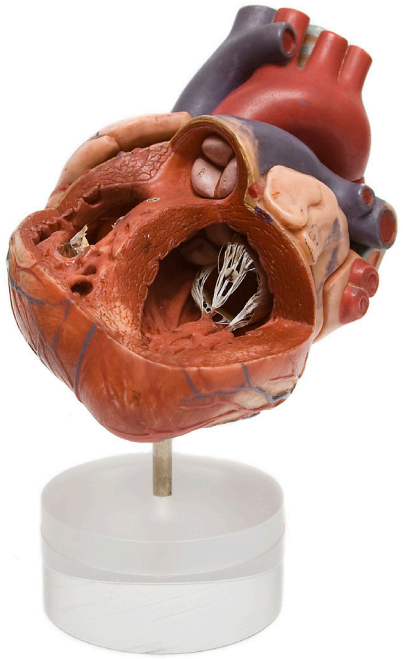
HIGH-TECH mini-ventricular assisted devices (mini-VADs) may replace the two left ventricular assist devices (LVADs) due to the smaller design, less invasive implantation route, and rechargeable battery. Currently in clinical trials, the device has been shown to increase the survival rates in advanced heart failure patients.

"There is a robust pipeline of mini-VADs providing partial circulatory support that should allow wider applicability," said Dr Michael Mack, Medical Director, Baylor Health Care System, Dallas, Texas, USA.

Previously, LVADs were used as an alternative to heart transplantation in what is known as 'destination therapy'. This does not require organ donors, and is used in many leading institutions resulting in its rapid utilisation in North America.

> "There is a robust pipeline of mini-VADs providing partial circulatory support that should allow wider applicability."
>
> *Dr Michael Mack, Medical Director, Baylor Health Care System, Dallas, USA*

A worldwide study of 6,000 patients reported that over the course of 3 years, 86% had been affected by LVAD complications such as bleeding, stroke, infection, device malfunction, or death. Bleeding, the main problem caused by the device, was due to patients developing acquired von Willebrand's disease. Due to the high stroke risk, patients must also undertake warfarin therapy.



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Additionally, gastrointestinal bleeding due to angiodysplasia and arteriovenous malformations is a common consequence of nonpulsatile continuous blood flow.

At the size of an AA battery, and as energy efficient, the current mini-VAD drawing the most interest is the CircuLite Synergy®, an implanted off-pump with a small right thoracotomy for left atrial access. The device fits into the pocket of the right deltoid-pectoral groove for axillary artery access, where inflow is from the left atrium and outflow into the right subclavian artery.

Further modifications will avoid the right thoracotomy, inflow via the subclavian vein, and outflow into the subclavian artery.

"The idea is that this will become a cath lab procedure. The device will sit in a pocket similar to a pacemaker," said Dr Mack.

Small patients, big benefits in latest TPV replacement

"If Melody® valve use is going to be expanded in this population of small patients, it may be important to further characterise the venous size requirements and necessity for preprocedural vascular imaging to better plan what access is appropriate in a given patient, or even if a percutaneous approach is feasible."

Dr Berman and colleagues, Miami Children's Hospital, Miami, USA

CHILDREN who weighed <30 kg and underwent transcatheter pulmonary valve (TPV) replacement for the treatment of right ventricular (RV) conduit dysfunction saw significant improvements over present challenges.

There are limited data for the Melody® TPV (Medtronic) Therapy in smaller patients, which prompted one research team, led by Dr Darren P. Berman, a Paediatric Interventional Cardiologist, Miami Children's Hospital, Miami, Florida, USA, to investigate the outcomes of 25 small children (median age of 8 years old and median weight of 21.4 kg, with 10 patients weighing less than 20 kg).

The route of passage for the TPV was entry via the femoral vein in 17 patients, while the right internal jugular vein was utilised in 4 patients, and the subclavian vein in the remaining 2 patients (implantation was not possible in 2 patients). A median conduit diameter of 17 mm was used.

The TPV implantation resulted in two patients having side-effects of mild pulmonary regurgitation, while seven others experienced adverse events (such as confined tears, abdominal haematoma, etc.), although there were no procedure-related deaths.

The median 16-month follow-up revealed that only one patient required conduit replacement for recurrent conduit stenosis, and stent fracture occurred in two patients who required a second TPV. Bacterial endocarditis developed in two patients, which was treated with antibacterial therapy; of the two patients, one underwent a further conduit replacement.

According to Dr Berman and colleagues: "If Melody® valve use is going to be expanded in this population of small patients, it may be important to further characterise the venous size requirements and necessity for preprocedural vascular imaging to better plan what access is appropriate in a given patient, or even if a percutaneous approach is feasible."

Burning hearts to treat atrial fibrillation

"The pressure-sensing catheter can improve patient outcomes and the durability of ablation treatments."

Dr David Wilber, Director, Loyola University Medical Centre, Maywood, USA

HEART tissues are being targeted for destruction after a multicentre clinical trial revealed the ThermoCool® SmartTouch® device, a high-tech pressure-sensing catheter, which uses heat to destroy tissues releasing errant signals that cause an irregular heartbeat, or atrial fibrillation (AF).

In a process called catheter ablation, an electrophysiologist inserts a catheter into an artery in the groin and directs it to the heart vessels. While other catheters are able to deliver targeted radiofrequency energy that heats and destroys the tissue sending out irregular signals, the tip of the ThermoCool® SmartTouch® device also has a pressure sensor, which enables an experienced physician to measure the angle of the tube and the amount of force being used in order to ensure enough firmness is used without punching a hole in the heart.

In AF, the heart beats irregularly as the result of a slip in signalling from defective tissues. This causes the upper chambers of the heart to tremor and inhibits blood from pumping fully. This can trigger blood clotting and leads to symptoms of dizziness, heart palpitation, chest pain, fatigue, shortness of breath, light headedness, and in some sufferers, ultimately to stroke and heart failure.

"A lot of people are disabled," said Dr David Wilber, principal investigator, Director of Loyola University Medical Center, Division of Cardiology and Section of Clinical Electrophysiology, Maywood, Illinois, USA. "They have no energy. They can't work. They have a very poor quality of life."

Other treatments to maintain a normal heart rhythm have been available for over 30 years; these include drugs and the more radical option of surgery. However, these options have various limitations and, in addition, AF is exacerbated due to an aging society and a culture of obesity.

Dr Wilber showed confidence in the device, saying: "The pressure-sensing catheter can improve patient outcomes and the durability of ablation treatments."

Anticoagulation denied after atrial fibrillation ablation

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> "We found a consistently high success rate and few complications in medium-to-high volume centres across Europe. But inconsistent use of anticoagulants and antiarrhythmic drugs at 1 year shows that follow-up needs to be improved."
>
> *Prof Josep Brugada, Hospital Clinic, University of Barcelona, Barcelona, Spain*

ANTICOAGULANTS are not being given after atrial fibrillation (AF) in one-quarter of high-risk cases. Although classified as high risk, 25% of patients were not taking any anticoagulant drug, whereas 50% of patients with a low stroke-risk status were still continuing with anticoagulation therapy.

"Our pilot study was in medium-to-high volume AF ablation centres and we would expect them to be following anticoagulation protocols. But often the follow-up is performed by a GP or general cardiologist at another centre. Good collaboration between the two centres is absolutely mandatory to ensure that patients receive recommended treatments," said Prof Josep Brugada, study author, Hospital Clinic, University of Barcelona, Barcelona, Spain.

The study spanned ten European countries and included 1,410 patients from 72 cardiology centres with a medium-to-high turnover rate of AF ablations per year.

The results showed that catheter ablation of AF maintained sinus rhythm in 74% of patients, while success was attained without antiarrhythmic drugs in 41% of patients. Excluding post-ablation atrial flutter/trachycardia, only 2.5% had complications and <1% were of serious concern.

Prof Brugada added: "We found that protocols for antiarrhythmic therapy were followed more strictly in Northern Europe. Physicians did not give the medication unless the patient had a documented arrhythmia recurrence. It could be that in Southern Europe there is a tendency to give antiarrhythmic drugs if patients have symptoms, without requiring specific documentation of an arrhythmia."

"We found a consistently high success rate and few complications in medium-to-high volume centres across Europe. But inconsistent use of anticoagulants and antiarrhythmic drugs at 1 year shows that follow-up needs to be improved. Close cooperation between centres performing ablations and physicians doing the follow-up is essential to ensure that all patients in Europe receive appropriate treatment after the procedure," Prof Brugada said.

Stents: 'til death do us part?

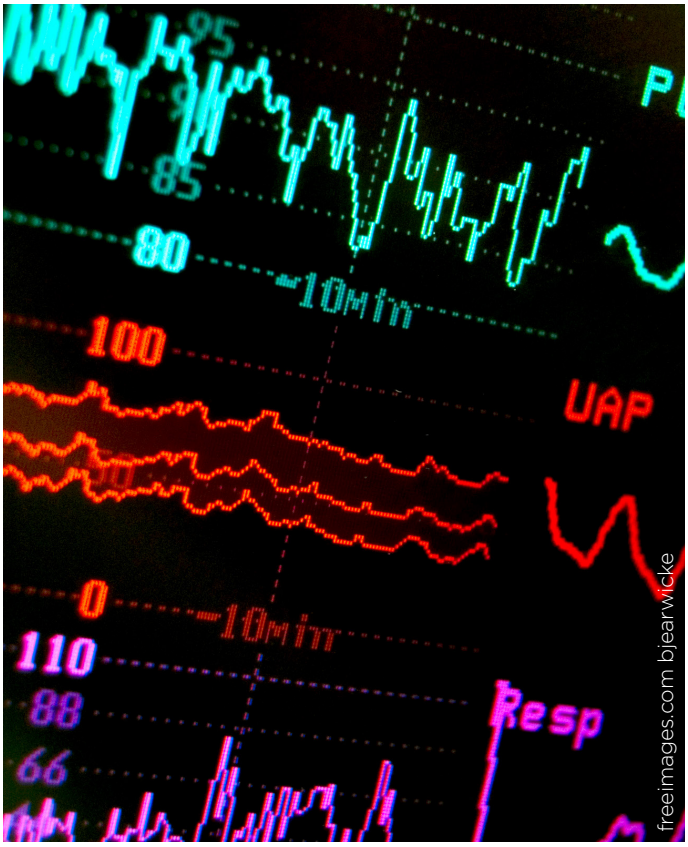
INNOVATIONS in the evolution of stenting have seen bare-metal stents replaced by durable polymer drug-eluting stents (DES), followed by biodegradable stents, and are soon to be supplanted by the emergence of bioresorbable stents.

Escaping the limitations of their predecessors (inflammatory responses which contribute to late stent thrombosis, increased risk of restenosis, and revascularisation), the transient bioresorbable stents have been designed to cover the arterial wall, disappearing over time to be replaced by normal tissue.

Along with many of the benefits of their ancestors, one such device is the cobalt-chromium everolimus-eluting stent, which has been found to be the most efficient and safe DES.

"You will go in your grave with a piece of metal in your coronary artery," says Dr Patrick W. Serruys, Department of Interventional Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. "Since the biological factors of restenosis are operational only for 6 months, why don't we put in something that is transient?"

Studies of one particular device showed that between 2 and 3 years a study cohort had a binary restenosis rate of 6%, no scaffold thrombosis, and a 3-year major adverse cardiac-event rate of only 10%. Tensile strength is an issue however, with a need for operators to inflate the balloon into the coronary artery without exerting too much pressure.



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While some believe that metal scaffolds will remain a significant tool in stenting, there is much investment in this new platform. In Europe there are already two CE marked products: Abbott Vascular's everolimus-eluting Absorb, and Elixir Medical's DESolve novolimus-eluting bioresorbable scaffolds.

"If you look at the first-generation biodegradable stents, it is a leap forward," says Dr Sripal Bangalore, Director of Research at the Cardiac Catheterization Laboratory and Director of the Cardiovascular Outcomes Group at New York University School of Medicine, New York City, New York, USA.

> "Since the biological factors of restenosis are operational only for 6 months, why don't we put in something that is transient?"
>
> *Dr Patrick W. Serruys, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands*

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Interventional Cardiology

Responsible for the development of some of the world's most important drug products in fields ranging from diabetes care to veterinary medicines, Bayer HealthCare is a giant and key innovator in the manufacturing of pharmaceutical and medical products. The Bayer subdivision's aim is to make state-of-the-art, ground-breaking products to improve the lives of patients worldwide. It aims to accomplish this through its consumer care, medical care, and pharmaceuticals divisions, with an eye on addressing some of the great challenges in the modern era. The company has bases in 5 continents, with approximately 55,300 people working for the subgroup in over 100 countries.

Internationally active in the healthcare sector, Bracco operates through its subdivisions: Bracco Imaging, Pharma, Acist Medical Systems, and the Centro Diagnostico Italiano diagnostic clinic in Milan. The company employs over 3,300 people with annual revenues of over €1.2bn. Bracco is well known in Italy for its over-the-counter products, which include dietetics, pharmaceutical, and nutraceutical products. The advanced systems produced by Bracco Diagnostic Imaging are used in the biggest global centres across 40 countries, and over 10 million people around the world have had cardiovascular angiographic procedures using this technology.

Daiichi Sankyo is a globally established pharmaceutical company that has origins in Japan, and now, provides a range of innovative products and services across over 50 countries worldwide. Daiichi has built up its scientific expertise for more than 100 years, and has a rich legacy of innovation to draw from as well as a continuous supply of ground-breaking new treatments for patients. Having built a 30,000-strong workforce possessing great knowledge and work ethic, the company is able to create new innovative medicines, as well as new methods of drug discovery and delivery.

At JenaValve, quality is of the utmost importance; it lingers on every aspect of the company's technological development, design processes, and device engineering. JenaValve is extremely proud of its German roots, and in 2011 the transapical JenaValve™ system was CE-marked for approval in the European market. Transcatheter aortic valve transplantation (TAVI) has become an established therapeutic alternative to surgical aortic valve replacement over the years for high-risk patients suffering from aortic heart valve stenosis. JenaValve is looking to further expand the advancement of TAVI technology in the years ahead in order to meet growing patient need.

Simbionix is a world-leading provider of a wide range of innovative training and education solutions for the healthcare industry. Founded in 1997, Simbionix combines innovative research and development, cutting-edge technology, and strong clinical relationships to promote adoption of the best medical practices. This would lead to the advancement of clinical performance and the optimisation of procedural outcomes. The company's comprehensive education solutions include top-of-the-line medical simulators and learning management systems, which can be found in simulation centres, hospitals, colleges, and other educational facilities in more than 60 countries.

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- BIOSENSORS INTERNATIONAL GROUP LTD.
- BIOTRONIK
- BIOVENTRIX, INC.
- BMS/PFIZER ALLIANCE
- BOSTON SCIENTIFIC
- BROSMED MEDICAL CO., LTD.
- C.R. BARD, INC.
- CARDIALYSIS
- CARDIONOVUM GMBH
- CERC
- COLIBRI HEART VALVE
- COMED BV
- CONTROL MEDICAL – DISTAL ACCESS
- COOK MEDICAL
- CORDIS, JOHNSON & JOHNSON MEDICAL NV/SA
- CORONADO MEDICAL
- COVIDIEN AG
- CREGANNA
- DAIICHI SANKYO
- DGM/GLOBAL INTERCEPTS
- DIRECT FLOW MEDICAL, INC.
- E-NOVEX
- EDWARDS LIFESCIENCES
- EKOS CORPORATION, A BTG INTERNATIONAL GROUP COMPANY
- ELI LILLY
- ELIXIR MEDICAL CORPORATION
- ENVISION SCIENTIFIC PVT. LTD.
- EPFLEX FEINWERKTECHNIK GMBH
- ESAOTE SPA
- EUROCOR GMBH
- HEXACATH
- IHT - CORDYNAMIC
- INFRAREDX
- INSITU TECHNOLOGIES
- INSPIREMD
- INTERVALVE INC.
- IVASCULAR
- JAPAN STENT TECHNOLOGY
- JENAVALVE TECHNOLOGY GMBH

Interventional Cardiology

- KEYSTONE HEART LTD.
- LEMER PAX
- LEPU MEDICAL TECHNOLOGY (BEIJING) CO., LTD.
- MAQUET
- MATERIALISE NV
- MAVIG GMBH
- MDT X-RAY
- MEDIS MEDICAL IMAGING SYSTEMS
- MEDTRONIC INTERNATIONAL TRADING SARL
- MENTICE
- MERIL LIFE SCIENCES
- MERIT MEDICAL
- MINVASYS
- MITRALIGN
- MULTIMEDICS
- NATEC MEDICAL
- OCCLUTECH
- OPSENS INC.
- ORBUSNEICH
- OSCOR INC.
- PEROUSE MEDICAL
- PERSONAL MEDSYSTEMS GMBH
- PHILIPS HEALTHCARE
- PIE MEDICAL IMAGING
- PLC MEDICAL SYSTEMS, INC.
- PULSECATH B.V.
- QUALIMED INNOVATIVE MEDIZINPRODUKTE GMBH
- RECOR MEDICAL
- REVA MEDICAL, INC.
- RONTIS AG
- S3V VASCULAR TECHNOLOGIES PVT. LTD.
- SAHAJANAND MEDICAL TECHNOLOGIES
- SHANGHAI MICROPORT MEDICAL (GROUP) CO., LTD.
- SIEMENS AG HEALTHCARE SECTOR
- SIMBIONIX USA CORPORATION
- SINOMED
- SIS MEDICAL
- ST. JUDE MEDICAL
- STENT FOR LIFE
- STENTYS
- SVELTE MEDICAL SYSTEMS
- SYMETIS
- TERUMO EUROPE
- THE MEDICINES COMPANY
- TORAY
- TRANSLUMINA GMBH
- TRYTON MEDICAL, INC.
- UMBRA MEDICAL PRODUCTS, INC.
- VASCULAR INNOVATIONS (UK) LIMITED
- VASCULAR SOLUTIONS, INC.
- VOLCANO EUROPE
- ZOLL MEDICAL CORPORATION

Transcatheter Cardiovascular Therapeutics (TCT) 2014

13th–17th September 2014

Washington DC, USA

TCT, the world's largest educational meeting specialising in interventional vascular medicine, is now partnered with the American College of Cardiology (ACC). This joint collaboration will offer invaluable opportunities for the medical community to discover the latest advances in the field. The scientific programme will include late-breaking clinical trials, stimulating poster presentations, innovative devices, and future therapies.

TRENDS Asia Pacific 2014 - Renal Denervation

27th September 2014

Shanghai, China

This 1-day workshop will focus solely on renal denervation, a new and exciting therapy used to treat severe resistant arterial hypertension. This catheter-based technique has slowly been gaining popularity and will attract a wide range of healthcare specialists including cardiologists, angiologists, and radiologists from around the world. There will also be additional data presented which will suggest potentially beneficial effects in a number of comorbid conditions.

Total Occlusion and Bifurcation Interventions (TOBI) 2014

2nd-3rd October 2014

Mestre, Italy

TOBI is an absolutely-live course for a closed number of interventional cardiologists with tight interaction between participants, faculty, and operators. The aim of this course will be to amplify the ability to perform complex coronary procedures in bifurcation and chronic total occlusion lesions, provide extensive discussion on modern approaches and technical innovation, and to deliver concise lectures by world experts.

Scripps Clinic's 25th Annual Cardiovascular Interventions

22nd–24th October 2014

La Jolla, USA

This conference is designed to provide a concentrated exposure to new developments in interventional cardiology that will positively influence patient outcomes. Through a program of lectures from world experts, live demonstration procedures, and participant-faculty interactions, attendees will learn the latest advances in the field. This event aims to be an ideal networking opportunity, attracting a wide range of specialists from around the world.

Left Atrial Appendage (LAA) 2014

14th–15th November 2014

Frankfurt, Germany

This informative course is designed to give an overview on all aspects of left atrial appendage closure for stroke prevention in atrial fibrillation. The scientific programme has been organised to provide total in-depth coverage of this condition, including surgical procedures and efficient and safe methods for dealing with complications. There will also be comprehensive coverage of current devices and those that are in clinical trials.

American Heart Association (AHA) 2014 Scientific Sessions

15th–19th November 2014

Chicago, USA

AHA Scientific Sessions is the leading cardiovascular meeting for basic, translational, clinical, and population science in the US. The programme is designed to improve patient care by communicating the most timely and significant advances in prevention, diagnosis, and treatment of cardiovascular disease. The Sessions will include comprehensive education provided by presentations with the invited faculty, and abstract presentations delivered by world leaders in cardiovascular disease.

41st Annual VEITHsymposium

18th–22nd November 2014

New York City, USA

This symposium aims to provide vascular surgeons, interventional radiologists, interventional cardiologists, and other vascular specialists with important updates in the treatment of vascular and endovascular disease. The event will feature rapid-fire presentations from world-renowned vascular specialists, with the emphasis on the latest advances, changing concepts in diagnosis and management, pressing controversies, and new techniques.

American Venous Forum Annual Meeting 2015

25th–28th February 2015

Palm Springs, USA

This annual meeting will bring together world leaders in the field of venous and lymphatic health to discuss cutting-edge scientific research. It will allow each participant to gain new insights into how venous and lymphatic health is evolving, and to take advantage of rapidly developing technologies. This event will draw a wide range of healthcare professionals such as vascular surgeons, radiologists, interventional cardiologists, and technicians.