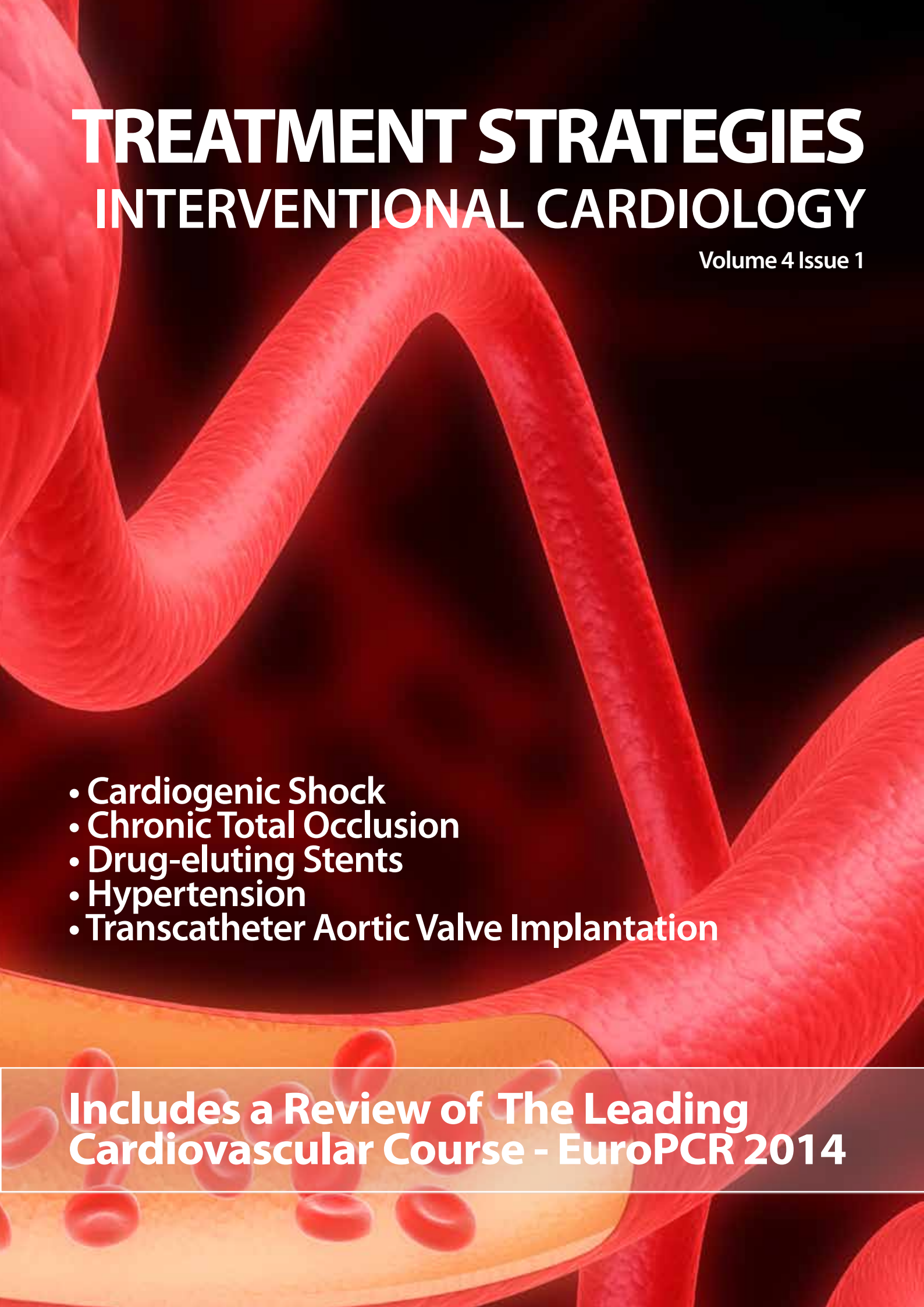
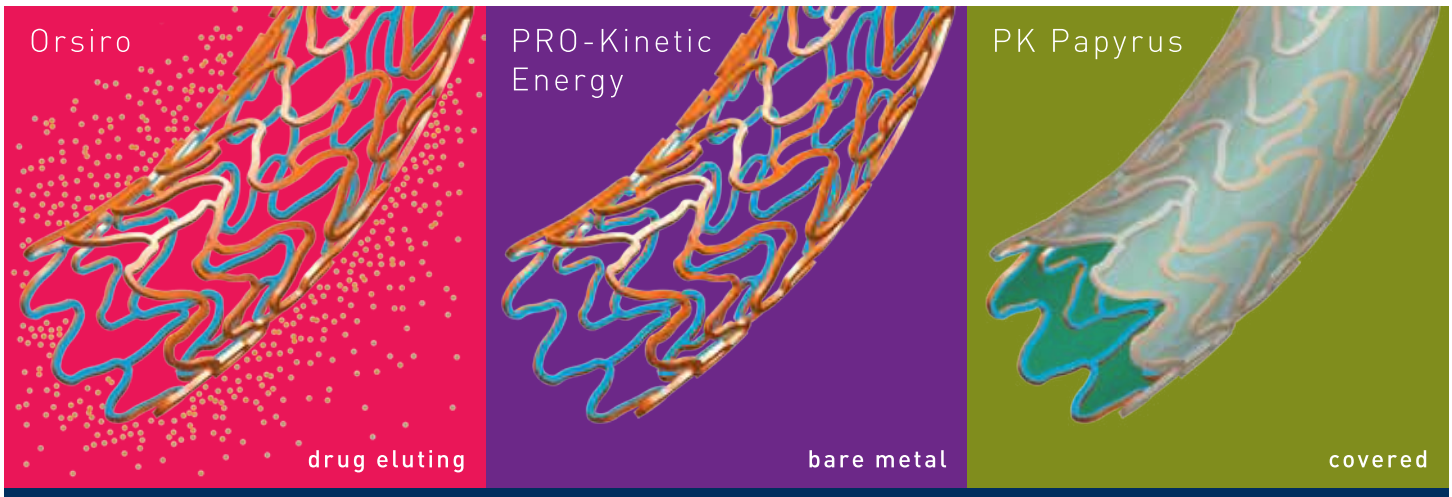
TREATMENT STRATEGIES
INTERVENTIONAL CARDIOLOGY

Volume 4 Issue 1



- Cardiogenic Shock
- Chronic Total Occlusion
- Drug-eluting Stents
- Hypertension
- Transcatheter Aortic Valve Implantation

Includes a Review of The Leading Cardiovascular Course - EuroPCR 2014



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TREATMENT STRATEGIES
Interventional Cardiology

TREATMENT STRATEGIES - - Interventional Cardiology
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Welcome...

to the latest edition of *Treatment Strategies - Interventional Cardiology*. This edition will address the key topical areas in the interventional cardiology field and feature an exciting collection of papers from esteemed interventionalists.

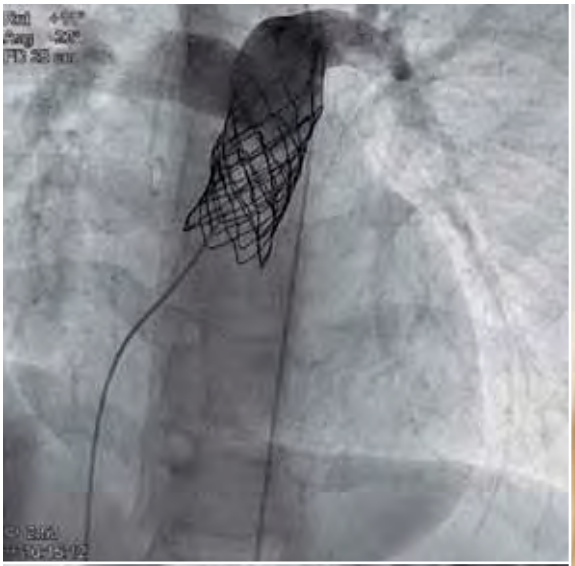
Treatment Strategies - Interventional Cardiology includes papers on topics such as cardiogenic shock, chronic total occlusion, drug-eluting stents, hypertension and transcatheter aortic valve implantation among others. We hope that this publication will provide you with a comprehensive review of the latest updates and technological advances in interventional cardiovascular medicine.

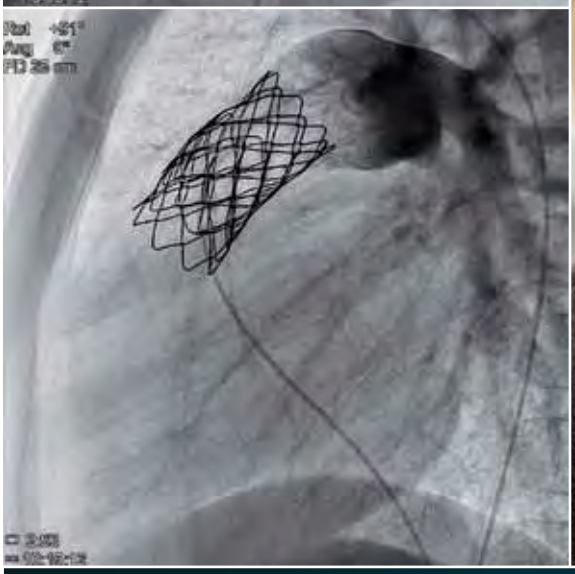
Following on from a successful visit to Paris, we have also included a review of the latest developments from this year's EuroPCR Congress. EuroPCR is the official meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Bringing more than 11,000 members of the cardiovascular community together, EuroPCR is an unmissable event for discovering the latest techniques, updates and breakthrough science in the field of cardiovascular interventions. We do hope you will find the review of EuroPCR interesting. The event once again proved to be an exciting and dynamic Congress, which we very much enjoyed attending.

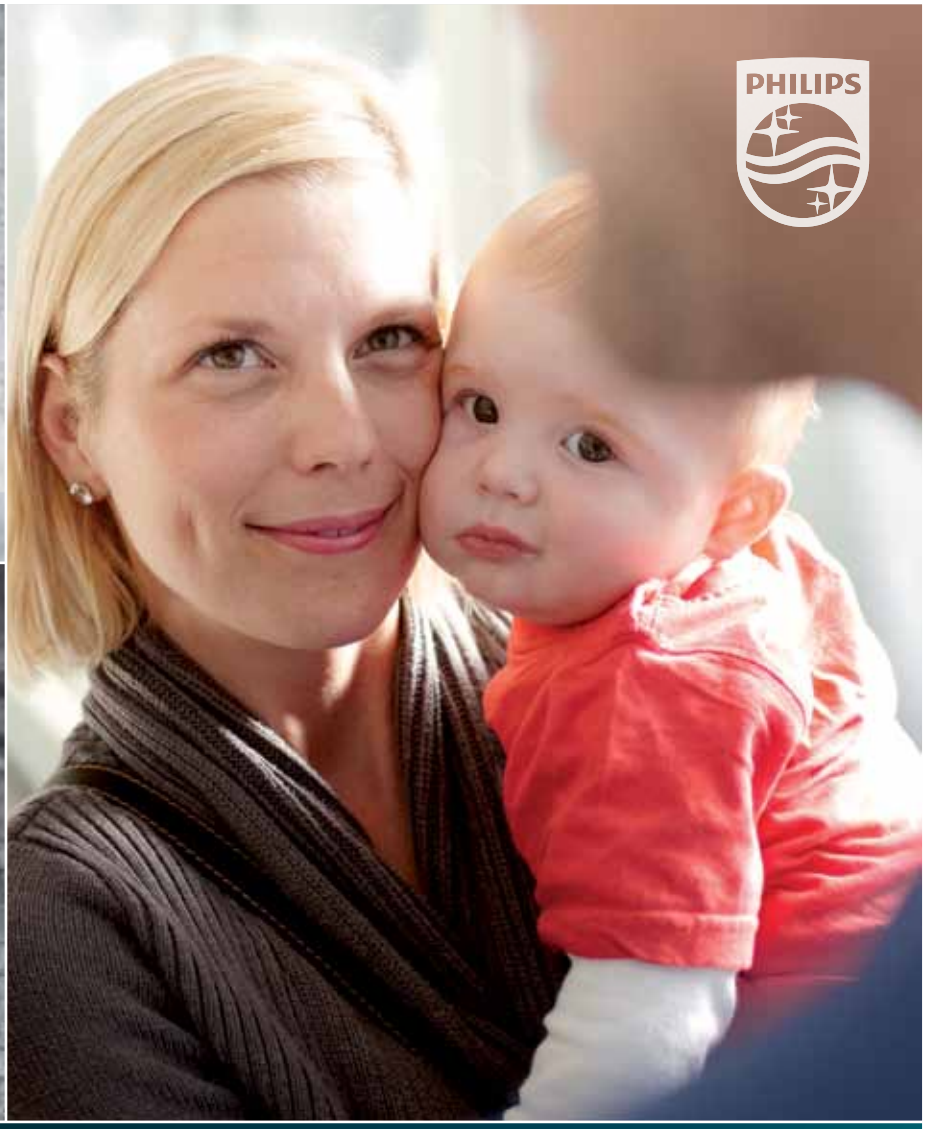
So far, 2014 is proving to be a fantastic year for The Cambridge Research Centre, with some exciting changes including Treatment Strategies TV, where you can find footage from the most important scientific conferences, meetings and congresses, as well as interviews, symposia proceedings, roundtable events and much more. We also launched our range of interactive eBooks on iBooks, which is a great new way to read and download our content to your devices. Have you liked our new Facebook page? Here you can find all of the latest news about new projects and upcoming releases, and the Treatment Strategies' team are also all active on Twitter and LinkedIn.

See you in Paris for EuroPCR 2015.
Nigel Lloyd, Managing Director

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.







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EDITORIAL ADVISORY PANEL

Foreword

Keith G. Oldroyd

Consultant Interventional Cardiologist and Director of Research and Development, West of Scotland Regional Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, Scotland

Welcome to *Treatment Strategies Interventional Cardiology Volume 4, Issue 1*. In this issue, a multinational group of eminent interventional cardiologists cover a number of extremely topical areas including percutaneous mechanical circulatory support (MCS) in cardiogenic shock, PCI for chronic total occlusions (CTO), developments in drug eluting stent (DES) technology, intervention for hypertension and finally transcatheter aortic valve replacement (TAVR).

Percutaneous MCS: A series of randomised controlled trials utilising intra-aortic balloon pumps have failed to demonstrate any improvement in clinical outcomes in patients undergoing either high risk PCI (BCIS-1) or anterior myocardial infarction (CRISP) or indeed cardiogenic shock itself (IABP-SHOCK). In the latter clinical setting there has been increasing interest in the use of alternative mechanical circulatory support devices including Impella, extra-corporeal membrane oxygenation (ECMO) and a variety of ventricular assist devices (VAD). Treatment strategies utilising these devices are expensive and only applicable to a small number of patients with cardiogenic shock. They cannot be employed without having highly trained and experienced teams available 24/7 and as time from the onset of shock to the institution of MCS is a major predictor of outcome, this raises the issue of whether such patients should be triaged to specific high volume centres with existing MCS/VAD/transplant programmes rather then to the nearest PCI centre. The Impella device can be inserted in the cath lab by the interventional team working alone but in most centres percutaneous ECMO requires support from a cardiac perfusionist and escalation to a VAD certainly involves a cardiac surgical team. In our own centre, we have had occasional patients who have been massaged for 30-40 minutes in the cath lab using the Autopulse device whilst preparing to initiate ECMO support with subsequent progression as needed to VAD and ultimately if needed transplantation. This sequence of interventions is literally life-saving but does raise multiple ethical issues including questions of consent in critically ill patients, appropriateness and futility.

Chronic total occlusions: the major difference between surgical and percutaneous revascularisation strategies in patients with coronary heart disease is a much higher rate of incomplete revascularisation with PCI. This usually relates to failure to successfully open CTO's. In recent years several new techniques have been developed for undertaking CTO-PCI including antegrade and retrograde dissection/ re-entry. These have been facilitated by a range of dedicated coronary guide wires and microcatheters and in some cases the use of specific re-entry hardware such as the Bridgepoint™ technology. In experienced centres success rates now exceed 90% even in very complex cases.

Drug eluting stents: the latest generation of DES have highly biocompatible or biodegradable polymers, are extremely deliverable, elute limus analogues and have very low rates of thrombosis and restenosis. In my view it is virtually certain that a contemporary re-run of the SYNTAX trial using any of these new devices would provide a completely different result to that obtained with the 1st generation paclitaxel eluting stent used in the PCI arm. Beyond metallic DES fully bioabsorbable vascular scaffolds are now available and although their mechanical performance does not yet match that of metal coronary stents they are likely to assume an increasingly important role in percutaneous revascularisation.

Intervention for hypertension: the recent negative SYMPLICITY-3 trial of renal denervation in patients with so-called refractory hypertension has emphasised the importance of having a sham-control group when new technologies like this are being assessed. We had learnt this already with laser revascularisation for angina in the 90s and percutaneous closure of patent foramen ovale for the prevention of stroke in the last decade. Nevertheless renal denervation will likely have some role in these difficult patients though it may require a deeper understanding of autonomic function in general and renal adrenergic nerve activity in particular to identify patients likely to respond.

Transcatheter Aortic Valve Implantation: this is now firmly established as a highly effective and safe alternative to surgical aortic valve replacement for high-risk patients. Attention is now focussing on how to further improve outcomes with newer devices designed to minimise paravalvular regurgitation, smaller devices and delivery systems aimed at reducing vascular access site complications and increasingly refined imaging strategies to determine optimal valve size and positioning.

I hope you enjoy reading this edition and find it useful to you in your own day to day clinical practice.

Professor Keith G Oldroyd is Consultant Interventional Cardiologist and Director of Research and Development at the West of Scotland Regional Heart and Lung Centre in the Golden Jubilee National Hospital. He holds a personal chair within the Institute of Cardiovascular and Medical Sciences, University of Glasgow. Following initial clinical training in Glasgow he was awarded a BHF Clinical Research Fellowship and received his MD degree with Honours for his thesis on the pathophysiological role of endogenous opioids in patients with coronary disease and heart failure. Subsequently he was a fellow in interventional cardiology at the University of Toronto. From 1995-2002 he led the development of the Interventional Cardiology Service at Hairmyres Hospital. In 2002 he moved to the Western Infirmary in Glasgow. In 2007 he became the first Clinical Director of Cardiology at the newly created West of Scotland Regional Heart and Lung Centre. In 2011 he took on the role of Director of R&D.

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EuroPCR 2014 Review

20–23 May 2014 - Paris

25th Annual Congress of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)

The Congress

News from EuroPCR 2014

The 25th EuroPCR Course - The Official Annual Meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI).

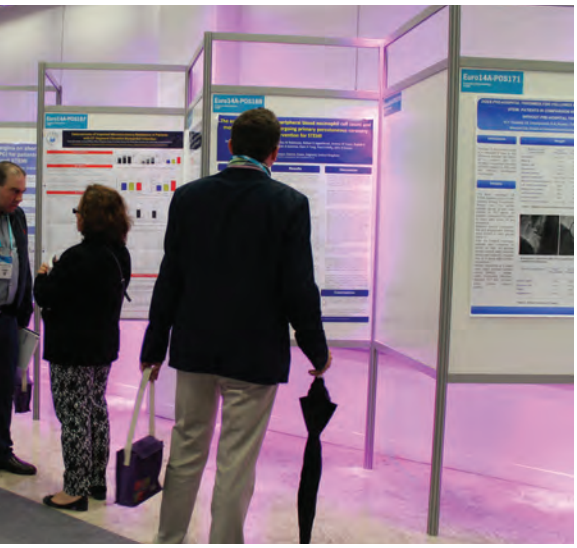
In this report, Nigel Lloyd, The Cambridge Research Centre, gives *Treatment Strategies Interventional Cardiology* a round-up of the debates, awards, sessions and other outstanding moments that made the 25th EuroPCR annual meeting such a great not-to-be-missed week in the interventional cardiology calendar.

The main theme for this year's EuroPCR event and a theme that will serve as the foundation throughout the week is *Personalised Medicine*.

The term *Personalised Medicine* has many definitions but appplied to interventional cardiology, personalised interventional care refers to each individual patient as being in the first place, as well as to the idea of inclusiveness.

Interventional medicine is inclusive by essence of prevention, diagnosis and complex, yet integrated; of multiple, interrelated disease states that are addressed by a wide array of disciplines and of diverse professions and related skills.

Personalised Medicine requires tailoring and the adjustment and management of practices and strategies in response to the needs of each individual patient.



Personalised interventional care aims at optimising outcomes for each patient. Each patient being seen as unique, with unique demands, living in a unique familial, social and cultural environment.

PCR Innovation Day

Facilitating a constructive interaction between the key stakeholders-physicians, inventors, entrepreneurs, investors, start-ups, medtech incubators, regulatory organisations and larger companies –in the ecosystem of European cardiovascular innovation was the focus of the first PCR Innovation Day.

Moving away from the classical approach of using just an economic view-point to innovation, on May 19th, at the Innovation Day, physicians posed questions to innovators presenting their early research/pre-clinical disruptive innovations. The day provided a chance for all the key stakeholders to meet and interact within a structured programme that focused on unmet clinical needs in the landscape of interventional cardiovascular medicine, with the ultimate aim of improving patient care and outcomes.

"From the feedback that we have received from the various quarters, a second edition is on target.....The idea came about because we realised that during the week EuroPCR 2014 is set to take place, we have to present in Paris, all the factors involved who eventually bring an invention to the bedside. The faculty is a reflection of a number of top-level people in Europe and beyond, and the dialogue between us interventional cardiologists and the industry and our aligned interests to improve outcomes for patients is vital for innovation to progress," said William Wijns, Chairman of PCR and Course Director of EuroPCR.

"For the Innovation Day, EuroPCR physician experts identified the areas of unmet clinical needs. Then, the opportunities for inventors and start-ups to show their innovative and disruptive technologies were defined and discussion was structured around this. There is well-regarded tradition of excellent research in cardiovascular medicine in Europe; on the other hand, the journey to innovation is not easy. We believe it needs to be supported and with that in mind, we have facilitated the coming together of all the actors in the ecosystem." said Thierry Herbreteau, Chief Executive Officer, Europa Group.

"We are totally rethinking the way we approve innovative medical devices in the coming months and years. There was a significant need for improvement as we were using an over 15-year-old directive and we are going to enter new regulation [expected to take effect in 2018]. The critical aspect is to continue to leverage the unique system of CE marking which has been demonstrated in the past to be an effective system to approve innovation rapidly for patients. At the same time, we need to prioritise patient safety," he noted. Bernasconi commented further on wishing to preserve the strengths of Europe as a critical space for innovation. "As an industry, we want to preserve and maintain the unique creativity from physicians in Europe and foster investment in innovation in Europe," said Serge Bernasconi, Chief Executive Officer, MedTech Europe.

"The interesting thing [about the Innovation Day] is that you have got the physician community and society standing up and saying that innovation is important; you have an opportunity for the small start-up companies to get exposure with the larger companies like the one that I work for, where we consolidate these companies and bring them to market. This is a day where that interaction is enabled, the environment is created where we can have successful conversations that help

advance the care for patients. So this type of day is an incubator for great concepts, and a forum for us to share ideas and challenges across the industry." Said Michael Onuscheck, vice chairman of the Cardiovascular sector of Eucomed and president of Boston Scientific.

The Great Debate

During the great debate that took place at euroPCR on the 20th May 2014, experts discussed and presented on the importance of two of the most valuable strategies to save the lives of STEMI patients. The two strategies were percutaneous coronary intervention and thrombolysis. Primary PCI, for most developed countries is the preferred strategy, while in developing countries, thrombolysis is still the number one treatment option.

Following a vote on the euroPCR website the community selected the topic "Primary PCI for STEMI: an emergency" as Thomas Cuisset, Chair of the Great Debate, noted. The expert panel for the session comprised the following members - Sajidah Khan, South Africa, Maciej Lesiak, Poland, Flavio Ribichini, Italy and Julian Strange, UK. Sajidah Khan, South Africa, informed the panel and audience "The most powerful method of reducing mortality is to use whatever method you have at hand to treat the patient within three hours, because that is the window of greatest opportunity for treatment to impact on survivals and outcomes".

Flavio Ribichini informed the attendees "Primary PCI is the most important thing we do in our daily life as interventional cardiologists because it has the potential to save lives in a matter of a few minutes. The guidelines suggest that if you are expecting delay, which might be an hour and a half to two hours, patients should receive thrombolysis before, and this is absolutely common sense. Primary PCI is not an antagonist to thrombolysis, these are two very effective treatments that actively save lives."

NEW PCR PIPELINE

A new web resource called PCR Pipeline was launched at this year's PCR event and brings together a wealth of information, from devices used in cath labs to renal denervation systems.

The PCR Pipeline website offers you easy and intuitive access to relevant and independent information about the medical devices used in your daily practice and allows you to search from broad items to specific details, depending on your needs.

SESSIONS

The session "Personalised medicine: clinical actions and their correlation with anatomo-pathology" was facilitated by Renu Virmani, Nicolas Amabile and Romain Didier. The facilitators alternated presenting cases featuring diffuse ectasia, late stent thrombosis, early stent thrombosis and severe calcification of the coronary artery, and attendees were permitted to interject at any point, whether they wanted to ask a question, get further clarification or express an opinion.

"The real value is helping interventionalists to understand what they are treating, then they start thinking that when they see an 81-year-old man, he is going to have calcification; should they be treating one way or another? If a young man comes in five years after having a stent implanted, they will start thinking they should do OCT, they should think about hypersensitivity, how should they treat this patient? These are the things that help them. Clinicians think about the underlying physiology of the disease and I think that that is where the money is for the interventionalists to start thinking about the underlying physiology of the disease, rather than just treating symptoms," Renu Virmani stated

euro PCR Awards...

INNOVATION AWARD

The EuroPCR 2014 Innovation Award went to antiplatelet therapy. According to Michael Haude, antiplatelet therapy was chosen for the collective award in recognition of the difference it has made to the outcome of patients with acute coronary syndromes.

"We have to think back to history and appreciate that this little platelet is of utmost importance when we talk about patients with acute coronary syndromes, as well as when we talk about patients who have percutaneous coronary intervention procedures, especially stent-related. It has significantly improved the incidence of stent thrombosis and the outcome in our acute coronary syndrome patients," he pointed out.

"In the initial days we really thought we could overcome this problem of ischaemic events by more aggressively addressing anticoagulation, but we were not able to prevent stent thrombosis like that. But on the other hand, we had excessive bleeding complications. I personally have to say that it was the value of dedicated scientists who worked out this strategy of antagonising the activation of the thrombus site in this process. We know that the antithrombins still have a dedicated role, but there is a clear shift towards the efficacy of antiplatelet drugs."

WINNERS OF 2014 TRAINING AND RESEARCH GRANTS

This year, the EAPCI offered a total of four fellowship grants thanks to the financial assistance from AstraZeneca, Edwards Lifesciences and Medtronic. This presents an opportunity for a one-year specialised research or clinical training for medical graduates at any stage of their career within the field of interventional cardiology but before obtaining a permanent, senior staff or consultant position, in an ESC member country other than their country of residence.

The EAPCI Fellowship Committee chaired by Prof. Michael Haude and Prof. Adam Witkowski announced the 2014 winners:

- Dr. John Jose from India has obtained a fellowship at the Heart Center, Segeberger Kliniken GmbH (Academic Teaching Hospital of the Universities of Kiel and Hamburg, Bad Segeberg (Germany) under the supervision of Dr. Mohamed Abdel-Wahab. The topic of his training is "Assessment of valve haemodynamics, regurgitation, ventricular remodeling and myocardial fibrosis following transcatheter aortic valve implantation with second generation devices compared to surgical aortic valve replacement using cardiovascular magnetic resonance study". This grant is supported by Medtronic.

- Dr. Luigi Biasco from Italy has been granted a fellowship at the Rigshospitalet, Copenhagen University Hospital (Denmark) under the supervision of Dr. Lars Sondergaard. The title of his training is "Anemia in TAVI patients, a possible indicator of poor prognosis?". This grant is

supported by Edwards Lifesciences.

- Dr. Shady Elnaggar from Egypt has been accepted for a fellowship at the University of Duisburg-Essen, West German Heart Center (Germany) under the supervision of Prof. Raimund Erbel. The topic of his training is "Outcomes of Sapien-3 THV in comparison to Edwards Sapien-XT THV: Real world single center experience". This grant is supported by Edwards Lifesciences.

- Dr. Giancarla Scalone from Italy has been awarded a fellowship at the Hospital Clinic de Barcelona – ICT (Spain) under the supervision of Dr. Manel Sabate. The topic of her training is "Endothelial function assessment in sudden death patients treated by primary percutaneous coronary intervention and hypothermia". This grant is supported by AstraZeneca.

ETHICA AWARD

Every year the EuroPCR Board recognises an outstanding professional for their contribution to the field of cardiovascular intervention as a teacher, scientist, care provider or pioneer with the presentation of the Ethica Award. The 2014 Ethica awardee is Adnan Kastrati.

"His [Adnan Kastrati] academic track record is amazing. The awardee belongs to the select group of cardiologists who have published over 500 original publications and numerous outstanding editorials. He is considered a top level trialist and reviewer by many journals of reference and funding bodies," William Wijns announced.

Robert Byrne added "First and foremost Adnan is a hands-on interventionalist. His office is the cath lab and it is a privilege to have learned so much about the practice of interventional cardiology from him. Secondly, in terms of clinical trial design, statistical analysis and scientific writing, his expertise is second to none. If I have taken even a modicum of his insight into discerning what the important issues of clinical equipoise in interventional cardiology are, I think it will serve me a career long."

Franz-Josef Neumann also added, "It always has been a great pleasure to work with Adnan: He is a wonderful doctor and an extremely skilful operator in the cath lab; he takes high work-loads and is always highly supportive to his peers and juniors. Starting with the first ISAR trial that established dual antiplatelet therapy after coronary stenting, Adnan's expertise and vision was key to many groundbreaking studies of the Munich group led by Albert Schömig. I admire him for his scientific strictness that has never been corrupted by any political consideration or any other opportunistic reason."

Adnan Kastrati is currently Professor of Cardiology and Head, Catheterisation Laboratory at the Deutsches Herzzentrum, Technische Universität, and Director, ISAResearch Center, Munich, Germany.

Upon collecting the award Adnan Kastrati said, "I am very flattered by this award, but I must say, I see this award not only for me, but for the whole ISAR team. It has been a great time to work with all these people."

The EAPCI Women Initiative

The EAPCI Women Initiative held a symposium for female interventional cardiologists attending this years course on the 21st May 2014. The aim was to review how the care of female patients with heart conditions can be improved and to discuss the overall aims of EAPCI Women.

Chair of EAPCI Women, Julinda Mehilli, said: "The session was very informative because it identified the barriers in diagnosis and treatment of women. The barriers include lack awareness of the gender disparities in the management of cardiovascular disease and that physician-related bias has led to the underuse of diagnostic and therapeutic tools in women."

ELECTIONS

The official announcement of the President-Elect, Secretary and Treasurer for 2014-16 was made during the General EAPCI Assembly at EuroPCR 2014.

- President-Elect: Prof Michael Haude, FESC (Germany)

Prof Haude is currently Director of Medical Clinic I, Städtische Kliniken Neuss, Lukaskrankenhaus GmbH. He has been involved within the EAPCI Board as Chair of the EAPCI Fellowship programme since 2009, he was appointed as Programme Committee Member for EuroPCR in 2013 and 2014. Finally, he was elected as Chairman of the AGIK (Working Group on Interventional Cardiology of the German Society of Cardiology) for the term 2011-2013 and has served AGIK since 2009, first as Chairman-Elect.

- Secretary: Prof Andreas Baumbach, FESC (United Kingdom)

Prof Baumbach is currently Consultant Cardiologist at University Hospitals Bristol, and Honorary Reader in Cardiology at the University of Bristol. He has been involved within the EAPCI Board as Chair and Co-Chair of the EAPCI Web & Communication Committee since 2006, was appointed as Programme Committee Member for EuroPCR in 2010 and EuroPCR Course Co-Director since 2012. Finally, he has served the British Cardiovascular Intervention Society (BCIS) in various positions since 2006: Council Member, Chair of Web & Communication, and he is currently the Chair of Training and Education.

- Treasurer: Dr Javier Escaned, FESC (Spain)

Dr Escaned is currently Consultant Interventional Cardiologist and Associate Professor of Cardiology, School of Medicine, Universidad Complutense de Madrid. He has been involved in the EAPCI Board as PCR Board Representative since 2011, was appointed as Programme Committee Member for EuroPCR in 2011 and 2012 and EuroPCR Course Co-Director in 2013 and 2014. Finally, he served in the Spanish Heart Foundation as Secretary in 2003 and was elected as Secretary of the Spanish Society of Cardiology in 2005.

Paris, France...

Paris, largest city and capital of France, has been one of the world's most important and attractive cities over the times.

Paris has one of the largest population clusters in Europe, with approximately 2.2 million people living in the dense, central city and almost 12 million people living in the whole area.

The River Seine rises 30 kilometres northwest of Dijon and flows in a northwesterly direction through Paris before emptying into the English Channel at Le Havre. It is one of Europe's great historic rivers, and together with a large part of the city, is a UNESCO World Heritage Site.

Paris is for its culture, entertainment, cuisine, fashion, painting, literature, and for the opportunities it offers for business and commerce.

Labelled the City Capital of Fashion, it is home to the world's finest and most luxurious fashion designers and cosmetics, such as Chanel, Dior, Yves Saint-Laurent, Guerlain, Lancôme, among many other top French brands.

The tradition of good cuisine, including culinary restaurants and excellent family style restaurants has facilitated the build-up of one of the largest numbers of Michelin-restaurants in the world.

With numerous iconic landmarks, and some of the most visited tourist site in the world; the Eiffel Tower; the Arc de Triomphe; the Notre-Dame Cathedral; the Louvre Museum; etc; Paris is one of the most popular tourist destination in the world.

These features make this fantastic city a great host for EuroPCR.

Treatment Strategies SnapShots

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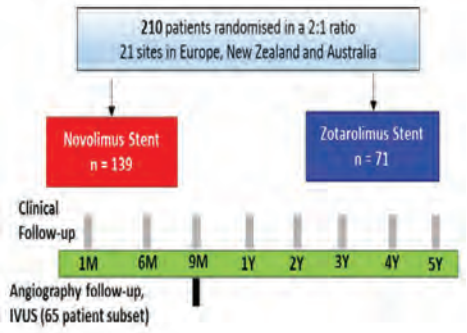
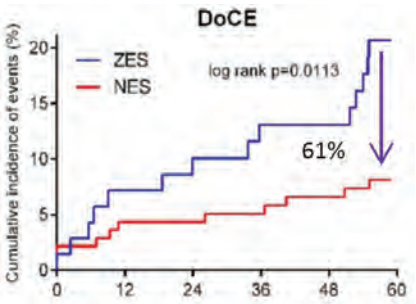
The EXCELLA II Trial was a randomised, prospective, multicenter, single-blind, non-inferiority study evaluating the DESyne® Novolimus Eluting Coronary Stent System (NES) compared to the Endeavor Zotarolimus Eluting Coronary Stent System (ZES) in the treatment of up to two de novo native coronary artery lesions. The primary efficacy endpoint was in-stent late lumen loss and the principal safety endpoint was a device-oriented composite endpoint (DoCE) comprised of cardiac death, target vessel myocardial infarction (MI) and clinically- indicated target vessel revascularisation (TLR). A total of 210 patients were enrolled at 21 International sites; the Coordinating Investigator for the Study was Professor Patrick W. Serruys, Erasmus University Medical Center, Rotterdam, the Netherlands.

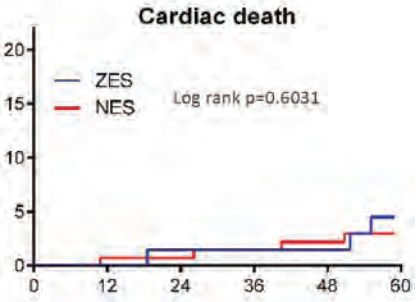


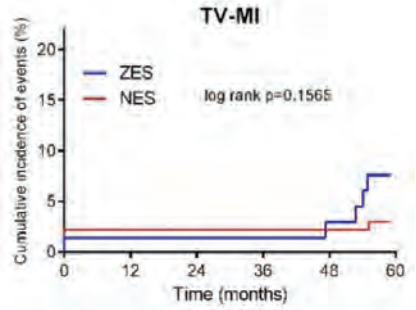
The DESyne Stent System was specifically designed to provide a highly flexible and deliverable cobalt chromium-alloy stent, delivering Novolimus, a metabolite of sirolimus, developed to provide similar efficacy as other currently available agents at a lower dose (5mcg/mm of stent length) and using an ultra-thin (<3µm) durable polymer coating.

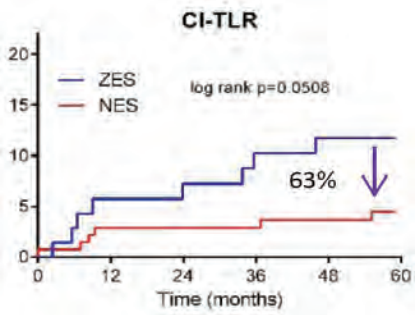
Results for the EXCELLA II Trial demonstrated both non-inferiority but also superiority of the DESyne Novolimus Eluting Stent to the Endeavor Zotarolimus Eluting Stent for the primary endpoint of in-stent late lumen loss (0.11 ± 0.32 vs. 0.63 ± 0.42; p=0.001). Additionally, at 5 years, the DESyne stent demonstrated a significant improvement in safety with a 61% decrease in the composite clinical endpoint inclusive of cardiac death, target vessel MI and target lesion revascularisation (KM 8.1% vs. 21.3%, p=0.01) as well as significantly lower (63% decrease) clinically-indicated target lesion revascularisation (KM 4.4% vs. 11.8%, p=0.05). There was no difference in cardiac death or TV-MI; definite and probable stent thrombosis rates were also similar.

The final 5-year results from the Excella II Clinical Trial demonstrated the superiority of the DESyne Novolimus Eluting Coronary Stent System vs. the control in both safety and efficacy through 5 years.









For more information visit: **www.elixirmedical.com**

Elixir® MEDICAL CORPORATION

Results from MASTER I Trial

InspireMD, Inc. attended EuroPCR 2014 where the MicroNet™ Technology was showcased and the results from the MASTER I Trial were presented in a symposium.

Entitled 'MGuard™ Embolic Protection Stent: The Importance of Thrombus Management in STEMI Primary PCI', in this symposium InspireMD shared the results of its MASTER Trial for the first time in Europe.

Data from the 12-month MASTER (MGuard for Acute ST Elevation Reperfusion) trial was discussed by the expert presenters during the symposium. The data demonstrated that the MGuard outperformed bare metal and drug eluting stents in all-cause mortality in ST segment elevation myocardial infarction (STEMI) patients.

In addition to the superb performance of the MGuard the MASTER trial achieved its primary endpoint in complete ST-segment resolution at 60-90 minutes post-procedure, which is historically a strong predictor of mortality. The secondary endpoint continued to show lower mortality rates with MGuard use as opposed to the control group.

In particular the symposium focused on and covered the importance of thrombus management in primary PCI for STEMI patients, provided an update on relevant clinical data on device selection in STEMI treatment and showcased real-life examples of how device selection can influence the outcome of STEMI patients.

InspireMD endeavours to make its products the industry standard for embolic protection and provide better solution to the key clinical issues of current stenting in patients with a high risk of distal embolisation, no reflow and major adverse cardiac events.

For more information please visit **www.inspire-md.com**

ACIST RXI™ System Presented During a Live Case at EuroPCR

ACIST, a Bracco Group company, a pioneer and a market leader of advanced contrast delivery systems presented its new ACIST RXi™, the world's first Rapid Exchange FFR system in a live case transmission at EuroPCR. A complex multi-vessel Percutaneous Coronary Intervention (PCI) procedure conducted by Dr. Nicolas van Mieghem and Dr. Roberto Diletti from Erasmus Medical Center, Rotterdam, The Netherlands, demonstrated the ACIST RXi™ Rapid Exchange FFR System to attendees at the congress.

A unique approach from the existing wire-based technologies, the ACIST Rapid FFR system utilises fiber-optic technology, resulting in greater signal stability and less potential for signal drift. The ultra-thin Navvus MicroCatheter features simple plug and play by not requiring calibration therefore saving time and increasing ease of use versus older FFR wire-base systems.

In this live case the ability of the ultra-thin ACIST Navvus™ Rapid Exchange MicroCatheter to facilitate FFR measurements in complex multi-vessel disease was showcased. Since the Navvus MicroCatheter can be used over a standard 0.014 inch guidewire physicians are given full control while maintaining wire position throughout the coronary procedure.

With the rapid FFR assessments before, during and post-intervention, physicians can quickly assess blockages that could require PCI.

This new and unique system provides reassurance of accurate and reliable FFR measurements and the advantages of Rapid Exchange technology.

A second live case transmission from Institut Cardiovasculaire Paris Sud Massy (France) demonstrated and featured RXi as a tool for rapid FFR measurement in daily routine. Both presentations demonstrated the evolution and advancement of technology developed by ACIST to simplify the complexities in the Cath Lab and empowering clinicians and their teams in providing superior patient care.

For more information please visit **www.acist.com**

Rapidly Deployable Right Sided Percutaneous Support

Abiomed, Inc., a leading provider of medical devices that provide circulatory support and breakthrough heart support technologies, showcased the Impella® RP Technology at EuroPCR 2014.

At their booth, Abiomed demonstrated the Impella RP, which recently received the CE Mark, and new simulators demonstrating bi-ventricular support of the Impella platform.

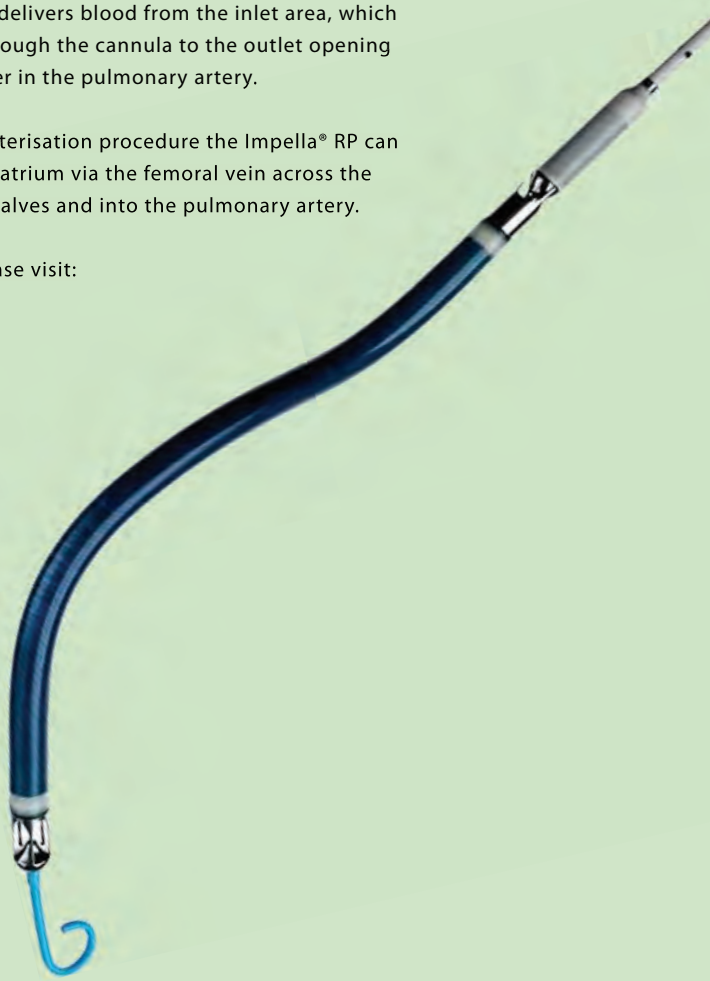
The Impella® RP provides rapidly deployable right-sided percutaneous support. Designed to enable the heart to rest by improving blood flow Impella® RP offers RP Impella® RP offers a new approach to and or performing the pumping of the heart.

The platform encompasses Abiomed 's percutaneous and catheter based devices such as the Impella® 2.5, Impella CP®, and the Impella® 5.0. Currently in development and not FDA-approved yet, the Impella® RP (right-side device) and the Impella® pediatric.

The Impella® RP Catheter delivers blood from the inlet area, which sits interior vena cava, through the cannula to the outlet opening near the tip of the catheter in the pulmonary artery.

Through a standard catheterisation procedure the Impella® RP can be inserted into the right atrium via the femoral vein across the triscuspid and pulmonic valves and into the pulmonary artery.

For more information please visit:
www.abiomed.com



CE Mark Approval for PARADISE™ - Ultrasound Transcatheter Renal Denervation System

The PARADISE™ Ultrasound Transcatheter Renal Denervation System new from ReCor Medical has recently received the CE mark approval.

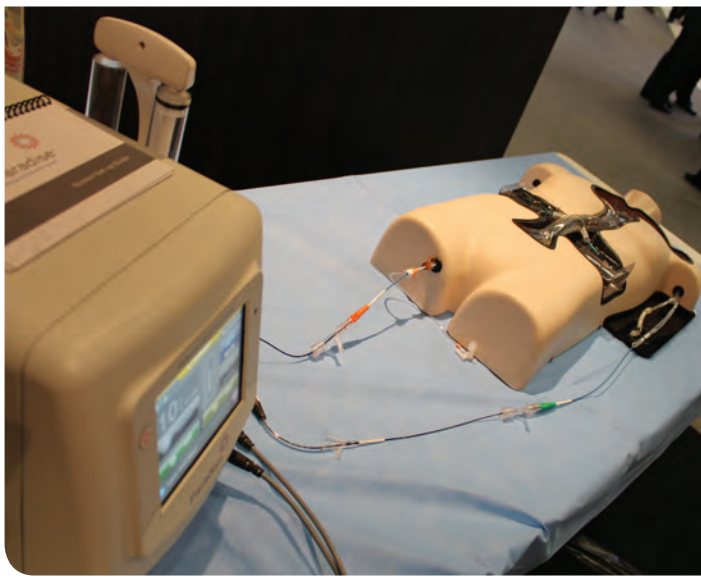
PARADISE® technology (Percutaneous Renal Denervation System) is a unique therapeutic non-focused ultrasound system designed to treat patients with resistant hypertension. It includes a 6 French catheter with a cylindrical transducer that emits ultrasound energy circumferentially, allowing for a more efficient renal denervation procedure.

Its advantage over other technologies is its ability to uniformly denervate all the way around the arterial wall while simultaneously cooling the endothelium, to help enable a safe, consistent, and fast renal denervation procedure. The use of an energy source that does not require direct tissue contact allows for a balloon to be inflated around the transducer and brings the following clinical benefits:

- PARADISE® balloon enables cooled fluid to circulate during the energy delivery process and keeps the artery wall cool, minimising damage to non-target tissues
- PARADISE® balloon centers the ultrasound transducer in the artery and enables controlled, uniform, and circumferential energy delivery
- PARADISE® controlled, uniform, and circumferential heating is independent of catheter positioning or tissue characteristics and reduces the number of treatment sites required to achieve renal denervation
- PARADISE® reduced number of treatment sites diminishes the overall procedure times and minimises pain and discomfort for the patient

The Company's CE-Marked PARADISE® System is unique in its use of a radial ultrasound energy source with water based cooling to simultaneously provide circumferential energy delivery and convective cooling for denervation of the renal nerves and arterial protection.

For more information please visit:
www.recormedical.com



TS – TV Talks to...
Göran Malmberg - CEO of Mentice

Sara Taheri, Treatment Strategies, interviews Göran Malmberg at EuroPCR 2014

Can you tell us about Mentice and why you are at EuroPCR 2014?

This is the biggest cardiology conference in Europe and a lot of our clients are here. As you may know, we work with the hospital market and the industry market, so our clients are both the exhibitors and the visitors here. So this is a great place for us to meet our clients and the amount of meetings we can arrange in a few days makes this a very cost-effective way for us to meet people.

Mentice. We're a Swedish based simulation company, and we provide endovascular simulation, which can be used for a couple of different purposes. It is used to train doctors on these procedures, so what we really do is provide an advanced way to practice off patients in a completely safe environment in a very realistic way. Real devices are used so that the doctor can get the correct tactile feedback and the real feeling of doing the procedure on a real patient.

So, we have this idea that doctors should practice on a simulator prior to doing a procedure on a patient. Today, with these procedures, it's fairly difficult to find other ways to train them, which could be either to practice on live animals or on the patients. So this is the only real alternative to those two others ways to practice.

Can you give us some information on the VIST® simulation system?

We call our family of products VIST®, the vascular training system. The VIST® is really a software and hardware family where we provide training programs for all kinds of vascular procedures from the head to the toes. So, we cover specialties like neurosurgery, cardiology, radiology and others - a list of around 20 different procedures

What are the applications for this system?

The primary goal for this system is to train physician, we can compare them to pilots, for aerospace. Pilots always train and retrain on simulators, and they need to do that continuously throughout their career. We want to provide the same structure for doctors. There's a lot of things happening in medicine, new techniques and new procedures and things like that so we want to provide an infrastructure for doctors to have a continuous learning experience on the simulator.

Also the industry clients we have, the people that exhibit here at this congress, they use our simulator to train their own staff on their procedures and techniques. They also interact with their clients to demonstrate and present their products.

Finally, what is unique about the VIST® system?

This is a very small market, a very specialised market, there are only around three or four vendors across the world that provide a solution for this. We are actually the only one in the world that do just this, this is the only thing that we do. We spend a lot of our efforts and a lot of research on providing the absolute best tactile feedback and the best realist, to really allow doctors to get as close as possible to the real scenario. We believe we are the best provider, in that we work hard to ensure physicians can use the real devices, the real handles, have the feeling in the hands - the tactile feedback would be the same as in the real patient.

The feedback from the screens and other information attained during the procedure would be the same as in the real world. We believe we have the strongest solution in terms of providing that environment for doctors.

Medical Vascular Simulation with the VIST®- Lab

A world leader in medical vascular simulation, Mentice were showcasing the VIST®-Lab solution during EuroPCR this year.

The Mentice VIST®-Lab is a stationary simulation solution, combining realism, ergonomics and ultimate flexibility which provides a solution for realistic work flow and team training, by mimicking the lab environment. The VIST® -Lab supports treatment through left and right femoral, radial and subclavian approaches.

This provides training in a virtual environment, which mimic all relevant functionality, including state of the art imaging (with full table, C-arm, shutters, image acquisition and management, and many more). It consists of a full body mannequin with femoral, radial and subclavian/jugular access options, and up to 4 screens setup (control screen, fluoro, cine and vitals).

This structured and comprehensive suite provides trainees with exposure to a wide range of patient scenarios, with real-life procedural accuracy whilst using real devices that are used in CathLabs. Cases are selected so that different levels of expertise are catered for and a powerful User Interface is used across all modules.

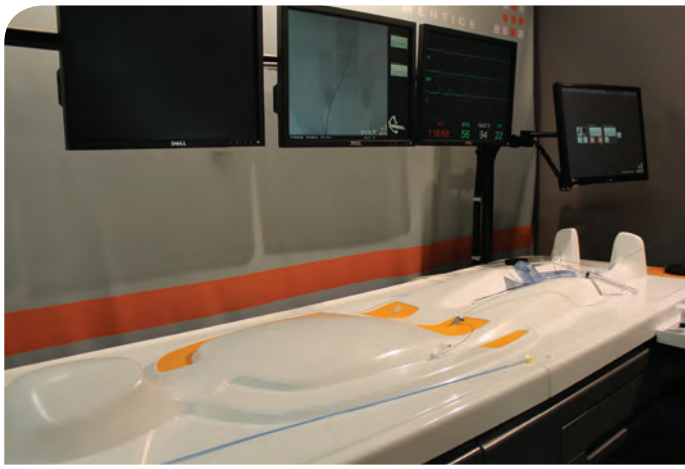
MR, CT, angiographical data and patient's medical report have been used to build a repertoire of Cases and Scenarios for the VIST®. These virtual patients are created with training objectives in mind and always in collaboration with senior physicians. Information is provided on the demographics, clinical representation, medical history, current medications, lab values and much more information necessary to make a first assessment.

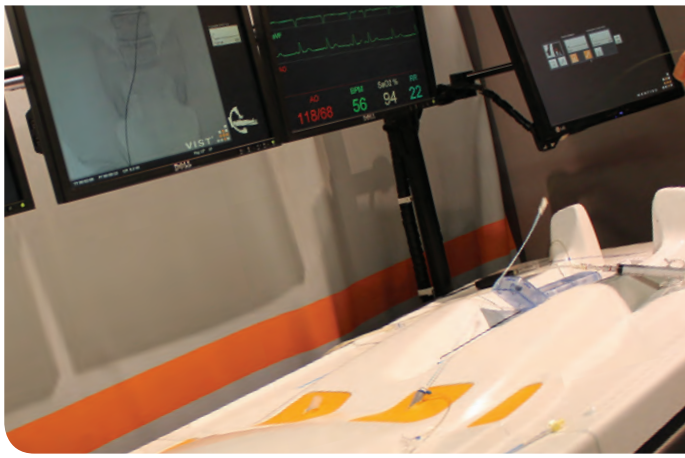
Features include:

- Height adjustable table legs on wheels
- Supports actual clinical devices
- Full bifemoral support with optional VIST-C extension
- Supports left and right femoral, subclavian and radial approaches
- Robust design
- External Control box
- Control box with fluoroscopy and table controls
- Solution easily moved around on the wheels
- Compatible with VIST® -C simulator and VIST®-C extension (for optional bifemoral access)

The VIST®-Lab allows for the system to be used either in a stationary setup or converted into one (or two) fully functional portable VIST®-C systems.

For more information please visit:
www.mentice.com





Coronary Angioplasty Procedure using BiOSS® during EuroPCR

BiOSS®, BALTON Ltd newest biodegradable polymer coronary bifurcation stent was used during one of the procedures presented at EuropPCR 2014.

BALTON Ltd. is one of the biggest producers of medical equipment in Poland and one their most important achievements is the production of stents for coronary and peripheral vessels as well as self-expanding stents.

During one of the interactive procedures from the selected European centres leading figures demonstrated both innovative and already performed solutions, which are still of huge interest.

Among the European hospitals this on-line transmission came form the Upper Silesian Medical Centre in Katowice-Ochojec. The complicated coronary angioplasty procedure was performed using many different methods of imaging, as well as the transmission of the full decision-making process and the "BiOSS" stent was used during the procedure.

The BiOSS stent is an innovative and technologically advanced solution dedicated to the treatment of coronary bifurcation. Bifurcation optimised stents for coronary vessels with one profiled balloon with diameters corresponding to dimensions of the coronary bifurcation vessels, guided on a single 0.14 guide wire for an easier and quicker implantation procedure.

The technology offers unique configuration of the delivery system ensuring safety and efficacy during the stent implantation procedure

This dedicated stent delivery system minimises the negative effects of the procedure and protects and prevents the side branch from occlusion and the carina tip from being crushed or damaged.

For more infomration visit:
www.balton.pl

Sirolimus Eluting Coronary Stent System from Meril

A young, dynamic global medical device company, Meril Life Sciences is dedicated towards design and development of novel, clinically relevant, state-of-the-art devices across various therapeutic areas including cardiology vascular interventional devices. Meril CardioVascular has been dedicated to the design and development of novel interventional technologies from DES to TAVI & beyond.

During EuroPCR 2014, Meril Life Sciences were exhibiting Meril's BioMime - Sirolimus Eluting Coronary Stent System. A successful concept this new generation DES is a novel, low injury coronary stent design.

The NexGen™ Cobalt Chromium (L605) alloy stent was Meril's primary design platform and has lead to the successful development of a new generation DES – BioMime™ Sirolimus Eluting Coronary Stent System. Built on an ultra-low strut thickness (65µm) cobalt chromium stent platform, using a hybrid of close and open cells which allow morphology mediated expansion, it employs a well known anti-proliferative – Sirolimus that elutes in 30days and a biodegradable co-polymer formulation that ensures high coating integrity and low coating thickness of 2µm.

Meril's current portfolio has the following product lines which are all locally approved and have CE mark-

BioMime™ – Sirolimus Eluting Coronary Stent System
NexGen™ – Cobalt Chromium Coronary Stent System
Crypton™ – Stainless Steel Coronary Stent System
Mozec™ – Rx PTCA Balloon Dilatation Catheter
Haiku™ – Inflation Device

For more infomration visit:
www.merillife.com

World's First and Only Dual Therapy Stent

During a symposium titled, 'Achieving the Goal of Stenting: the COMBO™ Dual Therapy Stent for an Open, Stable and Healed Coronary Artery', OrbusNeich reported the long-term results from its REMEDEE Trial.

The Symposium was chaired by Dr Renu Virmani, president of the CVPath Institute, United States and Dr Roxana Mehran, Mount Sinai Medical Center, United Statesfeatured , other speakers included:

- Dr Michael Haude, University of Essen, Germany - First read-out of three-year data on the first-in-man REMEDEE trial
- Dr Michael Joner, CEO of the CVPath Institute, United States – Head-to-head comparison of COMBO vs XIENCE; and the relationship between neoatherosclerosis, clinical restenosis and stent thrombosis
- Dr Robbert J. de Winter, Academic Medical Center, University of Amsterdam, the Netherlands – First read-out of real-world data on REMEDEE registry

Results from its REMEDEE Trial, Randomised Evaluation of an abluMinal sirolimus coatED bio-Engineered stEnt), a randomised clinical trial of the Combo Bio-engineered Sirolimus Eluting Stent (COMBO™ Dual Therapy Stent), for Treatment of Stenotic Lesions in Native Coronary Arteries were presented.

OrbusNeich is a global company that designs, develops, manufactures and markets innovative medical devices for the treatment of vascular diseases. Current products are the world's first dual therapy stent, the COMBO Dual Therapy Stent, and the world's first pro-healing stent, the Genous™ Stent.

The COMBO™ Dual Therapy Stent combines the pro-healing technology used in the Genous™ Stent for rapid endothelial coverage with an abluminal sirolimus drug elution for the control of neointimal proliferation. It is the first dual therapy stent to both accelerate endothelial coverage and control neo-intimal proliferation through the combination of the proven pro-healing technology with an abluminal sirolimus drug elution delivered from a biodegradable polymer that achieves full and complete dissipation by 90 days.

Results have shown that the COMBO™ Dual Therapy Stent is the only dual therapy stent that accelerates endothelial coverage and controls neointimal proliferation and shows no late target lesion revascularisation. The results presented also demonstrated that the stent proactively promotes functional vessel healing.

The key findings reported include:

- In the second and third years of the follow up on the REMEDEE trial, target lesion revascularisation remained stable at 5.7 per cent
- No thrombotic events were reported over the three years
- Complete polymer degradation and drug release by 90 days

For more information visit:
www.OrbusNeich.com

Optimising Pre-operation Workflow with the 3mensio Structural Heart™

With over 30 years of expertise in cardiovascular image analysis, Pie Medical Imaging provides a wide range of solutions for optimal assistance during medical diagnostics and interventions. With highly accurate and reproducible data their products provide an answer to the need in both clinical and in research settings.

Pie Medical Imaging has expanded its suite of solutions with new innovations that assist physicians in the treatment of Structural Heart diseases. One of the newest developments in the field of structural heart disease the 3mensio Structural Heart™ planning and sizing software is of great value to Pie Medical Imaging's product portfolio and was showcased at EuroPCR 2014.

The 3mensio Structural Heart™ has been especially designed with cardiologists in mind and is dedicated to the planning of aortic and mitral valve replacement and repair procedures and left arterial appendage closures.

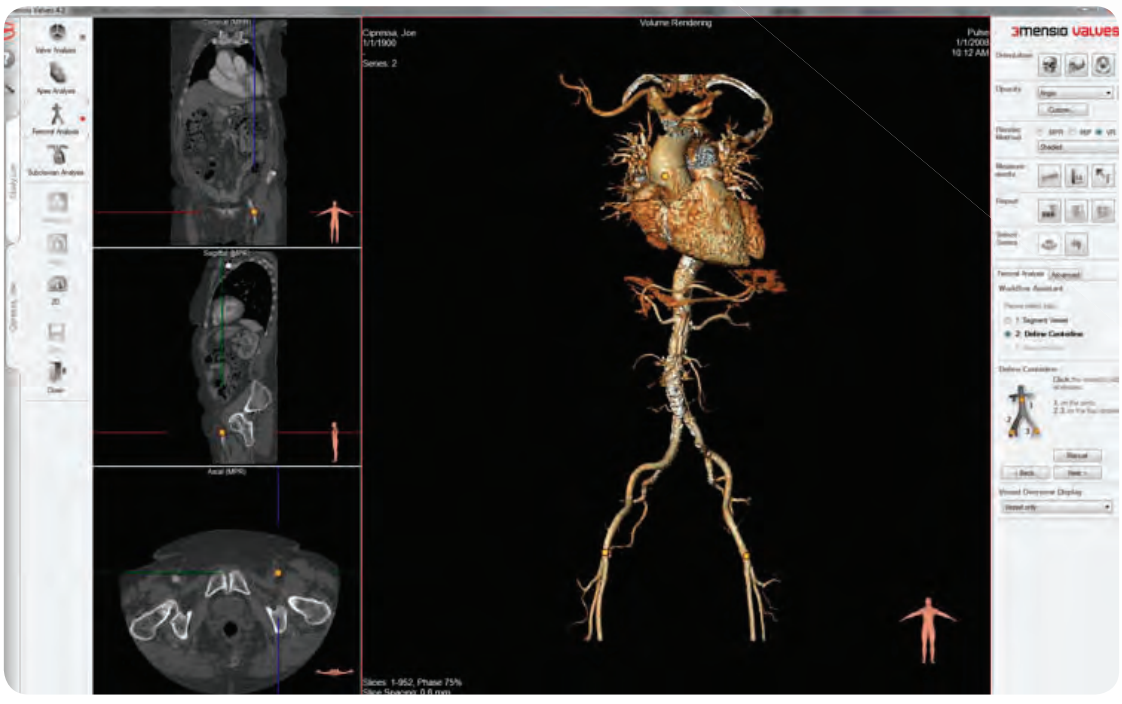
It has an in-built graphical user interface, which is dedicated to simplifying workflow, and allowing for quick and accurate visualisations and analysis of vasculature, aortic and mitral valve and left atrial appendage.

With the 3mensio Structural Heart™ cardiovascular specialists can plan aortic and mitral valve replacement and repair procedures and left arterial appendage closures with a better insight into the patient's pathology and through a less invasive but more precise procedures.

The 3mensio Structural Heart™ is dedicated to assisting in workflow and once the desired workflow has been selected the technology will guide the user through the preparations for measurements.

The 3mensio Structural Heart™ works with all major medical imaging formats and the software itself can be installed on virtually any modern Windows based laptop or desktop.

For more information please visit:
www.piemedicalimaging.com



A New Arrival for Minimally Invasive Procedures

Bentley InnoMed has expanded its portfolio with the launch of its BeGraft Peripheral Stent Graft System in November 2013. During EuroPCR this year, the BeGraft PERIPHERAL this a next generation covered stent, a new arrival for minimally invasive procedures was proudly presented by Bentley InnoMed.

Bentley InnoMed uses advanced leading edge technologies to develop innovative and unique products that focus on the customer usage and achieve superior quality by complying with international standards

With exceptional knowledge in the development of minimally invasive products based on years of work and collaboration with our customers and clients, Bentley InnoMed were able to combine their expertise to develop innovative, high quality products such as the BeGraft Peripheral Stent System.

This extraordinary product features a specially designed one-layer stent graft, which combines a cobalt-chrome stent platform with a micro-porous ePTFE membrane cover. The system is based on a low-profile catheter.

The BeGraft PERIPHERAL, Peripheral Stent Graft System is indicated for intraluminal chronic placement in iliac and renal arteries for:

- Restoring and improving the patency
- Treating aneurysms, acute perforations, acute ruptures and fistulas

For more information please visit:
www.bentley-innomed.com

On-line Image Processing Workstation

Volcano Corporation is focused on designing, developing and producing precision guided therapy tools for PCI procedures, including intravascular ultrasound (IVUS), and fractional flow reserve (FFR), products.

The FFR technology is used to determine whether or not a stent is necessary and the IVUS product line is used by clinicians to measure the stage and severity of the disease in cardiac and peripheral vessels and to guide stent placement and optimisation. IVUS offers unique features, including both phased array and rotational IVUS imaging catheters and advanced functionality options, ChromaFlo® and FFR technology. These IVUS ultrasound consoles can be integrated directly into any modern cath lab and single use disposable imaging catheters unique to the Volcano system.

With their comprehensive and wide-ranging suite of technologies, Volcano is transforming the medical device industry to make imaging and therapy simpler, more informative and less invasive.

During EuroPCR 2014 Volcano showcased the recently launched, FDA cleared and CE marked, SyncVision™ Technology System. An on-line image processing workstation for coronary catheterisations, this enables physician to navigate simultaneously on an angiogram and on an IVUS image in a single correlated view using co-registration of the Eagle Eye® Platinum catheter with x-ray angiography. To facilitate informed decisions, efficiency and enhanced workflow performance, SyncVision™ brings the detailed vessel, lumen and wall structure from angiography and the spatial localisation of Volcano's intravascular ultrasound images within the coronary tree together in a co-registered view.

The system is currently installed in multiple limited market release sites throughout U.S. and Europe and is expected to be in full market release later this year.

For more information please visit:
www.volcanocorp.com

TS – TV Talks to...
Michele Perrino - President, EMEAI, Volcano

Sara Taheri from Treatment Strategies TV Interviews Michele Perrino, President, EMEAI, Volcano

In a few words who is Volcano?

Volcano is an exciting book that has been written in the last 10 years by this organisation in the cardiovascular space. It was created in 2003 and went public with the NASDAQ in 2006. From that moment, we have been growing by double digits year on year, thanks to our technology and our capacity to really improve technology, intravascular imaging and physiology year after year. Through our focus and remaining our focus on this and not going outside of this space as well as our culture that makes Volcano a different company in this market.

What are your key highlights at EuroPCR this year?

EuroPCR is an exciting week every year for us. The first thing that we try to accomplish during this week is that we try to reset our success of the last 12 months and get ready for the next 12 months. That's why the first thing that we try to accomplish is to tell to the community who we are and what we have done so far. That is why this year in 2014 our focus is education, we are a leader in the business in physiology and imaging and in the last 12 months we have been educating more than 1000 people.

We are also enlightening our capacity to build and expand the market where we are, and we do this through clinical trials and again through education by training in the lab, training internationally and competing in different market in Europe and outside of Europe and of course also we have new products coming to the market.

Last year we launched iFR® and CORE™ and we are representing these two products this year as well. They have exciting stories, for iFR® we have been able to add more than 250 customers who are actively using this technology and for CORE™ where we have more than 10% of our initial base today active and using the new platform.

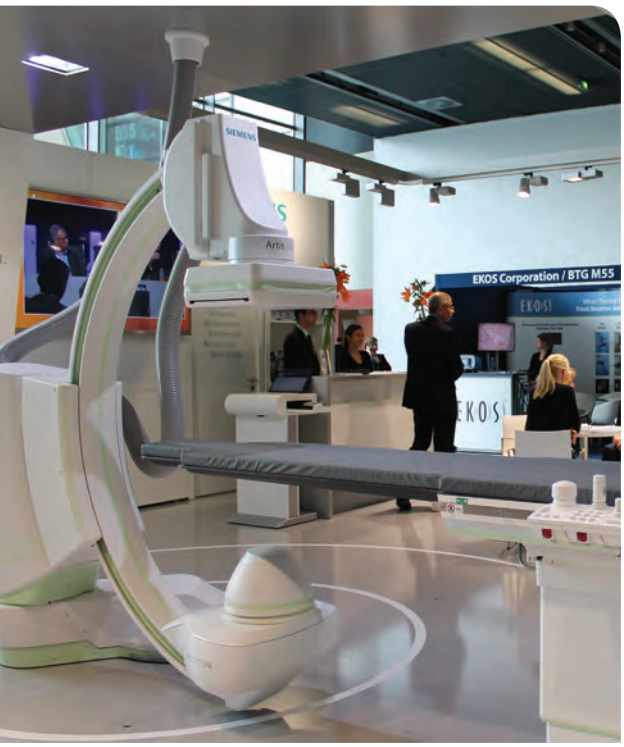
This year our major highlight and the product we are launching is SyncVision™. SyncVision™ represents a new capability, a new modality that we add to our platform that will enable us to combine angiography with imaging with all the other modality going forward.

Where do you see Volcano in five years time?

The next five years for Volcano will be even more exciting than the past. We plan to grow and to keep growing in double digits as we have down in the last 11 years. We plan to reinforce our leadership in intravascular imaging as well in physiology, where we are today.

We are also committed to entering new markets, new clinical space with this current technology as well as new spaces like peripheral for example where we want to add to our diagnostic leadership today the therapeutic leadership of tomorrow.

A Small Footprint with Large Returns



Designed to meet the essential imaging requirements in interventional cardiology, the impressive Artis® one® was on display at the Siemens booth during EuroPCr 2014.

Siemens had on display their impressive Artis® one® which has been designed to meet the essential imaging requirements for interventional cardiology.

The Artis® one® has been designed to support a wide range of procedures without compromising image quality and is expected to redefine the way interventions are performed.

With a big advantage for hospitals with limited space, the Artis® one® has a surprisingly small footprint, needing a room size of just 25 square meters it has the potential to offer large returns. Compared to ceiling-mounted systems that generally occupy 45 square meters or more, the Artis® one® allows for high utilisation of the lab, enabling higher reimbursement and increased efficiency.

Minimally invasive procedures are on the rise worldwide and cardiovascular specialists are now performing highly specialised interventions that are routine procedures on a daily basis.

Siemens already supports challenging cases with the well established Artis Q, Artis Q.zen and Artis zee families, but for routine interventions physicians need a system that could support a range of procedures with ease, without compromising image quality or dose saving.

The Artis® one® can adapt to different scenarios and provide tailored support for each task. At the same time it remains easy to understand, so that rotating teams can adjust to it - using it with ease. By providing high-contrast images with excellent spatial and temporal resolution, it also includes next-generation imaging tools that take image quality to a new level.

These tools, CLEARstent and HeartSweep work together tp provide optimal support along the entire cardiology workflow, from diagnosis and interventional guidance to procedural assessment and documentation.

- CLEARstent Live enhances the stent image in real-time, allowing confirmation of the stent and the

balloon markers at a glance.

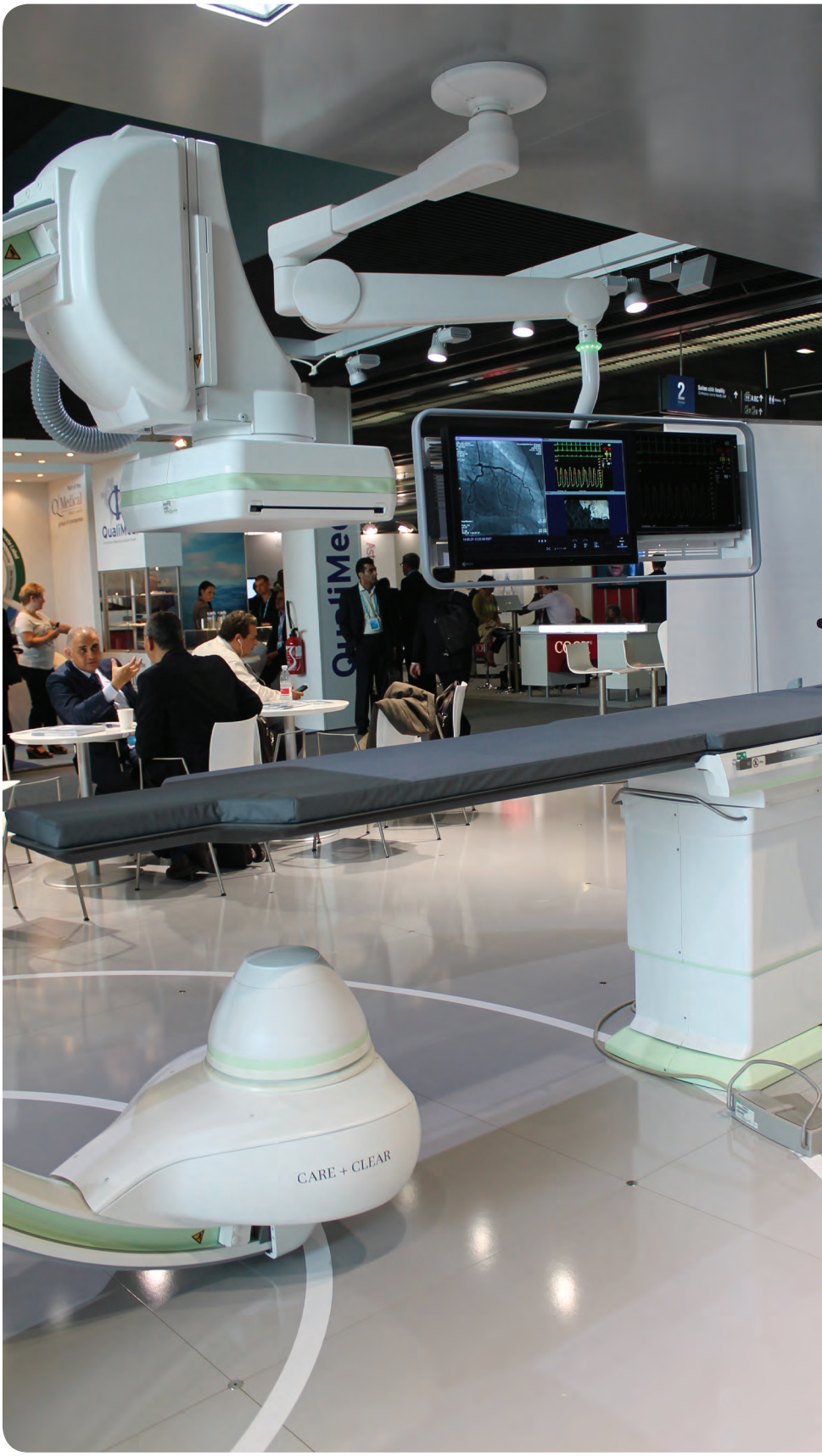
- HeartSweep provides all the necessary diagnostic cardiac angulations in a single sweep, avoiding foreshortening. This makes it easier to find and navigate to the ideal projection for an intervention, allowing reductions in dose and contrast agent.

In addition to these tools the Artis® one® also provides 3D imaging tools to assist enhanced anatomical understanding, together with the options to view other modality 3D volumes such as CT, MR, or syngo DynaCT images. These tools make planning and orientation easier for the entire interventional team.

When universal angiography labs need to conduct peripheral procedures, they require an imaging system that permits whole-body coverage without having to move the patient. Artis® one® offers a longitudinal coverage of 2.10 meters, supporting peripheral interventions from head to toe and instead of moving the patient around the system, the Artis® one® moves around the patient

Currently the Artis® one® is pending 510(k) clearance, and is not yet commercially available in the United States or other countries.

For more information visit:
www.siemens.com



A One-sheath Solution

The Destino™ Twist was launched in October 2013 by Oscor Inc., and was showcased in EuroPCR 2014.

The Destino™ Twist is a one-sheath solution intended to facilitate, simplify, speed up and make more affordable intracardiac, renal, and peripheral placements of diagnostic and therapeutic devices.

With its unidirectional deflectable tip with an ergonomic steerable handle, this is the ultimate tool in gaining access to the most difficult to reach locations.

The benefits of the Destino™ Twist include:

- Ergonomic handle with clear imprint of the curve deflection, french size and sheath length
- Tip position indicator showing neutral or deflected curve
- Accurate tip deflection response to handle collar rotation
- Soft, atraumatic tip reduces potential for trauma and provides smooth transition to catheter
- Radiopaque tip marker enhances fluoro visibility
- Curve retention for accurate catheter placement
- Hydrophobic coated sheath improves access
- Braided Flexsteer™ shaft provides exceptional control torqueability, and kink resistance
- Snap-locking dilator connector
- Accepts maximum guidewire up to 0.035”/0.89 mm

With over 30 years of experience, Oscor Inc is focused on cardiac medical devices, which include implantable and temporary pacing leads, adaptors, pacemakers, introducer sheaths, steerable sheaths, catheters, and more.

Further information available at:
www.oscor.com

Strong and Safe Performance Reported for the Lotus™ Valve System

Blood flow in and out of the heart is controlled by four valves, which the aortic valve is one of. Aortic valve stenosis is the process of thickening and stiffening in the valve, which can result in an abnormal narrowing of the aortic valve opening and reduction in blood flow.

During EuroPCR, Boston Scientific shared new data from the REPRISE II study proving the Lotus™ Valve System demonstrated impressive performance at six months in aortic valve stenosis.

The REPRISE II clinical trial is a study in which the use of the Lotus Valve System in symptomatic patients with severe aortic valve stenosis who are at too high risk for surgical valve replacement is being is evaluated.

REPRISE II enrolled 120 patients at 14 sites was later extended to an additional 130 patients at 16 sites in Australia and Europe.

The results from this clinical trial demonstrated that the Lotus Valve System delivered sustained safety and effectiveness. No severe cases of paravalvular aortic regurgitation (leaking) occurred amongst the patients and only 1.1 percent experienced moderate paravalvular aortic regurgitation.

A differentiated second-generation TAVI technology, 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 system has been designed to enable predictable and precise placement associated with early valve function, as well as bi-directional atraumatic repositioning and retrieval of the aortic valve implant at any time prior to its release.

A unique feature an Adaptive Seal™ designed to minimise the incidence of paravalvular regurgitation, which has proven to be a predictor of mortality.

The Lotus Valve System is only available as an investigational device and not yet for sale in the U.S., it has CE Mark approval and is available in CE Mark countries.

Professor Ian Meredith, director of MonashHeart, at Monash Medical Centre in Melbourne, Australia, and principal investigator of the REPRISE II trial presented this data during EuroPCR this year.

For more information visit:
www.bostonscientific.com

First Human Implants with FORTIS Mitral Transcatheter Valve

The global leader in the science of heart valves and haemodynamic monitoring, Edwards Lifesciences Corporation, presented the outcome of the first-in-human experience with Edwards' FORTIS mitral transcatheter heart valve.

Up until recently there appeared to be no solution for severely sick patients with mitral valve disease, now this disease is looking more treatable with a range of possible options. One option is Edwards' FORTIS transcatheter mitral valve, treated with bovine pericardial tissue the device features a cloth-covered, self-expanding frame designed to minimise paravalvular leak and a unique anatomical anchoring system.

The Heart Team at St. Thomas' Hospital in London performed the first three human implants of its FORTIS mitral transcatheter in February and March. The successful completion of these implants was presented during the late-breaking session on transcatheter mitral therapies at EuroPCR 2014 congress.

"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. Thomas. *"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."*

These first patients had severe mitral valve disease and suffered from severe mitral regurgitation, marked breathlessness, multiple co-morbidities and were not candidates for surgical mitral valve intervention. Although there were many risk factors that prevented them from undergoing surgery, after cautious evaluation

and consultations the physicians determined that this could potentially extend and improve their lives. The FORTIS mitral transcatheter heart valve was offered to these patients on humanitarian/compassionate grounds.

Vinayak Bapat, FRCS CTh, consultant cardiothoracic surgeon, St. Thomas' Hospital in London, and Martyn Thomas, MD, FRCP, clinical director of cardiovascular services, St. Thomas' Hospital, reviewed the first patient cases performed and reported that:

- Of the first four cases, three patients passed away between days 4 and 76 post-procedure.
- One patient continued to be followed at 76 days.
- A fifth patient was treated at St. Michael's Hospital in Toronto, Canada, and is recovering.

It was concluded that in continuing with this research physicians would be able to determine optimal patient selection, procedural steps and post-operative management.

At present the FORTIS transcatheter mitral valve is not approved for sale in any country.

Further information available at:
www.edwards.com

"We are confident that our commitment to addressing the unmet needs of patients will lead to transcatheter mitral valve replacement becoming a meaningful therapy." said Michael A. Mussallem, Edwards' chairman and CEO

The Stent with the Best in Class Efficacy for Heart Attacks

During the Hotline session at the EuroPCR congress, STENTYS, a medical technology company presented final results from the APPOSITION IV study of its novel Self-Apposing sirolimus-eluting stent (SES).

The Self-Apposing® Stent from STENTYS has been designed to address the stent-sizing dilemma that cardiologists face everyday when treating heart attack patients or patients with atypical artery anatomy.

With a flexible, self-expanding design, the Self-Apposing® Stent takes the shape of the patient's unique vessel anatomy and apposes to the irregular contours of a blood vessel. Post acute myocardial infarction (AMI) the vessel dilates and the clot dissolves and it is in this particular setting that the Self-Apposing® Stent reduces the risk of malapposition and complications associated with conventional stents.

APPOSITION IV is a prospective, randomised, four-arm, multi-centre clinical trial designed to evaluate the novel Self-Apposing SES. 152 patients experiencing ST-elevation myocardial infarction (STEMI) were enrolled to compare the STENTYS Sirolimus eluting stent (90 patients) with Medtronic Resolute® (62 patients).

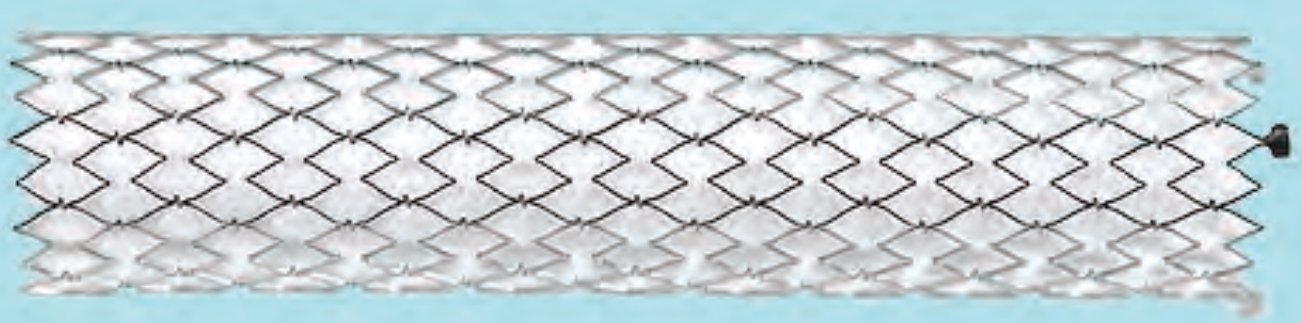
The progress made by each stent group was compared at two different time points, 4 and 9 months. The evaluation was based on two imaging modalities: Quantitative Coronary Angiography (QCA) to measure the difference in artery diameters between implantation and follow-up, and Optical Coherence Tomography (OCT) to quantify the number of stent struts apposed and "covered" by tissue, an indication that the endothelial cells lining the artery wall have grown around the stent and that the vessel has healed.

At 9 months, the STENTYS SES showed no reduction in artery lumen diameter with a near perfect arterial healing, demonstrating stent efficacy and safety. Stent apposition was statistically better in the STENTYS group at 4 months and a greater percentage of STENTYS stents were fully covered. At 9 months, strut apposition and coverage were similar in both groups. The results confirm that arteries with STENTYS SES healed faster than with balloon-expandable drug-eluting stents.

"With these study results, our sirolimus-eluting stent could receive CE Mark as soon as the second half of this year." said Gonzague Issenmann, CEO and co-founder of STENTYS.

The STENTYS Self-Apposing Stent has been marketed in Europe since receiving CE Mark in 2010. The STENTYS Sirolimus-eluting stent should receive the CE Mark during the second half of 2014.

For more information please visit:
www.stentys.com



Live Demonstration of the Breakthrough DESolve® 100 by Elixir

The breakthrough DESolve® 100 Novolimus Eluting Bioresorbable Coronary Scaffold System was showcased in a live case demonstration at EuroPCR, on Tuesday, May 20th 2014.

The demonstration was performed by Dr Stefan Verheye, M.D., Ph.D., ZNA Middleheim Hospital, Antwerp, Belgium. This was conducted in his cardiac catherisation lab in Belgium and streamed live to the audience in Theater Bleu at EuroPCR.

Designed and manufactured by Elixir Medical Corporation, the DESolve® 100 has recently attained CE Mark approval. It is the world's first fully bioresorbable scaffold with a dramatically thinner strut profile of 100µm.

The DESolve® 100 has been designed to degrade within a year and return the patients' coronary vessel to its normal state while providing market-leading deliverability and conformability. Elixir designed the DESolve® 100 to enable cardiology specialist to address the needs of more patients by making scaffolds more user-friendly

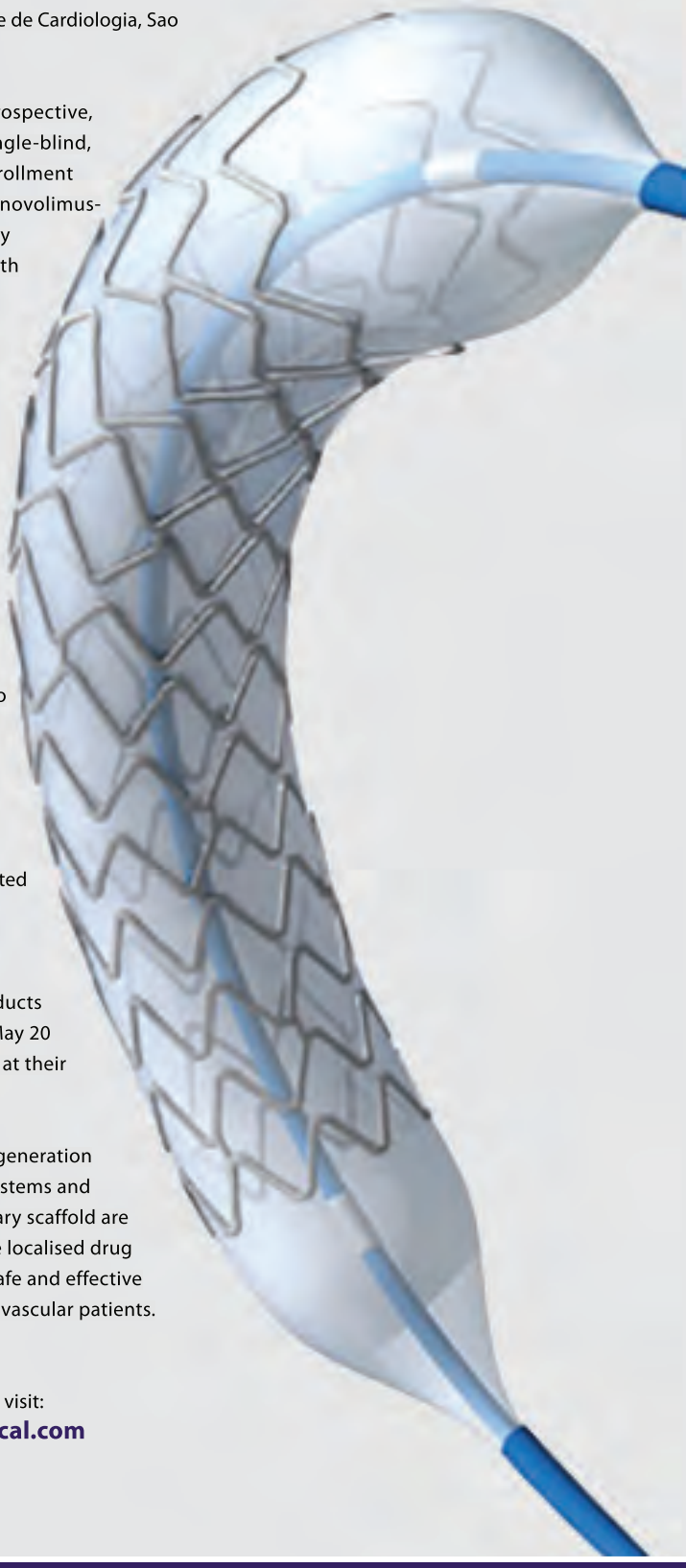
During the congress, Elixir also announced data on its drug eluting stent platforms in addition to an update on trials for DESolve family of scaffolds.

Overall highlights of the comprehensive set of activities Elixir undertook during EuroPCR entailed:

- Live Case Demonstration from Antwerp, Belgium - Stefan Verheye, MD, PhD, ZNA Middleheim Hospital, Antwerp, Belgium
- Multi-centre evaluation of the novolimus-eluting, fully bioresorbable coronary scaffold: 1-year clinical and imaging endpoints - Alexandre Abizaid, MD, PhD, Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil
- Elixir Medical Symposium - Innovating vascular restoration with the DESolve Novolimus Eluting Scaffold Platforms. Chaired by: Martin B. Leon, MD, New York – Presbyterian Hospital / Columbia University Medical Center, New York, NY, USA. Alexandre Abizaid, MD, PhD, Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil
- Multi-centre, prospective, randomised, single-blind, consecutive enrollment evaluation of a novolimus-eluting coronary stent system with bioabsorbable polymer compared to a zotarolimus-eluting coronary stent system - Ricardo Costa, MD, Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil
- Two poster presentations in the Poster Area and the Moderated Poster Area
- Exhibited and showcased products from Tuesday, May 20 - Friday, May 23 at their booth.

Elixir Medical's next-generation drug-eluting stent systems and bioresorbable coronary scaffold are designed to optimise localised drug delivery to provide safe and effective treatments for cardiovascular patients.

For more information visit:
www.elixirmedical.com



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HILTON PARIS LA DEFENSE

EuroPCR 2015...

The Leading Cardiovascular Course takes place in Paris between 19th to 22nd May 2015. *Treatment Strategies* takes a look at a number of the finest hotels Paris has to offer...

CONCORDE OPÉRA PARIS
108 RUE SAINT LAZARE, PARIS, 75008

Boasting an awe-inspiring lobby, decorated in a sumptuous, Napoleonic style and adorned with chandeliers, statues and Scottish granite columns; the Concorde Opéra Paris hotel is a symbol of timeless elegance in the heart of Paris. Set in the lively Opéra quarter, this majestic Paris hotel is conveniently located near some of the most beautiful cultural sites and attractions in the capital; including the Opéra Garnier, the Louvre Museum and the famous department stores, Galeries Lafayette and Le Printemps. Wander the wide, bustling streets of the Opéra district and discover tempting brasseries and restaurants, vibrant bars, high-end stores and chic boutiques.

Designed in a traditionally refined, Parisian style, the guest rooms and suites at this Opéra quarter hotel provide a tranquil haven in the busy city center. Enjoy contemporary amenities including complimentary WiFi, cable TV and a bathtub.

Enjoy a delicious 'bistronomic' experience in the warm and welcoming Terminus Café, which showcases simple, contemporary dishes created by talented Head Chef, David Le Quellec. The Golden Black Bar embodies the spirit of this Paris hotel perfectly. Its plush, inviting surroundings and exotic ambience make it the ideal place to savor cocktails from around the globe.

HILTON PARIS LA DEFENSE
2 PLACE DE LA DEFENSE CNIT - BP 210, PARIS, 92053

Located in La Défense, the heart of Paris' business district, and close to many of Paris' most popular attractions, the Hilton Paris La Défense hotel is perfect for travelers on business and leisure alike. Take a break to visit the local sights, and take in some history at the Arc de Triomphe, or enjoy a shopping trip to the Champs-Elysées, which offers an array of luxury shops, cafés and restaurants.

All rooms feature contemporary decor with cool, calm tones and marble bathrooms. Keep up with work at the desk, and check emails with high-speed internet access. Discover Paris with your family and choose the double Deluxe room with two comfortable double beds overlooking the shopping and conference center. Upgrade to a Hilton Relaxation Room for separate work and rest zones, a desk with ergonomic chair, and a bathroom with a whirlpool and inset TV. Surf the web in the hotel's 24-hour business corner, and hold meetings in one of nine meeting rooms, all with wireless internet access.
Keep fit in the hotel's 24-hour fitness center, equipped with cardio machines and weights. Embark upon a sightseeing tour and see Paris' most beautiful streets, or work out on the nearby running track. Indulge in gourmet French cuisine at the hotel's

restaurant, Côté Parvis, which offers both French and international dishes prepared with skill and creativity. Have a refreshing cocktail and contemporary French dish at the Tangerine Bar, a sophisticated bar with a stylish, monochromatic theme.

HILTON PARIS ORLY AIRPORT
ORLY SUD 267, ORLY AEROGARE CEDEX, PARIS, 94544

Relax in the Hilton Paris Orly Airport hotel guest rooms. Parquet floors and contemporary furnishings provide a touch of luxury. Deluxe Rooms offer a prime runway view, and our Junior Suite is a home from home. Family Guest Rooms which sleep two adults and two children are available. All rooms feature a WiFi enabled working area for convenience and soundproofed windows for your comfort.

Hilton Paris Orly Airport is an ideal place to get together with friends and colleagues. Natural daylight spills into all meeting rooms, hosting up to 380 guests in style. Take advantage of the well-equipped business center with workstations, fax machines and video conferencing.

The seasonally changing menu at Le Café du Marche features international specialties with pastas, seafood and meats from the grill on offer. Open for breakfast, lunch and dinner with extended hours, savor the fresh Rungis market produce, no matter what time travel is scheduled. Le Bar's contemporary feel sets the mood to enjoy a cocktail or a coffee, with light meals and salads available from morning to evening.

Maintain any exercise schedule in the Fitness By Precor® fitness center, where free weights and cardio equipment are available 24-hours a day.

HILTON PARIS CHARLES DE GAULLE AIRPORT
ROISSYPOLE, RUE DE ROME, BP16461, ROISSY, 95708

The Hilton Paris Charles de Gaulle Airport hotel is close to many of Paris' most popular attractions as well as being just five minutes by free shuttle away from Charles de Gaulle Airport. The central attractions of Paris are only 40 minutes away. Have a relaxing stroll down the banks of the River Seine and enjoy the bars and cafés on the Rive Gauche.

Choose from 385 spacious and sound-proofed guest rooms and suites that feature wireless internet access and marble bathrooms with large bathtubs and separate showers. Consider one of the 106 executive rooms for unlimited access to the private Executive Lounge. Refurbished to create a welcoming, bright atmosphere, the lounge serves complimentary continental breakfast and drinks and offers a selection of international newspapers and magazines.

Keep up with work in the business center, or host meetings in this Paris hotel's 24 function rooms. Savor modern French cuisine at Skylight Restaurant. The a la carte menu showcases fresh, quality and local produce with an emphasis on telling the story of the origin of the dishes. Alternatively, enjoy fresh snacks or salads and drinks at Skylight bar.

Swim a few laps in this Paris hotel's heated indoor pool, or work out in the fitness center. Enjoy a day of sight-seeing in Paris city center, and then relax in the hotel's sauna. Explore the local area and play a few rounds on the nearby golf courses, or have a game of tennis on the courts.

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Percutaneous Mechanical Support in Cardiogenic Shock – The Agony of Choice

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Introduction

Cardiogenic Shock (CS) is complicating a variety of cardiac diseases, predominantly acute myocardial infarction.[1] The incidence of CS complicating myocardial infarction has only slightly decreased since the mid-1970s.[2] Despite all medical progress the mortality of a patient suffering from cardiogenic shock (CS) remains high[1] but recent surveys show it could be remarkably reduced from 80% to 90% to about 50%.[2,3] To a large extent this is due to the far-reaching improvements in coronary reperfusion strategies and developed intensive care medicine.[2] Nevertheless, a mortality rate of about 50% remains high. Standard treatment of cardiogenic shock complicating acute myocardial infarction includes immediate percutaneous coronary intervention (PCI) and pharmacological inotropic support.

Mechanical cardiac support holds promise but is still a matter of intensive debate. Novel temporary cardiac assist devices (e.g. IMPELLA-pump, miniaturised extracorporeal membrane oxygenation systems) can be deployed in the cathlab and offer immediate haemodynamic support. However, not all systems are widely available. Moreover, there is actually no evidence from randomised prospective trials to grant clear recommendations.[4] We will thus give a short overview of the pathophysiology and clinical signs of CS and review potential temporary mechanical cardiac options including available evidence.

Pathophysiology and Clinical Signs of Cardiogenic Shock

Despite the variety of different cardiac diseases leading to CS the pathophysiology is substantially equal. The inability of the heart to pump an adequate amount of blood leads to inadequate end-organ perfusion. This is resulting in decreased oxygen and nutrition delivery and finally, if prolonged, in end-organ damage and multi-system failure. Failure of left or right ventricle is leading to systemic hypotension defined by persistent systolic blood pressure below 90mmHg or mean blood pressure 30mmHg lower than the patient's basic level. Additionally, an increased endogenous release of vasopressors (e.g. norepinephrine and angiotensin II) and consecutive elevation of systemic vascular resistance in combination with low cardiac output aggravates the compromised haemodynamic situation. If this progresses to the point that even the coronary perfusion is affected, a vicious circle of ischaemia and further myocardial damage is initiated.

Patients suspected for developing CS should undergo placement of a Swan-Ganz catheter for further haemodynamic monitoring and management. A severe reduction in cardiac index (<2.0l/min/m^2) and an elevated pulmonary capillary wedge pressure (>15mmHg) indicates CS.[4]

All shock forms have in common the cardinal signs of hypoperfusion such as hypotension, abnormal mental status, cold clammy skin, oliguria and metabolic acidosis. Most patients

Figure 1. IMPELLA 2.5. (source: Abiomed press kit).

with CS additionally present signs of pulmonary congestion. In many patients the onset of CS has a delay to the initial event. These individuals often present worsening hypotension, tachycardia, recurrent chest-pain and shortness of breath.[5,6] This delayed form of CS often develops insidiously and demands trained physicians for early diagnosis and initiation of live-saving treatments.

Figure 2. CARDIOHELP-System as an example for the new ECMO-systems. (source: MAQUET.com).

Mechanical Cardiac Support

Pharmacological inotropic support can maintain sufficient haemodynamics, but at the price of increased strain on the heart. Thus, mechanical cardiac support might be appealing as the damaged heart can be unloaded and is thus given time to recover. In addition, patients refractory to standard therapy including pharmacological inotropic agents will decease and mechanical cardiac support might be life-saving. We will review current options and discuss the available evidence.

Intraaortic Counterpulsation Devices

The most wide-spread form for mechanical support in CS is the intraaortic balloon pump (IABP).[7] The system consists of two parts: a flexible catheter und a mobile console. The catheter is inserted into the femoral artery and positioned under fluoroscopic guidance in the descending aorta with its distal end about 1cm below the origin of the left subclavian artery. The mobile console pumps helium gas helium ecg-triggered to the chambers of the catheter leading to deflating and inflating of the IABP-balloon. This leads to an increase in pressure in the ascending aorta during diastole, and a reduction of afterload during systole resulting in an increased mean arterial pressure and an increased coronary perfusion.[8,9] Because of this effect and the improved outcome IABP was gold-standard therapy in CS complicating myocardial infarction for centuries since its introduction in 1968[9] and was strongly recommended by the guidelines.[4] Especially from the era of thrombolysis, for primary treatment of myocardial infarction generated strong evidence from randomised trials for IABP use.[10,11] At the end of the 1990s primary PCI became the method of choice for treatment of acute myocardial infarction leading to an overthinking of the IABP-use. Several trials including a meta-analysis by de Waha et al. showed no clear survival benefit for IABP therapy in patients with CS complicating myocardial infarction undergoing primary PCI.[10] Recently, data from the SHOCK-II trial could finally demonstrate that these patients do not profit from an IABP-therapy leading to reconsideration of current guideline recommendations.[4,12]

Still the concept of mechanical cardiac support for haemodynamic stabilisation and unloading of the ventricles appears appealing and further percutaneous approaches have been developed.

Percutaneous Left Ventricular Assist Devices (Axial Flow Pumps)

The main representative of this group is the IMPELLA microaxial blood pump (Abiomed) (see Figure 1). The implantation is similar to the IABP. Through a percutaneous vascular access the 12Fr pump (IMPELLA 2.5) respectively through a surgical approach the 21Fr pump (IMPELLA 5.0) is inserted into the femoral artery and the inlet area of the catheter is positioned approximately 4cm below the aortic valve annulus and in the middle of the left ventricular chamber. The pump is based on the principle of an Archimedes screw, revolving with high speeds and by that drawing blood out of the left ventricle and ejecting it into the ascending aorta.[13] Clinical data for use of this pump in CS comes from Seyfarth et al. with superior haemodynamics compared to IABP. However, no survival benefit compared to IABP was observed in this small trial. Most studies on Impella have been published for haemodynamic support after cardiac surgery or in high risk PCI. The PROTECT-II trial initially designed to compare IMPELLA and IABP in high risk PCI was even stopped after 69% of planned enrolment for futility.[14] Newer studies are showing little benefit for IMPELLA-therapy in CS.[15,16] However, these studies were performed in only relatively small patient numbers. Still a prospective, randomised, controlled trial for use of Impella in CS is missing and so there's no clear evidence for improved survival in CS.

Extracorporeal Membrane Oxygenation Systems

There are two types of ECMO-systems. While a veno-venous-ECMO only provides respiratory support the veno-arterial approach additionally provides haemodynamic assistance. Since its first

description over four decades ago the devices have experienced an impressive development. The first systems had space-filling dimensions and were quite complicated in use demanding both a surgeon for vascular access and a perfusionist for operating the system. However the new systems are implanted percutaneously in Seldinger's technique by interventional cardiologists. The systems have become so compact that even interhospital transfers with ongoing cardiopulmonary assistance became possible.[17,18] Maquet and Lifebridge offer portable ECMO-systems which are depicted in Figure 2. Small studies and case reports are promising arguing in favour of a potential survival benefit from ECMO treatment in CS[19,20] and in-hospital cardiac arrest.[20] However, definitive evidence from larger randomised, prospective multicentre trials is missing.

ECMO use is associated with potential complications, which should be incorporated in the risk-benefit analyses.[21] Vascular complications at the insertion site due to large cannulas and bleeding complications associated with anticoagulation are potential risks for the patient. In addition, veno-arterial ECMO generates a persistent retrograde blood flow in the aorta thus elevating left ventricular afterload which in combination with severe reduced left ventricular function leads to high ventricular filling pressures. The resulting increase in wall stress increases myocardial energy consumption resulting in ischaemia and could thus reduce the likelihood of ventricular recovery; cardiac function can even further deteriorate.[22] Additionally, the high filling pressures can lead to pulmonary congestion resulting in prolonged and almost impossible weaning from ECMO and ventilator. To overcome this issue different approaches have been successfully pursued from surgical cannulation and drainage of the left atrium/ventricle[23] over atrial septostomia[24] to a primary veno-arterial-venous ECMO. In the latter, besides cannulation of the femoral vein and the femoral artery, a third cannula is inserted into the right jugulary vein supplying oxygenized blood to the right ventricle (see figure 3). Hence, blood flow of the arterial cannula can be reduced resulting in reduced afterload of the left ventricle and thus avoiding pulmonary congestion,[25] despite favourable haemodynamic effects and protection of end-organs.

In this regard, ECMO holds promise as life-saving therapy in patients suffering from CS refractory to standard therapy including pharmacological inotropy. Nevertheless prospective randomised controlled trials are missing to support ECMO-therapy in CS and should thus be strongly encouraged.

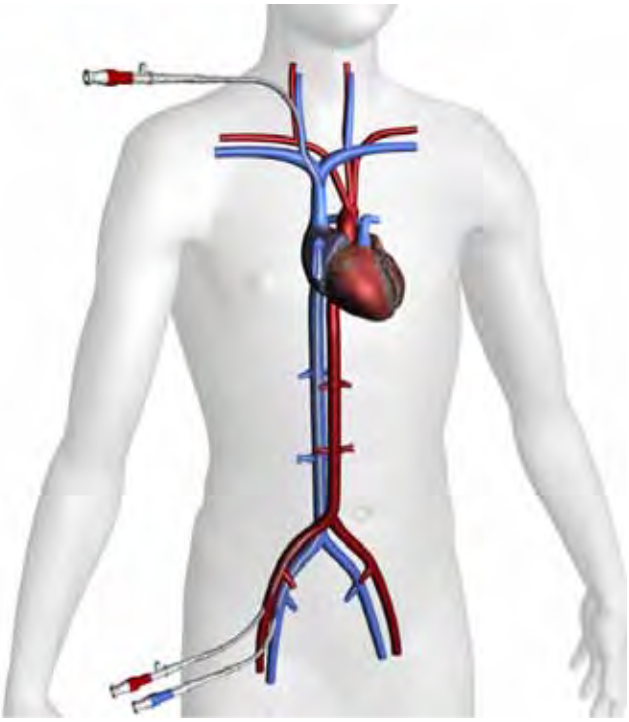

Figure 3. veno-arteriel-venous ECMO-cannulation. (source: MAQUET.com).

Conclusion

Despite all medical progress cardiogenic shock still remains a major challenge in intensive care medicine and is still associated with a high mortality. IABP use was widely accepted supported by evidence from the thrombolytic era. However, recent Shock II trial showing no benefit for IABP in CS complicating myocardial infarction in the PCI era led to changes in guidelines and daily clinical practice. Case-reports and small studies are showing promising results for both IMPELLA-pump and ECMO but proofed evidence given by randomised controlled trials is still missing. Until these data are available and implemented into guidelines the choice of the assist systems remains a case by case decision and a high level of experience in the treatment of CS is needed. However, in selected cases, refractory to standard therapy including pharmacological inotropic support, temporary mechanical cardiac support might be life-saving.

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Chronic Total Occlusion: Technical Developments and the role of Adjunctive Strategies

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A coronary chronic total occlusion (CTO) is defined as a lesion with TIMI 0 flow across the occluded segment and evidence, or high likelihood, the occlusion has been present for greater than 3 months.[1] In patients referred for investigation of chest pain, the overall incidence of CTO on coronary angiography is approximately 15% and up to 30% if there is significant coronary artery disease elsewhere.[2-4] Historically, CTO percutaneous coronary intervention (CTO-PCI) has been discouraged by low success rates, uncertain patient benefit and misperception of procedural morbidity. However, the last decade has seen a substantial improvement in procedural success and mounting evidence of clinical gain. In the presence of symptoms and proven ischaemia or viability relating to the occluded territory, successful CTO-PCI improves angina status, left ventricle function and exercise capacity while reducing the need for future coronary artery bypass grafting (CABG).[5-8] Successful CTO-PCI has also been reported to reduce mortality, albeit in non-randomised studies with patients having an untreated CTO reporting a threefold increased risk in cardiac mortality or complication during future acute coronary events.[5,9-10] Despite only limited evidence of successful surgical outcomes, identification of a CTO continues to be a strong predictor for medical or surgical referral and reluctance to consider patients for percutaneous revascularisation persists.[4,11-12]

Technical Developments and Adjunctive Strategies

Antegrade Wiring

Historically all attempts at CTO-PCI were antegrade and wire-based. In comparison to non CTO-PCI, luminal crossing is challenging given the characteristics of this lesion subset. Typically as an occlusion ages there is progressive fibrocalcification, a process that is exaggerated at the proximal and distal caps, negative remodelling with a reduction in true lumen diameter and neovascularisation.[13] A mature CTO is therefore resistant to crossing and prone to dissection.

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Antegrade Wire Escalation (AWE)

An inability to overcome lesion resistance and cross the true lumen to the distal vasculature is common. AWE refers to the use of increasingly penetrative or lubricious wires to overcome this difficulty. A flexible or "workhorse" wire is used to navigate the proximal vessel and reach the cap for ease and safety. Gentle probing of the cap to utilise any existing microchannels or loose tissue is common, particularly if lesion characteristics are favourable. Thereafter, escalation to increasingly penetrative wires ensues until progress is made. Microcatheters or over-the-wire (OTW) balloons provide additional wire support and allow exchange or reshaping without loss of position. Some operators advocate a rapid escalation without intermediate steps, particularly if lesion characteristics favour a penetration technique. It is argued this can save time, radiation and contrast while increasing success and reducing expenditure.

After some initial progress, procedural success rates of a single wire antegrade approach (70-75%) remain relatively static and significantly less favourable than conventional PCI, despite evidence of significant case selection.[14-16] Consequently attempts at CTO-PCI remained low, with an actual decline between 1997 and 2004 (9.6% versus 5.7%, $p<0.0001$ for trend) in a US registry of 5173 patients.[14]

Parallel Wire and See-Saw Technique

A frequent failure mechanism for antegrade single wiring is recurrent subintimal entry. Repeated wire manipulations can extend the dissection and lead to subintimal haematoma compromising the distal true lumen.[17-18] The parallel wire technique evolved as an attempt to regain the intimal path when subintimal entry occurs, but was limited by a lack of reproducibility and teachability.[19] The applicability of this technique is also limited to shorter occlusions and where the distal lumen remains visible.

Advances in antegrade wiring have been unable to overcome the many technical challenges of CTO-PCI, particularly in complex lesions. Predictors of antegrade wiring failure include severity of calcification, tortuosity, long lesion length (>20mm), bridging collaterals and a blunt or ambiguous proximal cap.[20-23] Good distal vessel visualisation is essential and not always present. The development of antegrade dissection/re-entry and retrograde techniques have revolutionised CTO-PCI by enabling unfavourable antegrade lesion characteristics or failure mechanisms to be overcome.

Antegrade Dissection/Re-entry

Dissection and re-entry methods circumnavigate resistant plaque by utilising the typically lower resistance to advancement encountered in the subintimal space. As such, these techniques are favourable when heavily fibrocalcific and long lesions are encountered.

STAR and Derivatives

In 2005 the subintimal tracking and re-entry technique (STAR) was described.[24] A tight umbrella-like bend or 'knuckle' is formed with the guidewire and advanced rapidly in the dissection plane. The 'knuckle' tracks the subintimal space and prevents wire exit. Once across the lesion the knuckled wire is rapidly advanced until it spontaneously re-enters the true lumen, typically at a sidebranch or when the distal vessel becomes too small to propagate the dissection. Alternatively, targeted re-entry is attempted by exchanging to a stiff wire with an acutely angulated tip. This is known as the limited antegrade subintimal tracking (LAST) technique. Another variation is the contrast guided STAR (contrast-STAR). After puncturing the cap, a microcatheter is advanced and 1-2ml of contrast injected. The true lumen may be identified in which case a floppy wire is used to cross the lesion or if there is resistance to contrast injection the guidewire then microcatheter is advanced followed by a repeat injection. If a dissection plane tracking along the CTO is visualised, further contrast is injected to propagate the dissection until the distal vessel is reached. The dissection may spontaneously re-enter the true lumen beyond the CTO.

The STAR technique was shown to have a very high procedural success (97%) in the original paper.[24] However there is significant potential for extensive dissection and sidebranch occlusion, with subsequent high restenosis rates and adverse outcomes. Consequently, STAR is no longer a recommended revascularisation technique, but has informed more modern practices.

CrossBoss and Stingray

The CrossBoss and Stingray devices (BridgePoint Medical, Figure 1) are used in concert as a dedicated CTO crossing and re-entry system. The CrossBoss is an over-the-wire blunt dissection microcatheter, which is rapidly rotated by a proximal torque device to advance through

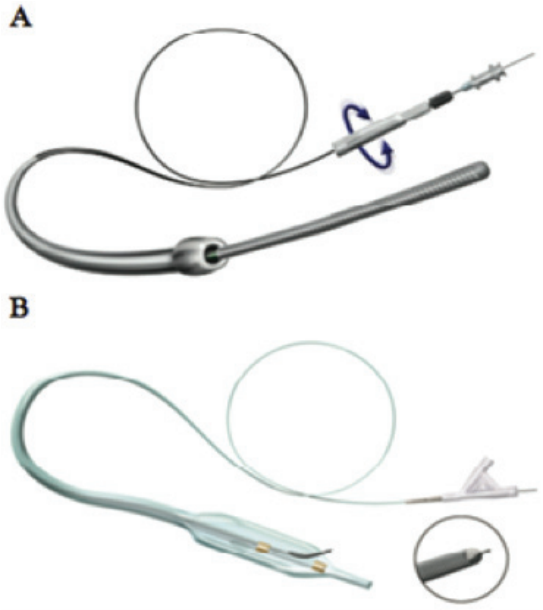

Figure 1. CrossBoss (A) and Stingray Re-entry system (B).

the lesion. If subintimal entry occurs, a smaller dissection plane is created compared to other techniques, which in turn eases re-entry. The Stingray balloon and guidewire are used to re-enter the true distal lumen. The balloon has two side exit ports located on diametrically opposite balloon surfaces and a unique flat design that orientates one exit port automatically to the true lumen on gentle inflation (4atm). The wire with a distal 0.0035" taper is passed through the appropriate port for re-entry. In the FAST-CTOs (Facilitated Antegrade Steering Technique in CTOs) trial of 147 patients in whom standard CTO-PCI strategies had failed, there was a 77% success rate with the combined system.[25] True lumen to true lumen crossing occurred in approximately one third of these cases with the CrossBoss alone.

Retrograde CTO-PCI

Retrograde CTO-PCI utilises collateral channels to tackle the occlusion from a reverse approach. It was first described using SV grafts, but the use of native septal and epicardial channels is now predominant.[26] The distal cap is often less fibrocalcific than the proximal cap and by approaching the lesion retrogradely, unfavourable antegrade characteristics such as an ambiguous proximal cap or a poor distal target for wiring and re-entry may be overcome. Navigating a collateral channel to the distal cap can be very challenging. Septal collaterals are preferred to epicardial as they tend to be shorter and less tortuous, while perforation is less likely to be significant as their interventricular course usually prevents tamponade.

If the CTO is ultimately crossed in a retrograde direction the wire must be externalised or an antegrade wire subsequently passed to allow stent delivery. Either way a microcatheter or balloon must cross the lesion retrogradely and equipment advancement can fail at the occlusion or along the small, tortuous collaterals. In response, the Corsair (Asahi Intecc Co. Ltd) collateral dilator microcatheter was

developed. First described in 2010, this microcatheter can obviate the need for collateral balloon dilatation and has improved microcatheter collateral channel tracking and retrograde occlusion crossing with a consequent increase in procedural success.[27-28]

Retrograde Wire-Crossing Technique

Once the distal cap is reached an attempt is made to cross the occlusion with a single wire. Standard wire escalation and manipulation techniques are used to overcome advancement difficulties. However, wire manoeuvrability is poor due to the long collateral access route and success rates are relatively low.[29]

Kissing Wire Technique

If difficulties with a single retrograde wire are encountered or anticipated, a bidirectional approach with a simultaneous antegrade wire can be used. The retrograde wire may serve simply as a marker (marker wire) of the distal vessel or if advanced into the occlusion creates a luminal channel, which assists the crossing antegrade wire. The antegrade wire is directed toward the retrograde wire until they meet or 'kiss'.

Successful retrograde wiring and the kissing wire technique have a combined success of 30-45%, depending on lesion characteristics.[30] Similar limitations as for antegrade wiring exist, with lesion length, vessel tortuosity and calcification representing limiting factors for wiring success. More commonly the wire enters the subintimal space and in comparison to an antegrade approach, dissection/re-entry is the commonest method of retrograde success.[30-32]

Retrograde Dissection/Re-entry: CART and Reverse CART

The controlled antegrade and retrograde subintimal tracking (CART) technique was first described in 2006.[33] An antegrade and retrograde wire are both advanced into the subintimal space until overlapping. A balloon is then inflated on the retrograde wire at the point of wire overlap. This enlarges the shared subintimal space, creating a connection, which allows the antegrade wire to be advanced into the distal true lumen. Reverse CART is similar except the balloon is advanced into the subintimal space over the antegrade wire and the retrograde wire advanced into the enlarged subintimal space and then the proximal true lumen. Since the introduction of the Corsair microcatheter, reverse CART has become the most commonly used retrograde re-entry technique, as retrograde balloon crossing is not required.[27,30]

Retrograde attempts at CTO-PCI have steadily increased since their introduction with a corresponding increase in overall CTO-PCI procedural success.[33-34] Although associated with unique complications including donor vessel injury (approximately 2% of cases) and

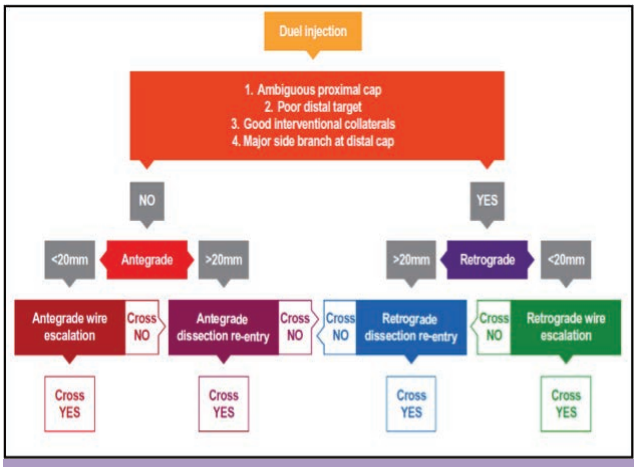

Figure 2. Hybrid approach to CTO-PCI.

retrograde perforation, overall procedural risk is low.[30] A 2014 meta-analysis recorded death at 0.7%, emergency CABG 0.7% and stroke 0.5% in 26 pooled studies of retrograde CTO-PCI.[30]

Hybrid Approach

The 'hybrid approach' to CTO-PCI (Figure 2), first described in 2012, sought to maximise overall procedural success and establish common ground between operators by integrating the many different techniques into a single comprehensive strategy.[35] It created a systematic algorithm, with emphasis on a prompt and seamless transition between antegrade, dissection/re-entry and retrograde techniques diictated by progress and lesion characteristics. The 'hybrid approach' has successfully evolved into a universal framework for CTO-PCI with standardisation allowing greater exchange of information, facilitating learning and assisting future development. Michael *et al.* (2014) reported by utilising the hybrid approach in a series of 73 cases, a technical success of 90.4% and procedural success of 86.3%. In successful cases the final CTO crossing technique was antegrade wire escalation in 50.0%, antegrade dissection/re-entry in 24.2%, and retrograde in 25.8%.[36]

Summary

To date, progress in the field of CTO PCI has been restricted by the limitations of wire-based techniques. Although technical developments in wires have partly addressed this, substantive progress has only been made more recently by more fundamental changes in procedural strategy.

The adoption of retrograde techniques and the use of blunt-dissection tools to address marked vessel tortuosity and calcium has broaden the range of patients that can be successfully treated. Challenges remain in ensuring that these techniques can deliver durable results and that they can be successfully taught to a broad range of clinicians. Only when this has been established and then implemented can the prospect of conquering the final frontier of interventional cardiology be realised.

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Chronic Total Occlusion Revascularisation Strategy: Contemporary Perspective

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Introduction

Coronary chronic total occlusion (CTO) is defined as the presence of TMI 0 flow within an occluded arterial segment of greater than three months standing[1] and is encountered in 15% to 30% of all patients referred for coronary angiography.[2] Several retrospective studies have shown prognostic benefit of successful CTO revascularisation in terms of symptoms relief,[3] Ejection Fraction (EF) improvement[4] and survival,[5,6,7] but CTO-PCI attempt remains low[8] mainly because of technical complexity, low procedural success rate and procedural complications. Notwithstanding, in the last few years, development of new devices, new techniques and operators' experience have increased success rates from 50%-70% to 80%-90% without a significant increase in rate of complications.[9,10]

Patient Selection

Patients with CTO can have different clinical presentation varying from acute coronary syndromes to silent ischaemia/chronic coronary artery disease. CTO can present both as culprit lesion or incidental finding in multi-vascular disease. The benefits of CTO-PCI are more evident in presence of symptoms related to the occluded vessel or documented residual ischaemia, viability or hibernated myocardium detected with appropriate imaging technique;[11] more than 10% of myocardium at risk has been recognised to be the cut-off point above which percutaneous treatment shows clear survival benefit.[1] ECG evidence of Q waves also seems to be related with theoretical benefit of CTO revascularisation,[1] while presence of collateral circulation supplying the occluded vessel doesn't correlate with myocardial viability. Conversely, even well developed collaterals can prevent myocardial necrosis but not myocardial ischaemia during provocative tests.[12]

Procedure Planning

There is a general consensus that CTO-PCI should not be performed as '*ad hoc*' procedure[1] in order to minimise X-ray and contrast exposure. Careful evaluation of diagnostic angiogram should be performed in order to determine in advance the revascularisation strategy. If needed, CT scan can be performed before the CTO-PCI in order to clarify occlusion length, presence of calcification and vessel tortuosity.

Procedure Strategy

Arterial access and guiding catheter selection are based on the operator's experience and preference, but there is a general consensus that distal target visualisation is mandatory and contralateral injection is necessary in more than 50% of procedures.[1,13] During the procedure, careful monitoring of coagulation is performed with seriate activated clotting time (ACT) measurements: ACT should be maintained >200" in antegrade and >300" in retrograde approach.

Antegrade Technique

Antegrade recanalisation is the most-used approach with a success rate varying from 50% to 80%. Ideally, a dedicated wire is used to cross the occluded segment and reach the distal true lumen. A guiding catheter is used to select the occluded vessel; sizing of the guiding catheter is left to operator discretion but some authors suggest larger catheter utilisation (7F or more) in order to increase passive support and multiple wire manoeuvrability. An 8F guiding catheter is generally suggested for concomitant IVUS and microcatheter utilisation. As discussed, contralateral injection via a diagnostic catheter is requested in half of the cases in order to obtain a clear visualisation of the distal target. Microcatheter utilisation is mandatory in order to increase penetration power and wire control and also to exchange the wires during the procedure

Several algorithms have been provided for strategy/wire selection;[14,15] in our experience the step-up/step-down technique, with wire stiffness and penetration power increasing (and eventually decreasing) during the procedure according to lesion's characteristics is effective and safe.

When wire migrates in subintimal space a second wire can be used in order to try to reach the distal target via a different pathway using the first wire as an adjunctive landmark (parallel wire technique).

Alternatively, the subintimal wire can be replaced with a softer umbrella-handle tip shape polymeric wire; after a hard push the wire is generally able to re-enter in distal true lumen; in fact in the non-diseased segment the resistance is lower towards the true lumen rather than adventitia.[16] A more proximal re-entry seems to be provided by softer new wires (Fileder XT and FC, Asahi Intecc, JPN).[17]

Specific tools have been created for controlled re-entry; the most promising (Stingray, BridgePoint Medical, Plymouth, MN, USA) is a dedicated 'flat' balloon self orientating according to vessel anatomy; the wire lumen has two opposed exit ports and a dedicate wire is advanced until the port is located in front of the true lumen and then pushed in order to establish a connection between the subintimal space and the distal target (Figure 1).

Retrograde Technique

Retrograde technique is based on the assumption of the fact that distal cap is usually softer than proximal one.[18] Initially used after a previous failed antegrade procedures, it can be used as a first choice attempt in very long occlusion, calcified vessel, ostial location when an adequate collateral circulation is present on diagnostic angiography.

Retrograde CTO PCI via collateral circulation can be performed via septal, epicardial, atrial channels or coronary bypass. Both the donor and the occluded artery are selected with a guiding catheter, a soft wire (Fielder and Choice family wire and more recently, Sion or Fielder XT family, Asahi Intecc, JPN) is delivered into the distal segment of the occluded artery and then eventually exchanged with a stiffer wire in order to cross the occluded segment. The collateral can be crossed selecting the more appropriate route via selective dye injections through microcatheter (Finecross, Terumo, JPN or Corsair, Asahi Intecc JPN, for example) or, using the 'surfing' technique, trying to select the more appropriate path with a soft wire; the last technique is reserved for septal crossing.

Retrograde procedure can be divided according to wire crossing (antegrade or retrograde) and CTO body dilatation or dissection (see Table 1).

The retrograde wire can be used just as a landmark in the distal segment of the occluded vessel in order to save contrast and have a clear visualisation of the distal target; in this case the antegrade wire crosses the CTO body and no dilatation or dissection of the CTO segment is required (Kissing wire technique).

A cornerstone in retrograde approach was Dr Kato's description of the Controlled Antegrade and Retrograde subintimal Tracking (CART) technique.[19] Once again the antegrade wire is used to cross the CTO body but the retrograde wire is inserted into the CTO segment and a retrograde balloon inflation is used in order to allow the conjunction of the two wires through a localised subintimal dissection (Figure 2).

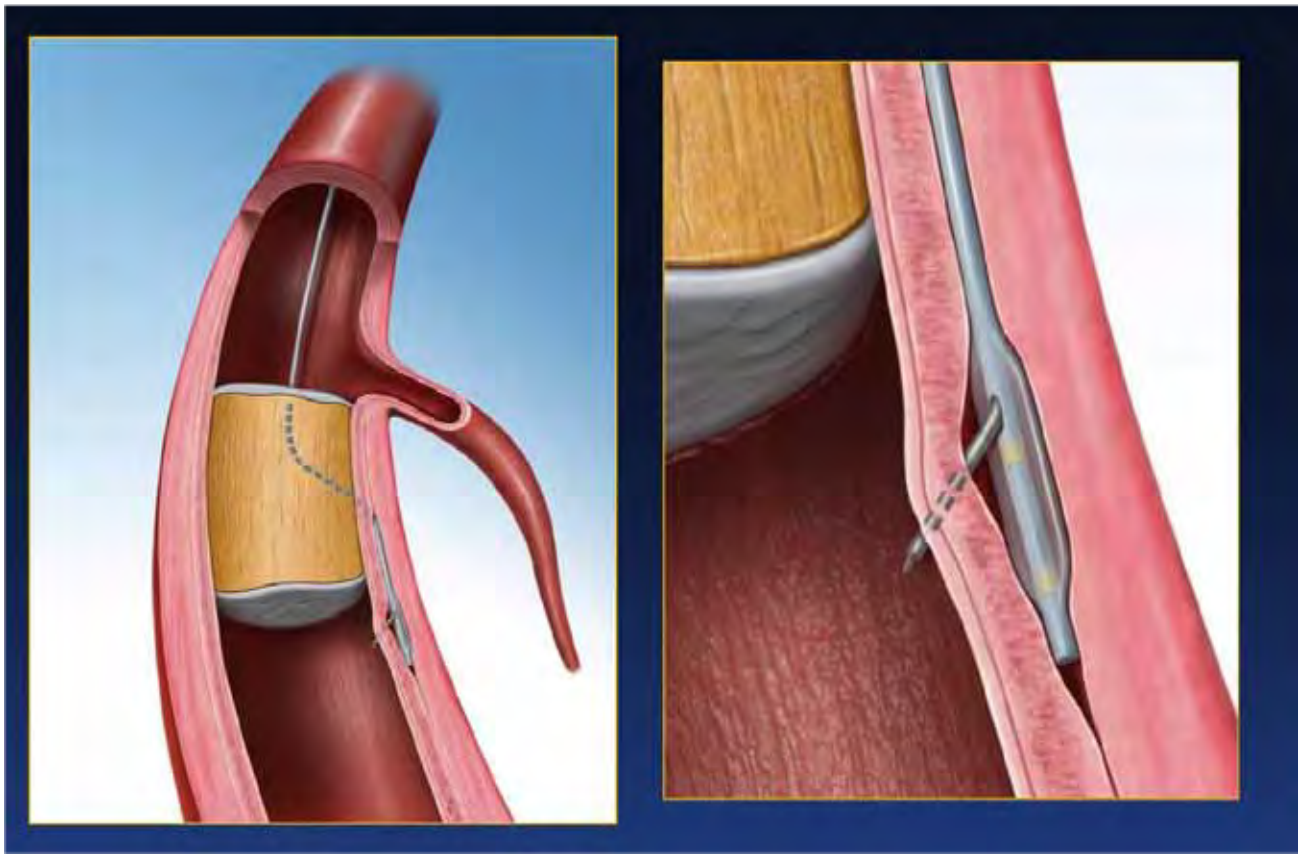

Figure 1.

	Wire crossing	
	Antegrade	Retrograde
CTO body dilatation/dissection	CART	XCART knuckle
No CTO body dilatation/dissection	Kissing wire	Retrograde crossing

Table 1. (modified by Prof. Ochiai presentation)

This technique has been nearly abandoned in the last few years in favour of the more predictable Reverse CART (XCART); after advancing both the wires in the CTO body, the CTO crossing is performed by the retrograde wire after an antegrade balloon dilatation. Antegrade stent inflation can be used after this technique fails in order to reduce the immediate recoil after balloon deflation (STENT Facilitated XCART).

In the Retrograde Crossing technique the retrograde wire crosses the lesion without any modification of the CTO segment.

The Knuckle Technique is a modification of the CART concept; in this case the subintimal dissection is obtained by forming a loop in the wire while the contralateral wire is used to reach the proximal or distal true lumen.

Intravascular Ultrasound (IVUS)

Intravascular Ultrasound (IVUS) utilisation is very important both in antegrade and retrograde procedure.

In antegrade IVUS can be used:

- To identify entry point in in blunt cap with a side branch in location. A conventional wire is inserted in the side branch and IVUS is advanced in order to locate the entry point segment. A clear visualisation of the CTO wire is generally very easy to obtain and is possible to identify the CTO wire position from the entry point. A central location is a strong indicator of procedural success, while a more lateral position is an indication of subintimal migration. With adequate gain modification it is possible to follow the wire in the very first portion of the CTO segment (Figure 3).

- To perform controlled re-entry. This is a very complex technique and is generally used after parallel wire failure and when no retrograde access is feasible. IVUS probe is advanced into the subintimal space created by the CTO wire and provides three dimensional information of the true lumen position. A very stiff wire is used to perform the puncture of the true lumen. Usually a 2.0 balloon dilatation is necessary in order to enlarge the subintimal space in order to advance the IVUS probe (Figure 4).

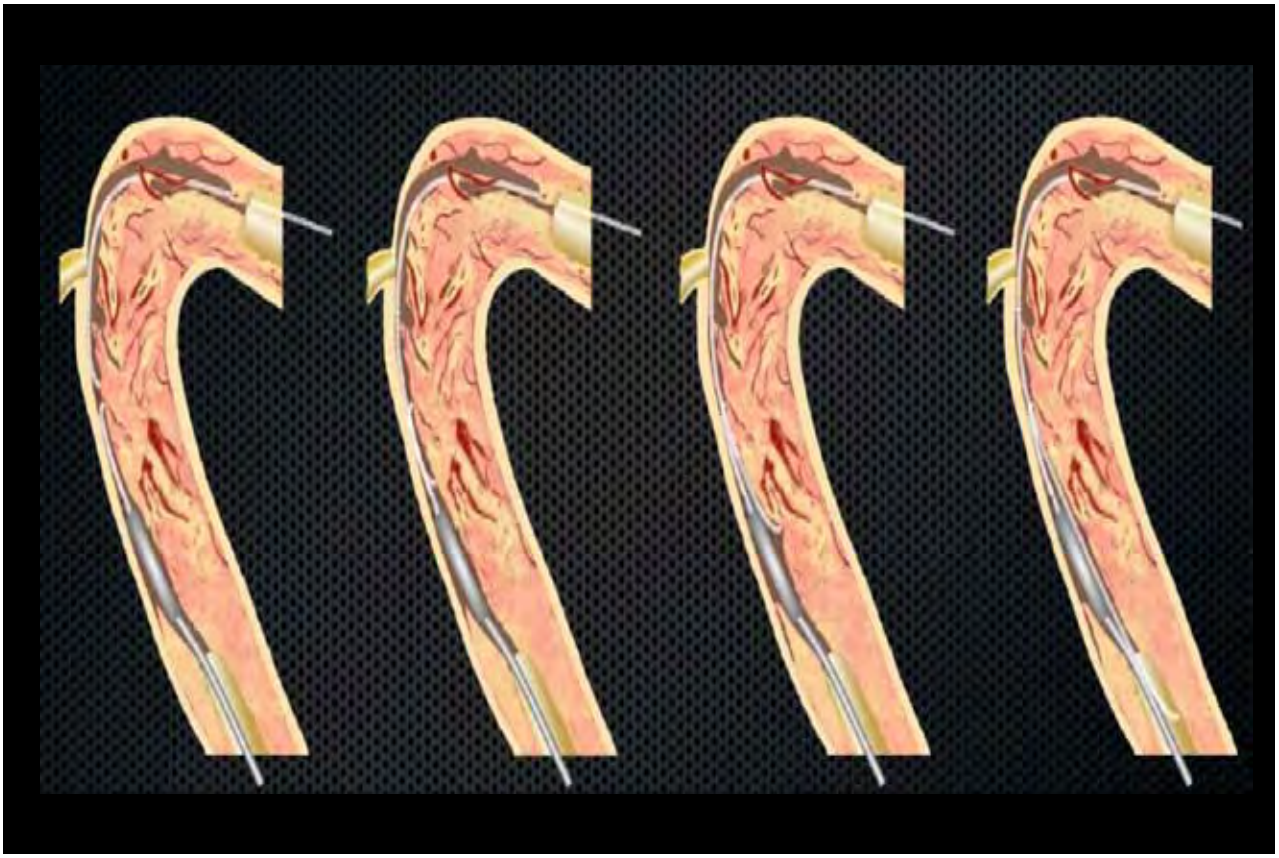

Figure 2. Concept of CART. Modified by Dr. Katoh.

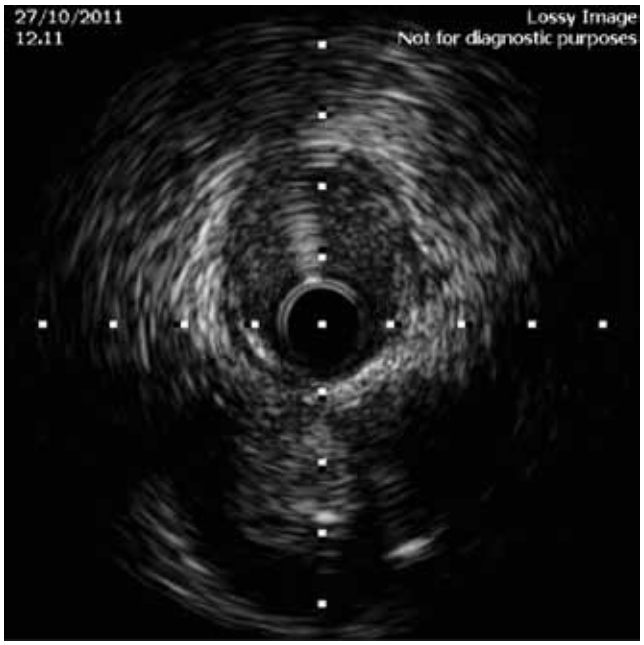

Figure 3.

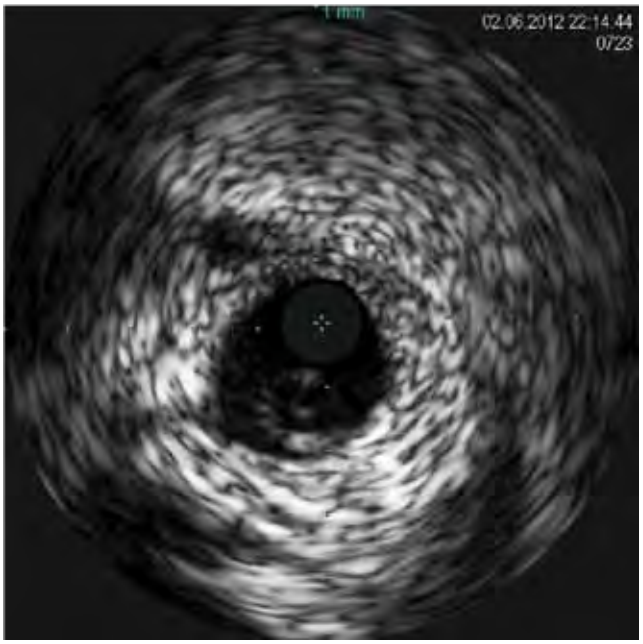

Figure 4.

In retrograde procedure antegrade IVUS can be used:

- To clarify the position of the retrograde wire compared with the true lumen/antegrade wire position.

- For balloon sizing in XCART technique selecting a 1:1 balloon ratio with vessel diameter.

- To identify the most promising location for balloon dilatation into the CTO body visualising the distance between the wires and extension and localisation of calcification.

After successful wire crossing IVUS can identify the length of the segment to stent and the size of the stent itself, avoiding antegrade dye injections which can expand the vessel dissection.

Conclusion

Despite being technically demanding and time consuming, CTO PCI has achieved a high success rate and can provide symptom relief, increase in EF and increase in survival. Full knowledge of dedicated devices and techniques can further increase the success rate.

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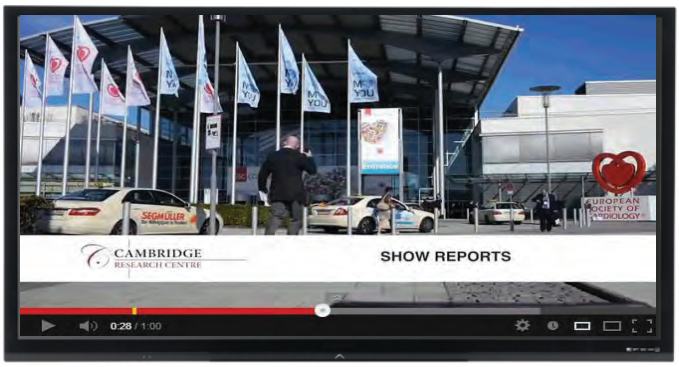

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Drug-eluting Stents in Clinical Practice Overview, Proposed Classification and Future of DES

Mark Kennedy and **Elvin Kedhi**

Isala Klinieken, Zwolle, Netherlands & Diagram Zwolle, Netherlands

Introduction

Drug-eluting stents (DES) were introduced in the market almost two and half decades ago mainly with the goal of reducing the high restenosis rates of their bare metal stent (BMS) predecessors. As this premise proved true, a fulminant widespread use of the first-generation of DES took place worldwide. However, after the initial euphoria, concerns emerged regarding late and very late stent thrombosis (ST) events reported for the first-generation DES, in turn associated with a high rate of death and myocardial infarction (MI).[1,2] Such events have been attributed mainly to the incomplete re-endothelialisation caused by drug-induced inhibition of endothelial cell proliferation, stent malapposition, accelerated neoatherosclerosis and, importantly, polymer-induced prolonged vessel wall inflammation. [3] While some of these factors are also inherent to BMS, polymer-induced vessel wall inflammation and impaired re-endothelialisation are more specific to DES and therefore the idea that such polymers have a deleterious effect and so should better be avoided, gained appeal.

Therefore to improve the general performance of the first-generation DES and in particular their safety profile, new DES devices were engineered. Between other safety impacting factors, the use of coating polymers was addressed in two different conceptual lines: the first line maintained the use of a polymer coating as drug carrier but employed for this purpose newer types of durable polymers with better biocompatibility than their predecessors giving rise to the second-generation durable-polymer DES (DP-DES) class. The second line opted to minimise the use of polymer carriers either by substituting the first-generation DES polymers with newer, bioabsorbable polymers, giving rise to a new line of DES: the bioabsorbable polymer DES (BP-DES). Other manufacturers completely avoided the use of a polymer drug carrier by designing stents that would elute their drugs directly from the metallic stent platform, giving rise to another class of DES: the non-polymeric DES. Nowadays, both these DES categories have undergone fast developments and newer devices and further design improvements have been introduced since. Meanwhile, large clinical trials, patient level pooled analysis of different trials as well as network meta-analysis, have shed light over the advantages and disadvantages of all these DES categories.

A description of the main DES categories together with a proposed classification, their clinical outcomes and impact in daily clinical practice as well as a glimpse in new directions where the research with intracoronary devices is focused will be discussed in this review.

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Detailed Description and Proposed Classification for Metallic DES

The major determinants of DES performance are the metallic scaffold platform, the delivery system and the drug carrier (often a polymer). Based on the combination of these characteristics the DES can be divided in different classes. Figure 1 represents a proposed classification of most currently used metallic DES categories while a detailed description of each DES class is described in detail below.

First-generation DP-DES

The first DES devices were the sirolimus-eluting stent (Cypher; Cordis Corporation, Johnson & Johnson, Warren, NJ, USA) and the paclitaxel-eluting stent (Taxus; Boston Scientific, Natick, Mass, USA). Both devices share a thick-strut, stainless steel slotted tube stent platform coated with a thick layer of a permanent, amorphous polymer to carry and control the release of the antiproliferative drugs. Despite the significant reduction observed with these devices in clinically driven

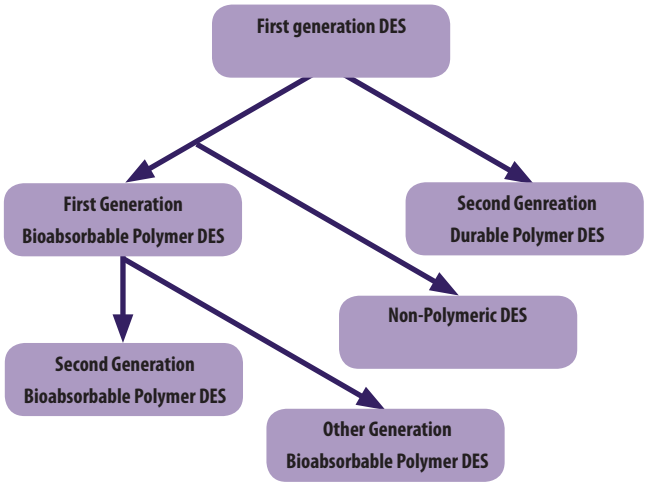

Figure 1. Proposed classification for existing drug-eluting stents. DES = drug-eluting stent. First-generation denotes bioabsorbable- or durable-polymer DES with thick struts (>100µm). Second-generation denotes bioabsorbable or durable polymer DES with thinner struts (<100µm). Non-polymeric denotes DES that employ no polymeric coatings. Other denotes bioabsorbable polymer DES that beyond drug elution from a bioabsorbable polymer employ simultaneously other therapeutic vehicles.

revascularisation rates as compared to BMS, the important safety issues, which emerged with these first-generation devices, between other factors, were believed to be for a large part related to the type of the permanent polymers employed. Indeed vessel wall toxicity and inflammatory reactions[4,5] as well as mechanical complications (polymer delamination and "webbed" polymer surface[6], resulting in impaired drug delivery and delayed vessel healing) were observed and, in turn, impacted the efficacy and safety outcomes of these devices.[3]

Second-generation DP-DES

This class of DES represents a newer generation of DES which shares three main characteristics:

1) durable but thinner and more biocompatible polymers with improved mechanical properties;

2) thinner stent struts, thanks to employment of newer metal alloys (mainly CoCr or PtCr);

3) more conformable open cell stent designs and overall improved stent delivery systems.

The first prototype of the second-generation DES, is the Xience V (Abbott Vascular, Santa Clara, CA, USA). The stent platform is composed of CoCr metallic alloy. The strut and the polymer thickness are both significantly reduced compared to the first-generation DES, respectively 7, 8 and 87µm. The durable polymer coating employed is a fluoropolymer, a compound known for its mechanical resistance and biopassive properties. This matrix layer elutes everolimus (a sirolimus-analog) with a drug load of 100 µg/cm^2.

Similar stent designs are also shared by other DES, with the most used being the Zotarolimus-eluting Resolute stent (Medtronic, Santa Rosa, CA, USA) and the Everolimus-eluting Promus Element Platinum Chromium stent (Boston Scientific, Natick, Mass, USA). Clinical randomised trials have proved non-inferiority of these devices compared to the Xience V stent.[7,8]

Preclinical studies have shown that these devices are characterised by an improved endothelial healing and reduced vessel wall inflammation post implantation as compared to the first-generation devices.[9]

The clinical programs with the second-generation DP-DES, the most studied prototype being the everolimus-eluting Xience V stent, have shown significantly improved overall clinical outcomes, in particular in safety endpoints, as compared to the first-generation DP-DES. Indeed two large prospective randomised trials, the Spirit IV[10] and COMPARE trial[11] both showed superiority of this stent compared to the first-generation paclitaxel-eluting Taxus stent for the respective primary endpoints as well as separate safety and efficacy endpoints. Importantly, both trials showed a reduced ST already at 30 days and maintained at 1 year. The superiority for both safety and efficacy endpoints as well as for ST was maintained up to the latest available follow-up (3 years for the SPIRIT IV trial[12] and up to 5 years for the COMPARE trial[13]). Furthermore, recent network metanalysis has shown that this stent is indeed associated with significant reduction on TVR, MI and definite ST rates also when compared to the sirolimus-eluting Cypher stent and importantly BMS.[14,15] Indeed these results have created a paradigm shift in that second-generation DP-DES are not only more efficient than the BMS, but their utilisation might also be associated with incremental safety advantages; or in another perspective: that novel durable polymer coated DES might be safer than BMS.

Bioabsorbable BP-DES (First-generation, Second-generation and Other BP-DES)

Refers to a class of DES that shares a common characteristic: a bioabsorbable polymer, employed to carry and release the active principle, after which it will erode and fully absorb over a period of time (mostly within a year). These devices are designed with the purpose of eliminating the permanent polymer-induced vessel inflammation, believed to be one of the main causes of very late safety events (more than one year post implantation). However, significant differences between the metallic platforms of these devices do exist. The first prototypes of this DES class were the bioabsorbable polymer biolimus-eluting stents, Biomatrix (Biosensors Inc, Newport Beach, Ca, USA) and Nobori (produced from Terumo, Japan under license from Biosensors, Inc). Both devices, which are almost identical, employ a biodegradable polymer, the polylactic acid (PLA) applied solely to the abluminal stent platform

surface from which Biolimus, a sirolimus analogue, is eluted at concentration of 15.6µg/mm. Both stents share a similar stainless steel platform with strut thickness comparable to that of the first-generation DP-DES. In this perspective they can also be considered a first-generation BP- DES. Further improvements in stent design in this class led to the development newer DES which, despite having a bioabsorbable polymer, differ from their predecessors in that, similarly to the second-generation DP-DES, they also employ thinner strut metallic stent platforms mainly composed of CoCr alloys and therefore can be similarly generalised under the name of second-generation BP-DES.

The most representative devices in this group are Yukon stent with bioabsorbable polymer (Translumina, Hechingen, Germany), Supralimus and Supralimus-Core (Sahajanand Medical Technologies, Pvt Ltd), as well as the more recently introduced devices as Synergy (Boston Scientific) and Osirio (Biotronik AG, Bulach, Switzerland).

The clinical evidence with these devices as compared with first generation DES, in terms of number of patients enrolled in clinical trials, is far more limited than with the second generation DP-DES. LEADERS trial[16] was the first randomised trial that compared in large scale a first-generation biolimus-eluting BP-DES (Biomatrix) with a first-generation DP-DES (the Cypher stent) in all-comer patients. This prospective randomised trial proved non-inferiority of Biomatrix for the primary endpoint: cardiac death, MI and TVR at 9 months. Similar event rates were observed also for the safety endpoints, cardiac death and MI at 9 and 12 months follow up. At 5 years the primary endpoint was not significantly different between the two stents, respectively 22.3% and 26.1%, p=0.07; however, a trend in favour of Biomatrix was evident.[17] The safety endpoints of cardiac death and MI were also almost identical for both stents with curves overlapping each other up to 5 yeas follow-up (cardiac death 8.0% vs. 8.4%, p=0.72, MI 9.9% vs. 10.5%, p=0.79); however, definite ST rates at 5 years showed a trend in benefit of the Biomatrix stent at 5 years (2,6% vs. 4.5%, p=0.06) and a significant advantage beyond 1 year (0.7% vs. 2.5%, p=0.003). Another large trial, the SORT-OUT V, which compared the Nobori stent (almost identical device with Biomatrix) with the first-generation Cypher stent, showed similar event rates for both stents but failed to prove non-inferiority for a composite of safety and efficacy primary endpoint (cardiac death, MI, definite ST and clinically-driven TVR), (4.1% and 3.1% respectively, p=0.22, p non inferiority =0.06).[18] Interestingly the rates of definite stent thrombosis at 1 year were significantly higher in the Nobori arm (0.7% vs. 0.2%, risk p=0.034).

Large-scale comparisons between the first generation BP and second-generation DP- DES are limited with only two trials, COMPARE II[19] and NEXT[20] so far comparing everolimus-eluting Xience stent with the biolimus-eluting Nobori stent; however, non of these trials was adequately powered to study safety endpoints. In the COMPARE II trial, the Nobori stent showed numerically higher event rates for the primary endpoint (Death, MI and TVR) than Xience (5.2% and 4.8%, respectively), but by using a non-inferiority margin of 4% (>80% of the observed 4.8% event rate) non-inferiority was claimed (p non inferiority=0.0001). The NEXT trial also proved non-inferiority of Nobori stent compared to Xience, but the trial was powered for TLR (primary endpoint), therefore further conclusions on safety outcomes cannot be drawn.

In the light of these conflicting results from the above-mentioned trials two large network metanalysis were conducted to study the impact of the first-generation biolimus-eluting BP- DES as compared to other first- and second-generation DP-DES.[21, 22] Both analyses founded improved safety endpoints (reduced rates of MI and definite ST, respectively) with the everolimus-eluting second-generation DES stent as compared to the first-generation BP-DES. Furthermore, in the first metanalysis,[21] posterior probability curves generated by means of Bayesian statistics for available FDA approved DES and biolimus-eluting BP-DES with Cypher as common comparator, showed that the second-generation DP-DES are associated with a more favourable profile than the rest of the other DES, including biolimus-eluting DES, regarding the safety endpoints of mortality, MI and probable and definite ST. They can therefore be considered as the safest DES to date (see Figure 2).

While both stent categories, the first-generation BP-DES and the second-generation DP-DES, have achieved the goal for which they were designed (the reduction of the very late ST events), the overall results are in favour of the second generation DP-DES mainly due to the improved outcomes already within the first year with these devices. Indeed the observed reduction in 30-day and one year ST thrombosis event rates, points to the importance of these events in the overall performance of any DES device on longer follow-up, as the majority of the ST events with DES, occur within the first year.[2,23] In this perspective, the favourable outcomes with the second generation DP-DES might be due not only to the improvements in the polymer coating but also to other differences between these devices, and mainly the thinner strut stent design. Indeed thinner stent struts have been associated with less mechanical trauma and inflammation of the vessel wall and faster re-endothelialisation in preclinical[9] and clinical[24] studies. Therefore these stent platform changes, which have since been incorporated in the design of the second-generation BP-DES might be associated with improved safety outcomes not only beyond one year, as is the case with the first-generation BP-DES, but also during the first year, as is the case with the second-generation DP-DES. The currently available data from randomised controlled trials is limited, but does point in this direction. Indeed the results of the ISAR-TEST IV trial comparing the bioabsorbable polymer Yukon SS stent (strut

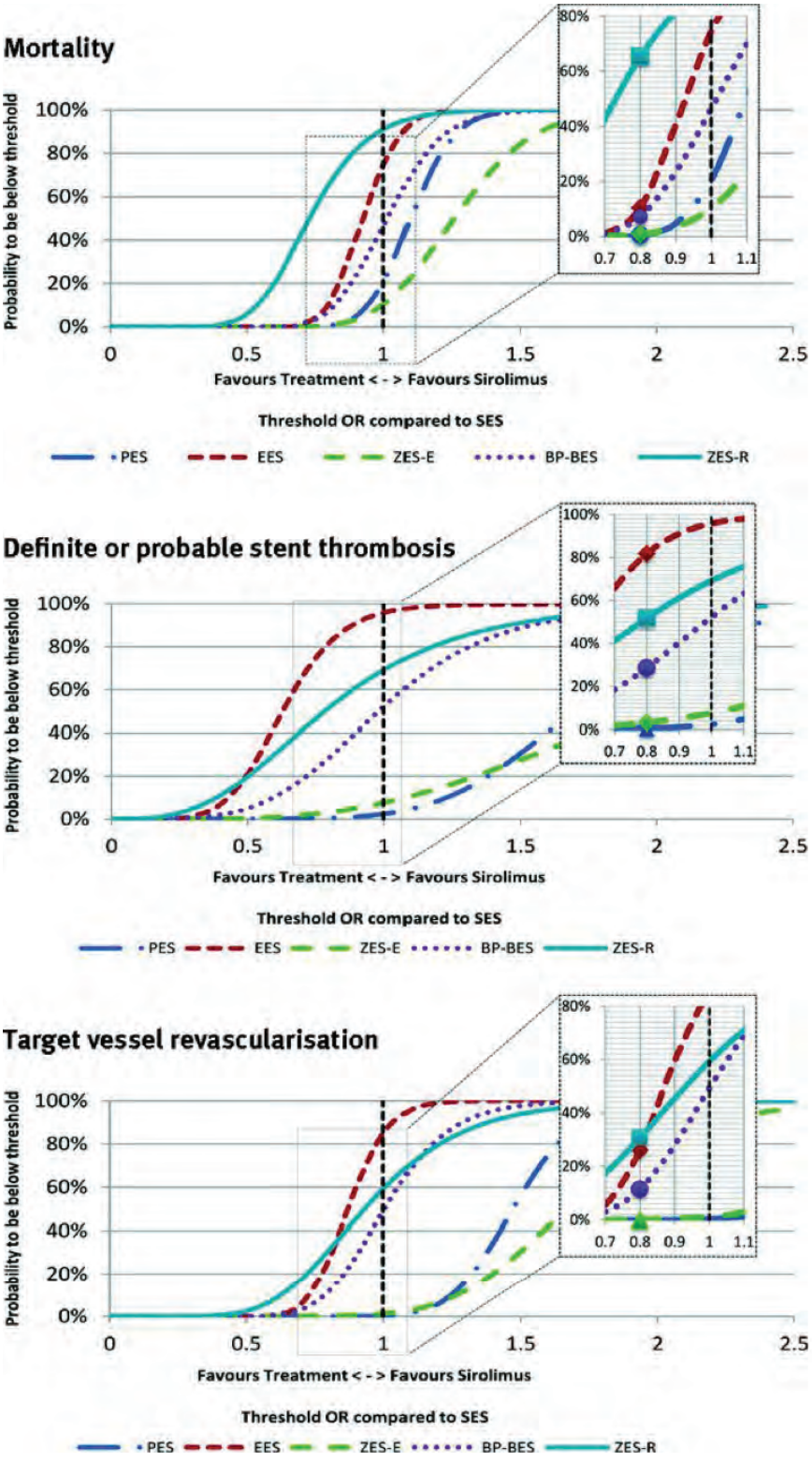

Figure 2. Posterior probabilities of different risk thresholds (odds ratios) for each stent compared with sirolimus eluting stent (reference treatment). Curves can be used to examine overall safety and efficacy profile of specific DES compared with reference treatment sirolimus-eluting stent (SES) (identity line=unit value); improved safety and efficacy profiles indicated by highest leftward shift of curve, as shown with Resolute zotarolimus-eluting stent (ZES-R) and everolimus-eluting stent (EES) with regard to mortality and myocardial infarction; curves allow inferences to extract probabilities of specific risk thresholds corresponding to minimal odds ratio compared with SES as reference treatment. For example, compared with SES, there is probability of 65% that ZES-R will reduce odds of mortality by at least 20% corresponding to an odds ratio of 0.80. Conversely, this probability is estimated to be close to 0% with biodegradable polymer biolimus-eluting stent (BP-BES), meaning no additional mortality benefit provided by BP-BES compared with SES. There is a probability of 56% and 49%, respectively, that ZES-R and EES reduced odds of myocardial infarction by at least 10% corresponding to an odds ratio of 0.90 but this probability is estimated close to 0% with BP-BES, meaning no additional myocardial infarction benefits provided by BP-BES compared with SES (reference treatment). PES=paclitaxel eluting stent; ZES-E=Endeavor zotarolimus-eluting stent.

thickness of 0.87µm) with DP-DES (a mix of Xience and Cypher) showed numerically very similar safety and efficacy outcomes at 1 and 3 years between this stent and Xience arm.[25,26] Similarly, the results of the Bioflow II,[27] which compared the Sirolimus-eluting ultrathin strut (60µm) bioabsorbable-polymer Orsiro stent with Xience Prime, are very promising with both stents having a very low rate of events (4.8% and 5.2% respectively, p=ns). Importantly, the OCT-detected mean neointimal area was significantly lower with the newer stent at nine months (when the polymer is still present), while the percentage of covered struts was 98.3% for Orsiro and 97.5% for Xience Prime (p=0.042), corroborating further the hypothesis that thinner stent may foster a very thin but uniform stent coverage. Similarly, the other novel second-generation BP-DES, Sinergy, as compared with the second-generation DP-DES Promus Element, in the Evolve trial[28] resulted in similar outcomes of clinical and angiographic endpoints. Although these trials were not powered for clinical endpoints, the emerging results for the second-generation BP-DES are promising and have promped further research with these devices. Indeed larger and adequately powered randomised trials like the ongoing Twente Bio-Resort (comparing Orsiro, Synergy and Resolute; NCT01674803) and EVOLVE II (comparing Synergy with the Promus Element stent; NCT01787799), will shed further light on the potential of these newer devices to further improve safety and efficacy outcomes compared to the actual golden standard, the second-generation DP-DES. Furthermore, the Twente Bio-Resort, might also give further insights on the impact of the polymer absorption time (3 months for the Synergy stent and up to one year for the Orsiro stent) seeing the related vessel wall inflammatory reactions related with the polymer degradation process.

Other BP-DES

This category comprises a limited group of DES technologies that also employ a bioabsorbable polymer similar to that

described above in combination with another alternative coating that serves for different purposes than drug carriage. A prototype is the Combo Stent™ (OrbusNeich Medical, Inc, Ft Lauderdale, Fla, USA), which consists of a metallic 100µm, stainless steel stent platform with an abluminal coating of a bioabsorbable polymer matrix formulated with sirolimus for sustained release, and an anti-CD34 antibody cell capture coating on the luminal surface which targets $CD34^+$ endothelial progenitor cells (EPCs) in circulation.

Non-Polymeric DES

In the effort to eliminate the use of the polymeric drug carriers, new DES in which the drug is eluted directly from the metallic platform without the need for a polymeric drug carrier, were designed. The main prototypes that have been or are being investigated in clinical trials are the Yukon Choice (Translumina, Hechingen, Germany), which employs a microporous metal stent backbone from which sirolimus and probucol are eluted, and the Biomatrix Freedom stent (Biosensors Inc, Newport Beach, Ca, USA), which employs microstructured surface holds to carry end elute Biolimus A9. Another interesting stent design in this category is the drug filled stent (DFS) (Medtronic, Santa Clara, Ca, USA) in which the drug is carried inside the lumen of a tubular stent platform and is eluted from small holes located in the abluminal side of the stent strut.

The evidence for the polymer-free DES to date is limited. The advantages these stents offer compared to other DP- or BP-DES is the absence of a polymer, which basically confers to these stents BMS properties once the drug is eluted. While this is perceived as a potential safety benefit, it should not be forgotten that, similarly to the other DES, these stents also elute an antiproliferative drug, which beyond the inhibition of smooth muscle cells also delays neo-endothelialisation at least for as long as the drug is eluted. Therefore the safety and efficacy outcomes for these devices is strongly dependent from the drug-eluting kinetics, with the risk that the safety advantages offered from a fast drug release can be counterbalanced from the disadvantages in efficacy endpoints. The most important clinical evidence for this group of devices comes from the ISAR TEST 5 trial,[29] which compared the Yukon Choice with the second-generation DP-DES, Resolute. The one-year results were almost identical for both stents with time-to-event curves fully overlapping. While non-inferiority was uncontestably proved, any potential benefits with the Yukon-Choice device remain to be adjudicated on long-term follow-up. Likewise, potential benefits, in terms of shorter dual antiplatelet therapy regimens, for this as for other devices in this category, although obviously logical, remains to be proven. Indeed the safety of these devices with shorter dual antiplatelet therapy regimens is being tested in the LEADERS Free trial,[30] which compares BioFreedom DES with an identical platform BMS. The trial assesses the potential to deliver the anti-restenotic benefit of a DES (designed for superiority vs. BMS for clinically-driven TLR) and maintained safety (non-inferiority of BioFreedom compared with BMS in terms of cardiac death, MI, and definite/probable ST) in patients with high risk of bleeding, receiving a short course (30 days) of dual anti-platelet therapy. Although the BMS are not the golden standard nowadays, they are still used particularly in this non-small category of patients, where indeed the polymer-free DES might be more appropriate than other DES.

Conclusion

The current generation of DES has improved safety profiles as compared to the first-generation DP-DES and has meanwhile fully dismantled the safety concerns with use of DES. However differences between the novel DES devices exist, with the second-generation DP-DES being associated with significantly improved safety outcomes, observable already early and maintained until very late follow-up as compared to its predecessors, the first-generation DP-DES and BMS, while the safety impact of the first-generation BP-DES, appears to be limited only to the very late thrombotic events. Direct comparisons between first-generation BP-DES and second-generation DP-DES are underpowered for safety endpoints but large network metanalysis shows a favourable safety profile for the second-generation DP-DES and therefore these devices can be considered as the golden standard of DES nowadays.

Second-generation BP-DES or polymer-free DES might carry the potential to further improve safety and efficacy outcomes compared to other first-generation BP-DES as well as second-generation DP-DES. However very large trials would be needed to prove any clinically meaningful differences between these devices.

Finally, as it has become apparent that the actual DES are in general very safe and efficient, major new developments can not be expected by further improvements in metallic frame or polymer structures. Therefore the future research in this field nowadays is being centered around the next generation of devices: the fully bioabsorbable drug-eluting scaffolds. The existing data with these devices, although limited, is promising and large ongoing trials, the results of which are expected in the next two years, will define whether these devices do indeed represent the new revolution in interventional cardiology.

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Drug-eluting Stents in the Setting of Unprotected Left Main Coronary Artery Disease

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Introduction

The recommended standard treatment for significant unprotected left main coronary artery (ULMCA) disease is coronary artery bypass grafting (CABG), which has been demonstrated to improve survival in affected patients.[1,2] However, in this subset of lesion, previously routinely excluded from interventional cardiology, encouraging results obtained with of drug-eluting stents (DES) have revolutionised the treatment of ULMCA. The availability of newer and more effective DES, improvement in diagnostic tools and importantly a better patient selection, allowed the interventional treatment a viable alternative to CABG in some subgroups of ULMCA patients. (See Figure 1).[3-4]

Historical Perspectives of ULMCA PCI and the Role of 1st Generation DES

If angioplasty alone was soon abandoned due to both high rates of procedural complications from elastic recoil and dissection and for poor long-term results, the advent of stents in the 1990s certainly opened the horizons to the percutaneous coronary intervention (PCI) in ULMCA disease. Initially, studies with bare-metal stents (BMS) reported inconsistent intermediate-term success and unacceptably high rates of restenosis-related complications manifested as repeat revascularisation or even sudden cardiac death. However, these early discouraging reports were confounded by poor patient selection and still-evolving procedural technique.[3] The introduction first-generation DES has significantly reduced the need for repeat revascularisation. In-stent restenosis, the result of a maladaptive neointimal tissue proliferation, is dramatically reduced by the long-lasting inhibitory effect exerted by the local elution of antiproliferative agents contained in DES. The evidence of a marked reduction of the restenosis rate below 5.0% for most lesion types, has rapidly led to their widespread and extensive use, even for the treatment of more complex lesions that are considered off-label, such as ULMCA stenosis.[5-7] The first-generation DES comprise sirolimus eluting stent ([SES], Cypher; Cordis, Warren, NJ) and paclitaxel eluting stent ([PES], Taxus; Boston Scientific, Natick, MA). Some early pilot observational studies (see Table 1), although limited by a non-randomised nature and by a small number of patients and a short follow-up period, proved promising outcomes for ULMCA-PCI using these devices, showing a dramatic decrease in restenosis rates when compared to the BMS.[3,8-10] Moreover, these studies have shown high procedural success rates, low procedural complications rates and encouraging mid-term outcomes. The 6–12 month mortality rate of PCI with first-generation DES ranged from 0% to 11.0%; the angiographic restenosis rates from 7.0% to 44.0% and target lesion revascularisation (TLR) from 2.0% to 38.0%. At 2-3 years follow-up, the rates of major adverse cardiovascular events (MACE) ranged from 11.5% to 20.3%.[10-13] What became clear was that the observed in-hospital and 1-year mortality depended strongly on patient selection, being as high in patients with poor left ventricular function, acute ischemic syndromes and emergency presentation, and as low in patients without such high-risk characteristics. Later, several studies confirmed these initial experiences, showing a good efficacy and safety profile of first-generation DES in ULMCA-PCI.[13-19] Moreover, from these favorable initial results it emerged that the disparity in restenosis rates reflected not only differences in patient selection, interventional techniques but also, most importantly, differences in the location of the ULMCA stenosis. The crucial importance of distal ULMCA disease as a predictor of adverse outcomes has been emphasised by Valgimigli *et al*. In this study the authors reported a 3-fold increase in MACE in distal ULMCA stenosis (30.0%) compared with those with no involvement of the bifurcation (11.0%) at a median of 18 months.[15] The importance of patients selection to identifying several patient subgroups at increased risk of adverse outcomes (i.e., acute presentation, patients with bifurcation lesions) and the procedural techniques (i.e. single stent technique in distal ULMCA, the IVUS use for procedural guidance) have still emerged as elements discriminating outcomes of this particular subgroup of patients in a recent large U.S. registry.[19] ULMCA PCI was

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Indications for Revascularization in Stable Coronary Artery Disease with Left Main Coronary Artery Involvement

	CABG		PCI		
Subset of CAD by Anatomy	**ESC**	**ACC**	**ESC**	**ACC**	
Heart team Approach for LM or complex CAD	I C	I C	I C	I C	
LM (isolated or 1VD, ostium/shaft)	**I A**	**I B**	**IIa B**	**IIa B**	
LM (isolated or 1VD, distal bifurcation)	I A	I B	IIb B	IIb B	III B
LM + 2VD or 3VD, SYNTAX scores <33	I A	I B	IIb B	IIb B	III B
LM + 2VD or 3VD, SYNTAX scores >32	I A	I B	III B	IIb B	III B

CABG = Coronary Artery Bypass Graft; PCI = Percutaneous Coronary Intervention; CAD= Coronary Artery Disease; ESC= European Society of Cardiology;ACC= American College of Cardiology; LM= Left Main; VD=Vessel Disease; SYNTAX score= 'Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery'.

Figure 1. Indication for CABG vs. PCI in Stable Coronary Artery Disease with Left Main Coronary Artery Involvement According to European and American Guidelines. Current indication for revascularisation strategies in patients with stable CAD and ULMCA disease according to the "2010 ESC/EACTS Guidelines Myocardial Revascularisation and the "2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention" [1,2]

performed in 4.3% (5,627/131,004) of patients in CathPCI Registry, primarily in patients with a high burden of comorbidities and frequently in those with high-urgency clinical presentations. In elderly ULMCA patients poor outcomes following PCI are common and are likely influenced by both patient and procedural characteristics as shown by the high in-hospital mortality that ranged between 2.9% to 45.1%. At 30-month, 57.9% of Medicare-linked cohort (≥65 years, N=2,765) experienced death (42.7%), myocardial infarction (MI) (8.2%), or repeat revascularisation (17.5%). Notably, DES demonstrated a lower 30-month mortality vs. BMS (hazard ratio [HR] 0.84, 95% CI 0.73-0.96), but similar composite of major adverse events (HR 0.95, 95% CI 0.84-1.06). Moreover, in this cohort intravascular ultrasound (IVUS) use was

	Park *et al.*	**Chieffo *et al.***	**Valgimigli *et al.***	**Lee *et al.***	**Price *et al.***
N	102	85	95	50	50
Distal Location, n (%)	72 (71)	69 (81)	62 (65)	30 (60)	47 (94)
Distal Stent technique					
Single (across circumflex), n	43	8	37*	10	4
T or Culotte, n	1	9	20	3	0
SKS or V-stent, n	17	12	2	5	34
"Crush" technique, n	11	30	3	12	8
Cardiac Mortality	12 months (0%)	6 months (3.5%)	12 months (11.0%)†	12 months (4%)	12 months (2%)
Angiographic Restenosis					
Overall, n (%)	6/86 (7.0)	12 (14.1)	Not reported	Not reported	21 (44)
Distal lesions, n	6	12			Not reported
Single stent, n	1	0			
T or Culotte	0	3			
SKS or V-stent, n	3	1			
"Crush" technique, n	2	8			
Ostial Circumflex Restenosis Location, n	4	5	1	Not reported	≥15
Target Lesion Revascularisation					
Overall, n (%)	2 (2.0)	11 (12.9)	6 (6.3)	5 (10)	19 (38)
Distal lesions, n	0	11	6	5	18
Single stent, n	0	0	3	Not reported	
T or Culotte	0	3	2	Not reported	
"Kissing" stents, n	2	1	0	Not reported	13
"Crush" technique, n	0	7	1	Not reported	5

*Numbers calculated from percentages provided; †all deaths within 30-days occurred in patients with ST-segment elevation myocardial infarction and cardiogenic shock; ‡ischemia-driven 9 (18%); SKS=simultaneous kissing stents. [3,8-10]

Table 1. Pivotal Studies Assessing First-Generation Drug-Eluting Stent for Unprotected Left Main Coronary Artery Disease

associated with a lower unadjusted incidence of both major adverse events (51% vs. 59%) and death (35% vs. 44%), adding to the growing body of non-randomised literature supporting its use during ULMCA stenting.[20] Conversely, the use of first-generation DES in elective and selected patients with non-bifurcation ULMCA-PCI appeared safe and effective. In a multi-center retrospective registry of 147 patients a MACE rate of 7.4%, a cumulative cardiac mortality of 2.7% at a median follow-up of 886 days were reported. Restenosis rate was only 1.0% at 6-month angiographic follow-up.[21] A systematic review and meta-analysis of 1,278 patients showed that the treatment of ULMCA lesions with first-generation DES was associated with a 5.3% (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%) at 10-month clinical follow-up.[22] Simultaneously, 2 registries reported positive long-term outcomes with first-generation DES in the treatment of ULMCA disease and the "French Multicenter Registry for Stenting of Unprotected LMCA Stenosis" FRIEND registry confirmed positive results in selected patients with a major adverse cardiac and cerebro-vascular events (MACCE) rate of 10.6% at 450 days.[23-25]

Regarding the choice of stent type, both SES and PES have been demonstrated to have similar outcomes with no differences in efficacy and safety. The "Intracoronary Stenting and Angiographic Results: Drug-eluting Stents for Unprotected Left Main Lesions" ISAR LEFT MAIN study randomised 607 patients undergoing PCI for ULMCA disease to SES or PES. At 12 months, there were no significant differences in outcomes, including the composite outcome of deaths, MI and TLR (SES 15.8% vs. PES 13.6%; relative risk [RR] 0.85; 95% confidence interval [CI] 0.56-1.29) or in-stent restenosis (SES 19.4% versus PES 16.0%; p=0.30). At 2 years, no significant differences were identified in definite stent thrombosis (ST) in the 2 groups.[26]

Head to Head Comparison of 1st Generation DES vs. CABG

From the introduction of the BMS, studies comparing PCI with CABG outcomes have reported the mid-term safety and feasibility of stenting in ULMCA disease (Table 2).[26-37] The "Revascularisation for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularisation" MAIN-COMPARE multi-center non-randomised registry confirmed good efficacy and safety of PCI with DES vs. CABG for ULMCA disease. Among 2,240 patients with ULMCA disease randomised to PCI (DES=784; BMS=318) or CABG (n=1,138), the risk of death (hazard ratio [HR] 1.13; 95% CI: 0.88 to 1.44, p=0.35) and the combined risk of death, Q-wave MI or stroke (HR: 1.07; 95% CI: 0.84 to 1.37, p=0.59) were not significantly different between the 2 groups at 5-year. However, the TVR rate was significantly higher in the PCI group (HR: 5.11; 95% CI:3.52 to 7.42; p<0.001). The cumulative incidence of definite ST was only 1.5%.[28] The safety and the effectiveness of first-generation DES vs. CABG amongst "real world" patients with ULMCA disease were also reported in the "Long-Term Outcomes After Stenting Versus Coronary Artery By-pass Grafting for Unprotected Left Main Coronary Artery Disease: 10-Year Results of Bare Metal Stents and 5-Year Results of Drug-eluting Stents From the ASAN-MAIN (ASAN Medical Center Left Main Revascularisation) Registry".[38] In the 5-years follow-up cohort of patients receiving DES, there were no significant differences in the risk of the

	Park *et al.*	Buszman *et al.*	Chieffo *et al.*	Palmerini *et al.*	Lee *et al.*	Sanmartin *et al.*	Wu *et al.*
Treatment	DES/BMS vs.CABG	DES/BMS vs. CABG	DES/BMS vs. CABG	DES/BMS vs. CABG	DES/BMS vs. CABG	DES/BMS vs. CABG	DES/BMS vs. CABG
Patients, n	1.102 vs. 1.138	52 vs. 53	107 vs. 142	157 vs. 154	50 vs. 123	96 vs.245	131 vs. 245
Study design	Registry	Randomised	Registry	Registry	Registry	Registry	Registry
Age, (mean, years)	62 vs. 64	61 vs. 61	64 vs. 68	73 vs. 69	72 vs. 70	66 vs. 66	62 vs. 64
Diabetes, (%)	29.7 vs. 34.7	19.0 vs. 17.0	18.7 vs. 23.2	26.1 vs. 25.3	36.0 vs. 31.0	19.0 vs. 32.0	27.0 vs. 29.0
Distal Lesion, (%)	49.5 vs. 53.8	56 vs. 60	81.3 vs. NA	80.3 vs. 82.5	60.0 vs. NA	62.0 vs. NA	68.0 vs. 70.0
EuroSCORE, (mean)	NA	3.3 vs. 3.5	4.4 vs. 4.3	6.0 vs. 5.0	NA	27.0% vs. 3.5%~	4.0 vs. 4.0
SYNTAX score, (mean)	NA	25 vs. 24	28 vs. 29	NA	NA	NA	NA
Follow up, (years)	5	1	5	1	1	1	4
Cardiac Death, (%)	9.9*	NA	7.5 vs. 11.9	NA	2.0 vs. 1.6	NA	NA
MI, (%)	1*	1.9 vs.5.6	0.9 vs. 7.7	8.0 vs. 5.0	NA	0.0 vs. 1.3	NA
TLR, (%)	NA	NA	18.7 vs. 8.4	25.5 vs. 2.6¶	NA	NA	NA
TVR, (%)	9.7*	28.8 vs. 9.4®	28.0 vs.9.4	NA	7.0 vs. 1.0	5.2 vs. 0.8§	18.0 vs. 9.0
CVA, (%)	1.8*	0.0 vs. 3.7	0.9 vs. 4.2	NA	NA	0.0 vs. 0.8	NA
ST/Symptomatic	NA	NA	0.93 vs. 2.8	NA	NA	NA	1.5 vs. 1.6
Graft Occlusion MACCE, (%)	NA	30.7 vs. 24.5	32.4 vs. 38.3	NA	17.0 vs. 25.0	10.4 vs. 11.4	27.0 vs. 22.0

MI: myocardial infarction; TLR: target lesion revascularisation; CVA: cerebro-vascular accidents; ST: ARC definite/probable stent thrombosis; MACCE: major adverse cerebro-vascular events; *cumulative for overall study population; NA: not available; ®: p= 0.01; •: p=0.004; †: p=0.02; ¶: p=0.0001; ~: Euroscore>6; § p=0.02.[26-31]

Table 2. Pivotal Studies Comparing Percutaneous Coronary Intervention vs. Coronary Artery By-pass Grafting in Unprotected Left Main Coronary Artery Disease

composite outcome of death, Q-wave MI, or stroke (HR: 0.91; 95% CI: 0.45 to 1.83; p 0.79) compared to those with concurrent CABG. However, the rates of TVR were higher in the DES than the CABG group (HR: 6.22; 95% CI: 2.26 to 17.14; p< 0.001). Recently, the "CREDO-Kyoto PCI/CABG Registry Cohort" ULMCA sub-study reported outcomes of 1,005 patients with ULMCA disease (365 patients with PCI vs. 640 CABG patients). The adjusted outcome incidence of death/MI/stroke at 3-year was again not different between the PCI and CABG groups (HR1.30, 95% CI:0.79 to 2.15, p=0.30).[39] A large European all-comers multicenter registry, the "Drug-Eluting Stent for Left Main Coronary Artery Disease The DELTA Registry: A Multicenter Registry Evaluating Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting for Left Main Treatment" also reported comparable outcomes of first-generation DES vs. CABG.[40] A total of 2,775 patients with ULMCA disease were included: 1,874 underwent PCI and 901 underwent CABG. In the PCI group, 893 (47.6%) patients had PES implantation, and 893 (44.7%) had SES. Both in the propensity analysis as well as in the propensity matched analysis, no difference was found at a median follow-up of 1,295 (IQR 928 to 1,713) days in the occurrence of death, MI, and cerebrovascular events between DES implantation and CABG (17.6% PCI vs. 16.9% CABG; unadjusted HR: 1.11; 95% CI: 0.89 to 1.36; p=0.38; adjusted HR: 1.11; 95% CI: 0.85 to 1.42;p=0.47). However, there was still an advantage of CABG over PCI in terms of MACCE (30.3% in the PCI group vs. 20.1% in the CABG group; unadjusted HR: 1.58; 95% CI: 1.32 to 1.90; p<0.0001; adjusted HR: 1.64; 95% CI: 1.33 to 2.03; p <0.0001), that was exclusively driven by a lower incidence of TVR as well as TLR. Additionally, ULMCA PCI in this European registry has demonstrated to be a safe procedure, and this is testified to by the low occurrence of ST and mortality despite the "all comers" design.

Simultaneously with these observational studies, the role of first-generation DES vs. CABG for ULMCA disease was evaluated by several randomised trials (see Table 3).[32-37] The first, LE MANS, used a surrogate endpoints such as the change in left ventricular ejection fraction. Whereas, the others trials had a non-inferiority design with respect to hard endpoint (death, MI, TVR and cerebrovascular events). These studies reported similar rates of the composite end point of death, MI, and stroke. Conversely, TVR remained significantly higher in patients treated with PCI. Five-year outcomes for the 705 patients with ULMCA enrolled in "Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery" SYNTAX have been recently reported and are consistent with the findings at 12-month.[41] At 5 years, MACCE were similar between the PCI with PES and CABG groups (36.9% vs. 31.0%, respectively; HR 1.23, 95% CI 0.95-1.59, p=0.12). PCI-treated patients had a lower stroke but a higher revascularisation rate vs. CABG , (Figure 2). A meta-analysis which evaluated first-generation DES vs. CABG in patients with ULMCA disease confirmed that at 1-year the rate of MACCE defined as death, MI, TVR or stroke was non-significantly different in the PCI group compared with those assigned to CABG. As in each of the individual studies analyzed, the rate of stroke was higher amongst those treated with CABG. Conversely, higher rates of TVR were observed in the PCI cohort.[42] Another meta-analysis including 24 studies and 14,203 patients similarly suggested that PCI with DES is a safe and durable alternative to CABG for the revascularisation of ULMCA stenosis in select patients at long-term follow-up.[43] There was no significant difference in MACCE between the 2 groups. No significant difference for all cause mortality was found between first-generation DES or CABG at 1 year (OR: 0.792, 95% CI: 0.53-1.19), 2 years (OR: 0.920,95% CI: 0.67-1.26), 3 years (OR: 0.94, 95% CI: 0.60-1.48), 4 years (OR: 0.84, 95% CI: 0.53- 1.33), and 5 years (OR: 0.79, 95% CI: 0.57- 1.08). As expected, the need for TVR was significantly higher in patients undergoing PCI at all time points. Again, the occurrence of stroke, however, was significantly less frequent in patients treated with PCI. Lately, another meta-analysis that used different statistical methodology, confirmed that the 2 procedures have similar mortality: the odds of one-year mortality comparing PCI to CABG were not different among randomised controlled trials, matched cohort studies, and other types of studies (odds ratios 0.99, 95% CI 0.67-1.43; 1.10, 95%

Trial name	N Patients Included	Follow-up	Primary Endpoint	Event rate		P value	Major Secondary Endpoint	Event rate		P value
				PCI	CABG			PCI	CABG	
LE MANS	105	1 yr	Change in LVEF	3.3 ± 6.7%	0.5 ± 0.8%	0.047	Death, MI, TVR, CVA, ST	30.7%	24.5%	NS
Boudriot *et al.*[6]	201	1 yr	Death, MI, TVR	19%	13.9%	0.19*	Death, MI	5.0%	7.9%	0.01*
PRECOMBAT	600	1 yr	Death, MI, TVR, CVA	8.7%	6.7%	0.01*	Death, MI, CVA	3.3%	4.0%	0.83
SYNTAX	705	3 yr	Death, MI, TVR, CVA	26.8%	22.3%	0.20	Death, MI, CVA	13.0%	14.3%	0.60

*Noninferiority comparison.
CABG = coronary artery bypass graft; CAD = coronary artery disease; CVA = cerebrovascular event; EXCEL = Evaluation of XIENCE PRIME Everolimus Eluting Stent System (EECSS) or XIENCE V EECSS Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation; LE MANS = Study of Unprotected Left Main Stenting Versus Bypass Surgery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MILESTONE = Revascularisation Strategy (PCI With DES Implantation vs CABG) in Patients With Non ST Elevation Acute Coronary Syndrome With Multivessel and/or Unprotected Left Main Coronary Disease; NA = not applicable; PCI = percutaneous coronary intervention; PRECOMBAT = Premier of Randomised Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; RCT = randomised clinical trial; ST = stent thrombosis; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; TVR = target vessel revascularisation.[32-37]

Table 3. Completed Trials of Percutaneous Coronary Intervention vs. Coronary Artery By-pass Grafting for the Treatment of Unprotected Left Main Coronary Artery Disease

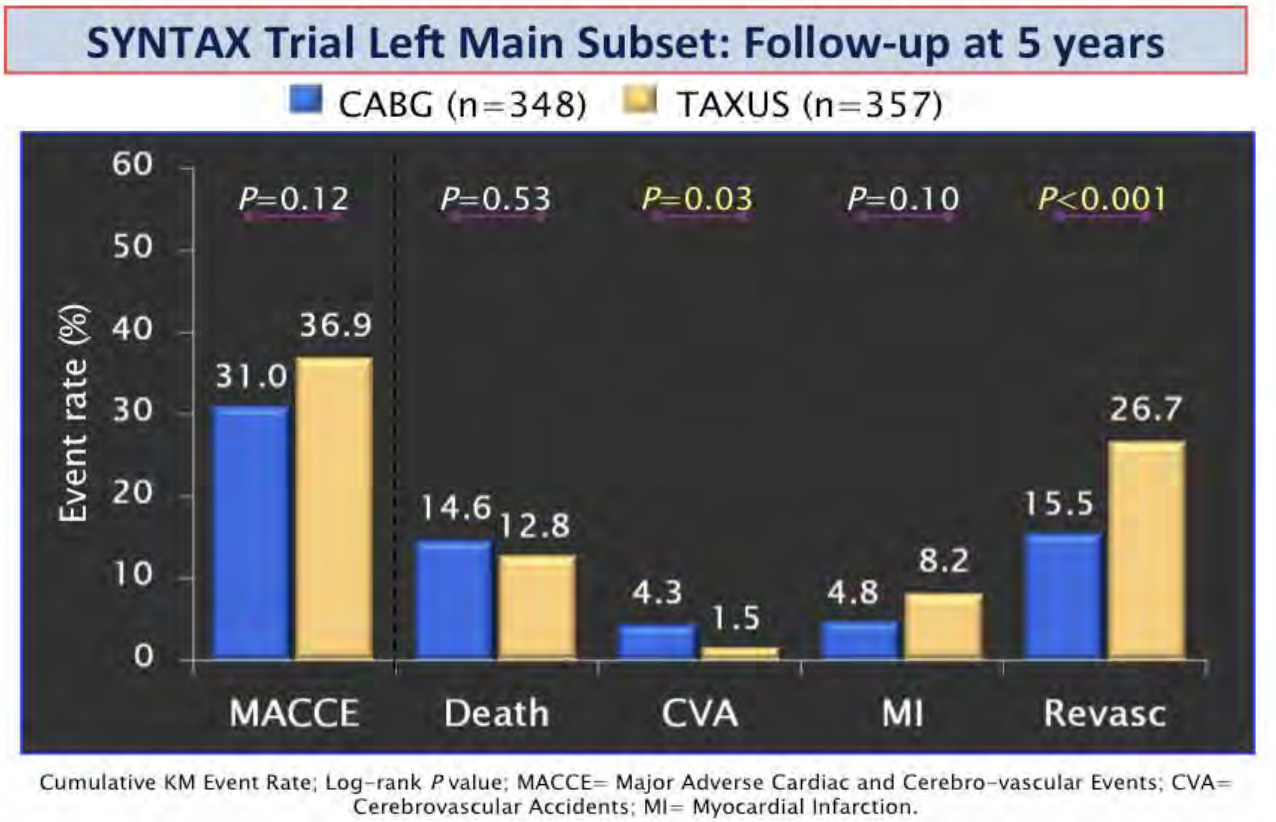

Figure 2. Five-year Outcomes in Patients with Left Main Disease Treated with Either Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting in the SYNTAX Trial. At 5 years, MACCE were similar between the PCI with PES and CABG groups. Mortality rate was also equivalent in PCI and CABG patients. Conversely, stroke was significantly increased in the CABG group and repeat revascularisation in the PCI arm.[41]

CI 0.75-1.73; and 0.93, 95% CI 0.58-1.35, respectively).[44]

What it has been emerged from these studies is that first-generation DES are comparable to CABG in terms of major clinical outcomes in high-volume centers with very experienced operators. However, accurate patient selection is mandatory to improve the clinical outcomes. 'Heart Team' collaborative approach is also a fundamental prerequisite in the evaluation of these patients. Risk models can help the interventionalist in clarify the decision making for PCI vs. CABG. The extent and the complexity of associated coronary artery disease should accounted for when choosing between surgery and PCI, because patients with high SYNTAX scores the benefit in favor of CABG over PCI with stenting increases. For patients with lower complexity coronary disease who can undergo PCI at an acceptable risk and with reasonable probability for success, PCI may be an acceptable or even preferred option. Until awaited results of new trials comparing new-DES vs. CABG available, best practice is engagement of Heart Team for SYNTAX score <32 and when feasible, CABG for SYNTAX >33.[1-2]

The Role of 2nd Generation DES

Despite an impressive benefit of first-generation DES in reducing the restenosis when compared to BMS, safety concerns have been raised regarding the long-term safety of these devices, in particular with regards to late ST.[45-47] Various mechanisms such as delayed endothelialisation, local hypersensitivity and endothelial dysfunction owing to the durable polymer coating and/or the drug itself have been suggested as possible causes of this phenomenon.[47] Improving the stent's safety and the efficacy is particularly important in patients with ULMCA disease, where the occurrence of restenosis or ST could be catastrophic. With this concern in mind, engineering and clinical research is currently focused on increasing the efficacy and safety of DES. The currently available DES have undergone significant changes in the platforms, polymers and the drugs, aiming at improving biocompatibility and long-term outcomes of patients undergoing PCI. The second-generation DES include the zotarolimus (ZES, Endeavor Resolute; [Medtronic Inc., Minneapolis, MN, USA]), the everolimus (EES, Xience V/Xience Prime, [Abbott Vascular, Santa Clara, CA, USA] and Promus/Promus Element [Boston Scientific, Natick, Massachusetts, USA]) and biolimus A9- eluting stents (BES, Biomatrix [Biosensors Inc., Newport Beach, California, USA]; and Nobori [Terumo Medical Corp., Tokyo, Japan]). These newer devices have already provided a reduction in restenosis, ST and mortality rates when compared with first-generation DES.[6] The impact of the second-generation DES in left main population was initially reported in the "LEft Main Xience V" LEMAX registry. Among 173 patients with ULMCA disease treated with EES, death, MI, and TVR were 2.9%, 4.7%, and 7.0%, respectively, with a cumulative MACCE rate of 15.0% and a rate of definite/probable ST of 0.6% at 1-year clinical follow-up. The clinical outcomes in the ULMCA lesions treated with ZES have been evaluated retrospectively in 40 patients, with a MACE rate of 15.0% at an average clinical follow-up of 12.4 months.[49] To date, data on safety and efficacy of overall second-

Ongoing Randomized Evaluating Unprotected Left Main Revascularization with PCI vs. CABG

	NOBLE	EXCEL
N patients, sites	1,200 ; 26 European Sites	1,900; 126 sites in 17 countries
DES	BES Biomatrix®	EES Xience V/Prime®
LM location	Ostial, shaft, or bifurcation	Ostial, shaft, or bifurcation
LM severity	Angio DS >50% or FFR ≤0.80	Angio DS ≥70% or ≥50% - <70% + either FFR ≤0.80 or IVUS MLA ≤6.0 mm^2 or non-invasive evidence of extensive ischemia
Other anatomic inclusion criteria	≤3 additional non-complex lesions (excludes length >25 mm, CTO, 2-stent bifurcation, calcified or tortuous vessels)	SYNTAX Score ≤32
Primary endpoint	Death, CVA, non-index MI, revasc	Death, CVA, MI
Timing of primary EP	2 years	Median 3 years
Duration of follow-up	5 years	5 years

Figure 3. Ongoing Randomised Evaluating Unprotected Left Main Revascularisation with Percutaneous Coronary Intervention vs. Coronary Artery Bypass Grafting. The "Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation trial" EXCEL, will answer the question whether EES is non-inferior in the composite incidence of death, MI or cerebrovascular events to CABG at 3-year in the treatment of ULMCA disease in patients with SYNTAX score ≤32. The "Nordic-Baltic-British Left Main Revascularisation Study Coronary Artery Bypass Grafting Versus Drug-eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis" NOBLE will evaluate the primary combined endpoint of death, stroke, non-index treatment related MI and new revascularisation in patients with ULMCA disease treated with BES vs. CABG.

generation DES in ULMCA PCI comes from the "New Generation Drug-eluting Stent Experience in the Percutaneous Treatment of Unprotected Left Main Coronary Artery Disease" NEST registry. This study evaluated 154 patients underwent to ULMCA-PCI with all currently available DES in 2 high volume Italian centers.[50] The population analyzed in this prospective study was at clinical and anatomical intermediate risk (as shown by a mean EuroSCORE and SYNTAX scores of 4.7 ± 2.6 and 27.5 ± 8.3, respectively). Moreover, 81.8% of the patients included had a complex distal left main lesions with 76.3% true Medina bifurcations. EES, ZES and BES were implanted in 44.2%, 29.9% and in 25.9% patients, respectively. At a median clinical follow-up of 551.5 days (360.8-1045.5 days), MACE rate was 18.8%. Moreover, the safety profile of these stents was encouraging, as demonstrated by the low rates of overall and cardiac mortality and absence of MI or definite ST. Finally, TLR occurrence was low (4.5%) despite the presence of a high number (57.9%) of complex distal ULMCA bifurcations requiring a 2-stent approach. This study demonstrated that currently available DES, even in patients with complex ULMCA disease, appear to be promising in terms of safety and efficacy at 2-year clinical follow-up.

Moreover, the performance of various second-generation DES has been evaluated in the "Prospective Randomised Trial of Everolimus- and Zotarolimus-eluting Stents for Treatment of Unprotected Left Main Coronary Artery Disease " ISAR-LEFT MAIN 2 trial.[51] The study was designed to assess the non-inferiority of ZES vs. EES regarding the incidence of MACE a composite of death, MI, or TLR at 1-year follow-up. A total of 650 patients with ULMCA lesions were randomised to treatment with ZES (n = 324) and EES (n = 326). Interestingly, MACE rate was not different in the 2 groups (17.5% in ZES vs. 14.3% in EES; HR, 1.26; 95% CI, 0.85-1.85; p=0.25). Moreover, TLR was comparable (11.7% in ZES vs. 10.7% in EES; HR, 1.26; 95% CI, 0.78-2.06; p=0.35). Definite ST was 0.6% in both groups, while probable ST occurred in 0.3% of the ZES group and 0% of the EES group. Angiographic restenosis at 6-9 months follow-up occurred in 21.5% of the ZES group and 16.8% of the EES group, indicating that the use of both devices in ULMCA lesions in relatively unselected patients is feasible, safe, and effective.

1st vs. 2nd Generation DES

The "Premier of Randomised Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease" PRECOMBAT-2 study reported the outcomes of the EES in the treatment of ULMCA stenosis in 334 consecutive patients in comparison with those of historical controls of patients receiving SES or CABG in the PRECOMBAT randomised study.[52] At 18 months the composite incidence of death, MI, or stroke did not differ among patients receiving EES (3.3%), SES (3.7%; aHR of EES: 0.63; 95% CI: 0.27 to 1.47; p = 0.29), and CABG (4.8%; aHR of EES: 0.67; 95% CI: 0.29 to 1.54; p= 0.34). EES (8.9%) showed also a comparable incidence of MACCE vs. SES

(10.8%; aHR of EES: 0.84; 95% CI: 0.51 to 1.40; p =0.51) and CABG (6.7%, aHR of EES: 1.40; 95% CI: 0.78 to 2.54; p= 0.26). Although the need for repeat revascularisation was higher after EES than after CABG, EES had risks of angiographic and clinical restenosis comparable to those of SES.

Data comparing SES vs. EES were also reported from the "Efficacy of Xience/promus versus Cypher in rEducing Late Loss after stENTing" EXCELLENT, an all-comer registry that had no angiographic exclusion and included patients with acute coronary syndrome, cardiogenic shock.[53] Among 5159 patients included, 275 received ULMCA PCI with EES (160) vs. SES (115). One-year MACE was comparable between the 2 groups (7.5% for EES vs. 13.9% for SES, HR: 0.55, 95%CI:0.26–1.17, p = 0.117). Notably, after multivariable or propensity score adjustment, the risk of MACE was significantly lower for EES vs. SES (multivariable adjusted aHR: 0.42 [0.19–0.92], p = 0.030; propensity score aHR: 0.43 [0.20–0.95], p = 0.037). These results were mainly driven from the numerically lower rate of repeat revascularisation in the EES group (2.5% for EES vs. 7.0% for SES, p = 0.096). As for hard endpoint (death or MI) and ST, no differences were found between the 2 groups.

The "Clinical and Angiographic Outcomes of Patients Treated With Everolimus-Eluting Stents or First-Generation Paclitaxel-Eluting Stents for Unprotected Left Main Disease" demonstrated the superiority of EES over PES in patients with ULMCA disease.[54] Among 390 patients, 224 received PES and 166 EES. The 1-year MACE rate was 21.9% in the PES group and 10.2% in the EES group (p= 0.002). The difference in MACE rate was mainly driven by the TVR rate, which was significantly lower in the EES group (4.2% vs. 13.4%, p= 0.002). Data from the "French Left Main Taxus" FLM Taxus and the "LEft MAin Xience" LEMAX registries reported similar findings at 2-year follow-up.[55] After propensity score matching, there were 172 patients for each group treated with PES vs. EES. EES use was associated with a decreased rate of target lesion failure (TLF) at 2-year, driven mainly by decreased ST and target vessel MI. This difference in safety and efficacy was progressively more pronounced as the lesion complexity increased. Indeed, EES were shown to be significantly beneficial in patients with a high SYNTAX score with regard to the composite endpoint of TLF, with a trend towards significance in the intermediate SYNTAX score group. In the FINE registry, 93 (50.0%) patients with ULMCA disease were treated with first-generation DES (49 SES and 44 PES) and 93 (50.0%) with new-generation DES (73 EES, 11 ZES and 9 BES),(56). Notably, IVUS guidance was more frequent with new-generation DES (46.2% vs. 61.3%; p=0.040). At 2 years, new-generation DES as compared with first-generation DES led to a trend towards a reduction of MACE (31.2% vs. 19.6%; p=0.070). A benefits in MI (4.3% vs. 0%; p=0.044) and TVR (23.7% vs. 12.0%; p=0.038) were also observed, as well as a trend towards lower cardiac mortality with new-generation DES. Definite ST occurred also less frequently with new-generation DES. In addition, the use of PES was associated with MACE. Overall, all these studies suggest the superiority of the new-DES in the treatment of ULMCA disease.

Future Perspectives

These results are certainly encouraging, however larger ongoing multi-center randomised trials utilising currently available DES will provide to resolve the question of whether these devices will represent a viable alternative to CABG in these patients (see Figure 3). In theory, these new stents are considered able to push the boundaries beyond the current limit of a SYNTAX score>32.

Waiting for the results of these ongoing trials, the perspective is that future continuous advances in the field of ULMCA-PCI will improve the treatment of these patients, leading an equivalence between PCI and CABG, especially for specific patients with ULMCA disease. Even some anecdotal cases with bioabsorbable scaffolds [BVS, (Abbott Vascular, Santa Clara, CA, USA)] implantation in ULMCA lesions have been recently reported, there is still a need for further development of these devices. Indeed, several manufacturer limitations still make BVS implantation in ULMCA an "in utero" treatment. One limitation remains the lack of large sizes of BVS: the largest BVS available is 3.5mm which has dilatation limit of 4.0mm and too small for many ULMCA lesions. Moreover, these stent size provide the dilatation limits of BVS to avoid the potential for scaffold disruption. Dilatation of struts in case of large and diseased left circumflex, with >2.5mm balloon may result in scaffold disruption. When the left circumflex is larger than 2.5mm and needs treatment at the ostium, BVS on the left main may not be ideal. Provisional stenting is recommended, with final kissing balloon inflation only when necessary. Indeed, these bulky devices may preclude several 2-stent techniques. T or "TAP" stenting with a metal DES in the side branch is preferable if is needed. In careful selected cases with a high-angle left main bifurcation two-BVS T-stent technique can be performed. ([57]). Despite these limitations, theoretical advantages of BVS are the possibility to later revascularisation with percutaneous or surgical techniques if the need arises and the potential absence of late ST due to the absence of polymers or stent struts, which have failed to endothelialise or that continue to stimulate inflammation or vessel irritation.

Conclusion

Percutaneous treatment of the ULMCA remains challenging. Numerous data confirmed the safety and efficacy of first-generation DES vs. CABG. With the advance of new catheter-based technology, particularly the availability of new-DES, the outcome of ULMCA PCI has shown to be comparable, or even superior to the outcome obtained using first-generation DES. However, patients undergoing ULMCA-PCI remain to have increased incidence of MACE mainly driven by increased TVR. Large, randomised controlled trials at longer follow-up are needed to elucidate whether new-DES will be non-inferior to CABG in low to intermediate risk complexity coronary artery disease associated with ULMCA disease. Moreover, even theoretically promising, the use of new-generation bioreabsorbable scaffolds will be further addressed in this setting.

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Hypertension and Kidney: Interventional Strategies for Resistant Hypertension

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Introduction

Hypertension (HTN) is highly prevalent and one of the most frequent chronic diseases worldwide.[1] Overall the prevalence of hypertension appears to be around 30–45% of the general population, with a steep increase with ageing.[2]

Hypertension is generally treated with drugs, but in some specific cases interventional procedures might be considered. One is the renovascular secondary hypertension, and the other is that secondary to sympathetic nervous activity (SNA).

Secondary Renovascular HTN:

There are two fundamental mechanisms at the base of renovascular hypertension: renin independent and renin dependent hypertension. In case of unilateral renovascular disease, a well-functioning contralateral kidney warrants the pressure natriuresis and this shows the key-role of the renin-angiotensin-aldosterone axis (RAA) in determining hypertension (Goldblatt's 2 kidney 1 clip model). Instead, when both kidneys are affected, the RAA axes activation is temporary and hypertension is volume dependent.

To activate RAA system the stenotic lesion must generate a distal pressure fall at least 10-20% below aortic pressure, i.e. a cross-sectional area of occlusion of 70-80%.[3]

Resistant Hypertension Related to Increased Renal SNA

Increased renal sympathetic nerve activity (RSNA) is known to decrease renal excretory function.[4-6] Afferent and efferent sensory, chemo and baroreceptor nerve fibres, form a neural network within the adventitia of the renal artery. The renal effects of increased RSNA include renal tubular sodium reabsorption leading to sodium retention; decreased renal blood flow and glomerular filtration rate with renal vasoconstriction and increased renal vascular resistance. Furthermore, augmented renin release stimulates angiotensin-II production.[7] These effects influence both short and long term blood pressure regulation. (See Figure 1).

Considering the above-mentioned factors, the physiologic targets for interventional treatments of hypertension include improvement in blood flow to the kidney by renal artery angioplasty and stenting and by autonomic modulation via renal sympathetic denervation.

Renal Artery Stenosis

Renal Artery Stenosis (RAS) is present in 1% to 5% of people with hypertension[8] and the prevalence among people older than 65 years of age may be as high as 7%.[9] The most frequent causes of renal artery stenosis are atherosclerosis and fibromuscular

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The Cardiovascular Interventional Unit performs coronary and peripheral interventions (over 2000 diagnostic and 800 interventional cases per year), with a 24 hours emergency service for the area around the city of Verona (500.000 habitants). It is the Provincial referring centre for paediatric invasive cardiology, and structural cardiology and is one of the two referring centres for renal denervation in the Region of Veneto.

dysplasia. Other less common causes of renal artery occlusion are aneurysms, Takayasu's vasculitis, extrinsic compression of renal artery, etc. In spite of the large number of causes, the pathophysiology of the renovascular disease is the same. Occlusive renovascular disease can manifest itself in multiple clinical manners ranging from incidental finding of malignant hypertension, ischemic nephropathy or flash pulmonary oedema. Clinical clues to suspect the presence of renal artery stenosis are: unexplained renal function impairment, kidney size discrepancy more than 1.5 cm, flash pulmonary oedema, worsening of renal function following the administration of ACE-inhibitors or ARB, and onset of hypertension at young age.

Endovascular interventions may play a role in renovascular hypertension, although it is not certain whether revascularisation of a stenotic renal artery is beneficial over medical therapy alone. There are evidences that surgical intervention leads to stabilisation or improvement in renal function,[10] and several experiences reported beneficial effects of renal artery angioplasty and stenting.[11-12] However, all randomised studies that compared renal artery stenting with medical therapy failed to show any advantage of endovascular procedures.[13-15]

According to the American Heart Association (AHA) Guidelines[16] renal percutaneous revascularisation is indicated in patients with hemodynamically significant RAS and recurrent episodes of flash pulmonary oedema or congestive heart failure. Furthermore it may be considered if:

• patients have hemodynamically significant RAS and accelerated or resistant or malignant hypertension or has hypertension with an unexplained unilateral small kidney or suffer of hypertension with intolerance to medication.

• patients have hemodynamically significant RAS with unstable angina.

• patients have progressive chronic kidney disease with bilateral RAS or a RAS in a solitary functioning kidney.

Despite such recommendations, the results of randomised trials comparing stenting with medical therapy limit the possible indications of stenting to patients with rapidly progressive renal dysfunction and episodes of pulmonary oedema in high-risk patients where optimal medical therapy has failed.

The principal studies that have assessed the value of renal angioplasty are briefly summarised:

• STAR: involved 140 patients which were randomly assigned to medical therapy associated to renal artery stenting group or to medical therapy alone. At the end of the study the 2 arms did not differ in blood pressure control, in cardiovascular morbidity and

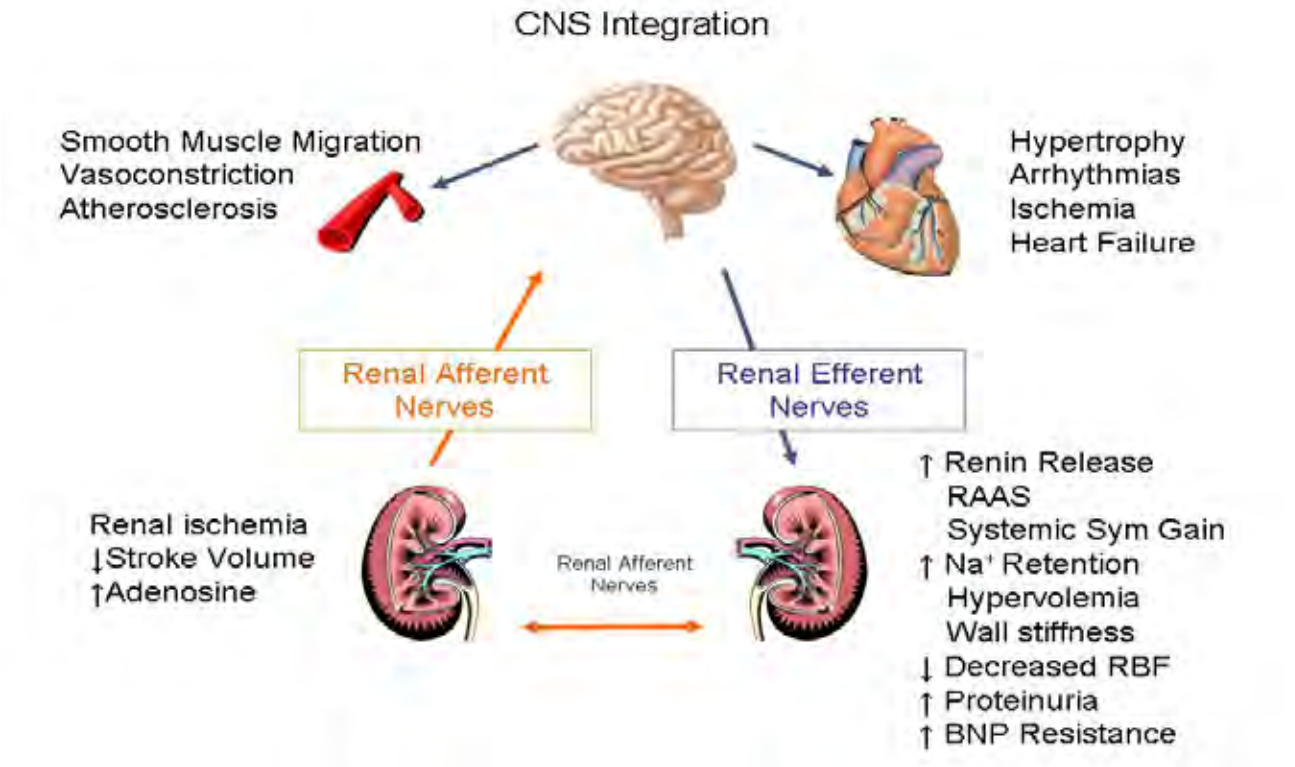

Figure 1. Physiopatologic role of sympathetic nervous system in developing of hypertension. Modified from Markus P. Schlaich *et al.* Hypertension 2009;54:1195-1201. RAAS indicates renin-angiotensin-aldosterone system; Na, sodium; RBF, renal blood flow; BNP, brain natriuretic peptide; sym, sympathetic.

	Inclusion	Exclusion
Symplicity HTN-1	Elevated office SBP (>160 mm Hg) despite taking >3 antihypertensive drug classes, 1 of which was a diuretic, at target or maximal tolerated dose.	Estimated glomerular filtration rate (eGFR) of <45 mL/min per 1.73 m^2, type 1 diabetes mellitus or a known secondary cause of hypertension (other than sleep apnea or chronic kidney disease. Significant renovascular abnormalities i.e. multiple main renal arteries, short length main renal artery, and hemodynamically significant renal artery stenosis). Age <18 years.
Symplicity HTN-2	Patients aged 18–85 years with a SBP of 160 mm Hg or more (≥150 mm Hg in patients with type 2 diabetes), despite compliance with three or more antihypertensive drugs.	Estimated glomerular filtration rate (eGFR of less than 45 mL/min per 1 73 m^2) type 1 diabetes, contraindications to MRI, substantial stenotic valvular heart disease, pregnancy or planned pregnancy during the study, and a history of myocardial infarction, unstable angina, or cerebrovascular accident in the previous 6 months.
Symplicity HTN-3	SBP of 160 mm Hg or higher and to be taking maximally tolerated doses of three or more antihypertensive medications of complementary classes, one of which had to be a diuretic at an appropriate dose. No changes in antihypertensive medication in the previous 2 weeks were allowed. Automated 24-hour ambulatory BP monitoring to ensure a SBP of 135 mm Hg or higher.	Known secondary causes of hypertension and more than one hospitalisation for a hypertensive emergency in the previous year. Anatomical exclusion criteria were renal-artery stenosis of more than 50%, renal-artery aneurysm, prior renal-artery intervention, multiple renal arteries, a renal artery of less than 4 mm in diameter, or a treatable segment of less than 20 mm in length.

Table 1. Patient Selection For Renal Denervation From The Main Clinical Trials.

mortality and renal failure progression. In the stent arm some procedure-related complications were observed. On the basis of these results, authors favored a conservative approach.[14]

• ASTRAL: randomised, un-blinded study, on 806 patients with atherosclerotic renovascular disease. Patients either underwent medical therapy alone or endovascular procedure associated with medical therapy. Primary outcome was renal function, secondary outcomes were blood pressure, mortality, time to renal or cardiovascular events. The Authors concluded that revascularisation carries a substantial risk without adding benefit to any outcomes considered in the study.[13]

• CORAL: designed to test if renal artery stenting associated to optimal medical therapy improves cardiovascular outcome in patients with RAS. The Authors concluded that renal revascularisation does not change major outcomes such as death, renal and cardiovascular events.[15]

General consensus considers catheter angiography the "gold standard" for the evaluation of atherosclerotic renal artery stenosis and a stenosis is defined as hemodynamically significant if it causes a luminal reduction >50%. In our opinion this threshold overestimates the actual functional severity of the stenosis, and this is an important variable to consider when analysing the disappointing results of renal artery stenting. In our Centre renal artery stenosis are assessed by the measurement of the trans-lesional gradient with a coronary pressure wire, regardless of the angiographic aspect. (See Figure 2). It has been demonstrated that an hyperemic systolic gradient >21mmHg provided the highest accuracy in predicting hypertension improvement after stenting, suggesting that a gradient of 21mmHg is indicative of significant renal artery stenosis.[17] Mangiacapra and colleagues[18] demonstrated that the trans-lesional pressure gradient better identifies patients who could have an advantage from stenting than patients treated on angiographic basis, supporting the concept of a physiologically-guided renal angioplasty rather than a procedure based on angiographic bases. More studies are however, needed to validate this interesting hypothesis.

Renal Sympathetic Nerve Activity

The effect of the nervous peripheral system on different organs is not uniform. There is no doubt however that the pathophysiological setting of hypertension includes an increased sympathetic tone and parasympathetic downregulation. The renal sympathetic nervous system has been identified as a major contributor to the complex pathophysiology of hypertension, states of volume overload and progressive renal disease, both experimentally and in humans.[19] Among others, possible mechanisms include increased sympathetic nerve firing rates, altered neuronal norepinephrine (NE) reuptake, diminished arterial baroreflex buffering of sympathetic nerve traffic, and facilitation of NE release by neurohumoral factors such as angiotensin-II.[20]

In the absence of appropriate drug control in severely hypertensive patients, therapeutic splanchnicectomy and even radical surgical sympathectomy were used since the 1930s. However this surgical therapy, although has been shown to significantly reduce blood pressure and mortality, was burdened with numerous adverse effects and was quickly abandoned.

The safety of this therapeutic rationale has been shown by human transplant experience that clearly demonstrated that

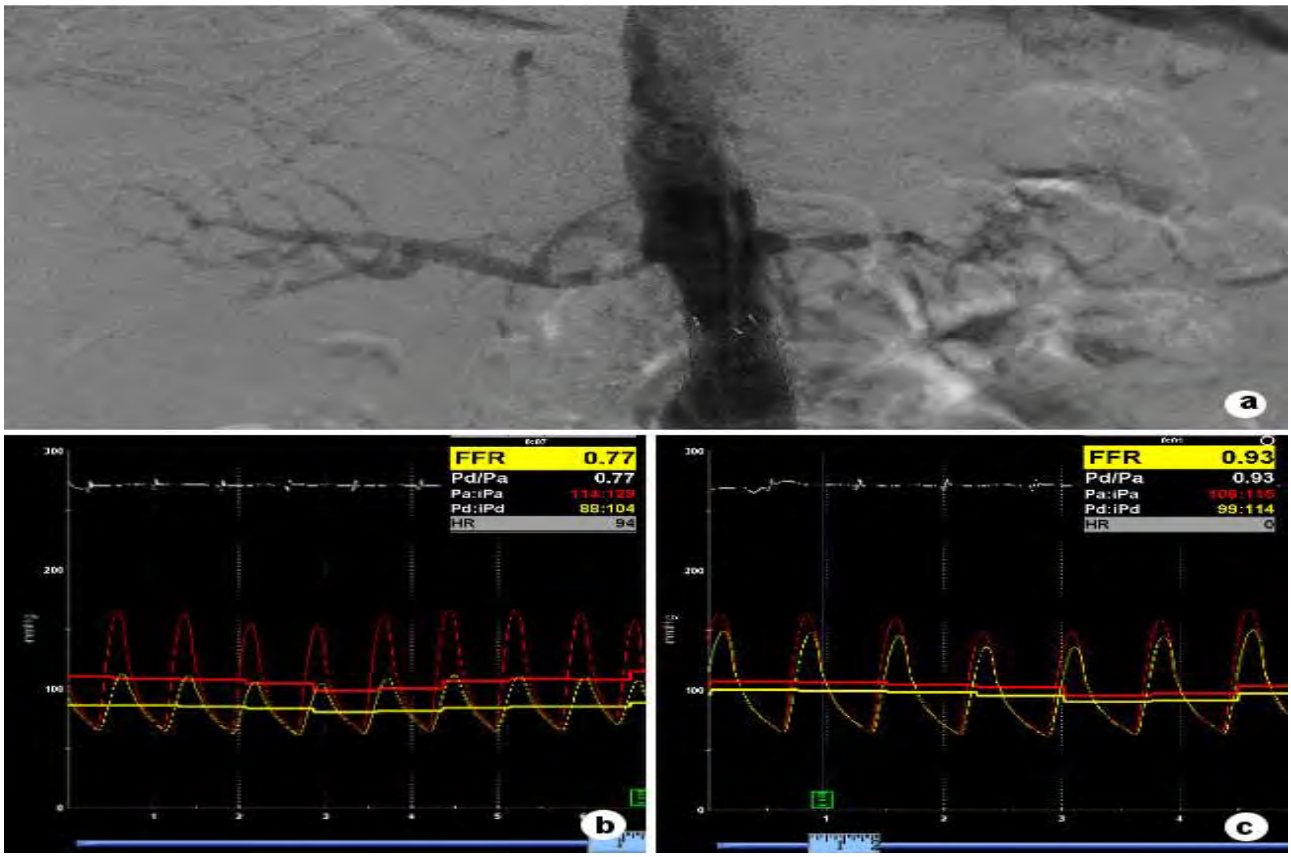

Figure 2. Angiography of abdominal aorta and the two renal arteries. The two renal arteries are characterised by bilateral severe stenosis a); pressure measurement at baseline in right renal artery b); pressure measurement at baseline in left renal artery c). Of note, trans-lesional pressure measurement are different in the two arteries despite a similar grade of stenosis. This phenomenon could be explained by a different condition of renal microcirculation, more compromised in the left renal artery. Interventional treatment might be indicated on the right side, but not on the left.

the denervated kidney reliably supports electrolyte and volume homeostasis in free-living humans.[21]

The convenient location of the sympathetic nerve endings in the renal artery adventitia suggests that both the efferent and afferent fibres can be targeted by catheter-based approaches, thereby re-setting renal blood pressure regulation.

The technique has been shown to reduce sympathetic nerve activity,[22] norepinephrine spillover[23] as well as blood pressure[24] in patients with resistant hypertension.

To date, due to the absence of agreed guidelines, the indications for renal denervation are based on the inclusion criteria of the available clinical trials.[25-27] These are briefly summarised in the Table 1.

Currently, only few studies have been performed to test the clinical effectiveness of the procedure of RDN. The first two trials, designed without a control group treated with placebo, showed a marked reduction in blood pressure among patients undergoing RDN. Conversely the results of the multi-centre, single-blind, randomised, controlled study did not confirm a statistically significant blood pressure reduction of renal denervation compared to medical therapy. All these trials have been conducted using the Simplicity™ catheter system (Medtronic, Mountain View, California).

• SYMPLICITY HTN-1: this was the first multicenter, open-label cohort study performed on 153 patients with resistant arterial hypertension. Primary results were reported in *Lancet* in 2009 and long-term results were reported in 2011.[23,25] At baseline the mean blood pressure was 175/98 mmHg and the reduction was on average by 20/10, 24/11, 25/11, 23/11, and 26/14 mm Hg at 1, 3, 6, 12, and 18 months, respectively. At 24 months within-patient reduction in systolic and diastolic BP was significantly higher in the RDN group (32/14 mmHg). The presented 36-month long-term follow-up of this non-randomised small study confirmed a sustained BP-lowering effect.[27] There was a non-significant difference in the number of antihypertensive medications and no change in renal function over the course of the study.

• SYMPLICITY HTN-2: In this multicentre trial a total of 106 patients with resistant HTN were randomised to endovascular RDN with medical treatment versus medical treatment alone.[24] At 6 months results based on office-based BP and also on home-based BP measurements showed that RDN resulted in a significant BP decrease

(a between-group difference of 22/12 mmHg and 33/11 mmHg respectively) while the control group experienced no significant changes. There was no difference in estimated GFR, serum creatinine, and cystatin C levels between the two groups. An extension study of SYMPLICITY HTN-2 recently reported that 37 patients treated with renal sympathetic denervation had improved blood pressure during exercise testing, lower resting heart rate, normal heart rate response to exercise, and improved heart rate recovery after exercise.[28]

• SYMPLICITY HTN-3 enrolled 535 subjects with uncontrolled hypertension that underwent bilateral renal denervation. This study was more rigorously designed to assess the safety and the efficacy of the renal denervation procedure, as all patients randomised to the control arm underwent a sham procedure. The study ruled-out any safety concern, but failed to show that treatment with the investigational procedure causes a sustained reduction in systolic blood pressure. After 6 months, the mean change in systolic blood pressure in the renal denervation arm vs the sham-controlled arm was not statistically significant (14.13 mmHg in the renal denervation arm vs 11.74 mmHg in the sham-controlled arm). Also regarding the change in the 24-hour ambulatory systolic blood pressure at 6 months there was no significant difference between patients in the RDN arm and patients in the control arm (6.75 mmHg in the renal denervation arm vs 4.79 mmHg in the control arm).[26]

There exist therefore a discrepancy between the results obtained in several experiences and those derived from the only available blinded study. Many explanations can be speculated to analyse these findings and certainly more observations are required to better understand the effects of patient's selection, the role of a high compliance to the medical therapy, and that of a placebo effect.

Conclusions

• Randomised clinical trials have consistently demonstrated that angioplasty and stenting of renal artery stenosis as selected with angiography does not provide advantages over medical treatment, and that the systematic intervention of "stenotic arteries" is useless and may be even harmful. However, angioplasty is effective in controlling renovascular hypertension in selected cases; therefore, it is reasonable to investigate the effects of a physiologically-guided selection of candidates and an accurate interventional technique associated to adequate medical treatment in order to identify good candidates to renal artery stenting.

• There is interesting evidence of effective blood pressure reduction in selected cases of patients with resistant hypertension treated with SRD. Also in this case, the only blinded randomised study has shown that the technique requires further validation, and likely a more accurate clinical selection. SRD is currently performed in many Countries, with several different devices and more clinical data will be available soon to better understand its real benefits and limitations.

• There is clearly a need for further studies to better define populations that may benefit from correctly indicated invasive interventions in patients with resistant hypertension having a well established renovascular or hyper-sympathetic tone functional substrate. Multidisciplinary collaboration is essential to the appropriate diagnosis and patient's selection, and an accurate follow-up program is needed to evaluate the results of interventions. Interventional techniques to treat resistant forms of hypertension can be effective in selected cases, but at the current stage, its use must be limited to very strictly defined populations according to a multi-disciplinary decision.

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Dilemmas in Transcatheter Aortic Valve Implantation: Asymmetrical Annular Calcifications

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Background

Transcatheter aortic valve implantation (TAVI) requires the presence of some degree of calcification of the native valve complex in order to ensure appropriate anchoring of the prosthesis in its desired position. On the other hand, extensive aortic calcifications may prevent adequate expansion of the new valve and its apposition to the surrounding tissue, thereby causing paravalvular leakage,[1-3] which is an established predictor of mortality after the procedure.[4-6] In this respect, not only the severity of valvular calcification is predictive of residual aortic regurgitation (AR), but also their location represents an important predictor of paravalvular leak, with calcium at the level of the annulus and base of the leaflets having a deeper impact on final AR degree compared to calcification of the free margins of the cusps.[7,8] This finding is not surprising, as it can be hypothesized that calcium on a mobile element of the valve can be displaced by the prosthesis; for the same reason, bulky calcifications of the leaflets represent a risk factor for coronary obstruction, particularly when coronary ostia are low.[9]

On the other hand, if calcium cannot be displaced during the procedure, the radial energy applied during dilatation and valve deployment may translate into a traumatic force over the surrounding tissue, with possible tears occurring particularly at the interface between the calcification and the more compliant area. In this regard, the left ventricle outflow tract (LVOT), due to its thin structure, represents a weak spot in the aortic valve complex. Indeed, LVOT calcification, together with excessive valve oversizing, has been identified as a major risk factor for annular rupture.[10]

CT scan is a particularly valuable tool in assessing valve anatomy and its usage has been shown to be associated with better outcomes;[11,12] it can also easily identify the pattern of calcium distribution over the valve. Limited data are available about asymmetric annular calcifications, also because this parameter is not easy to classify and standardize. However, in our experience, this situation is particularly prone to result in post-procedural paravalvular leakage, as bulky calcific nodules prevent the sealing between the prosthesis and the surrounding tissue. Hayashida et al. proposed that there might be a "vulnerable area" represented by the part of the annulus in direct continuity to the epicardial fat and the pericardium; on CT scan this area is located between 4 and 6 o'clock in standard short axis view.[13] This site is in direct contiguity with the mitroaortic junction and – also according to our experience – calcifications extending from this part of the LVOT towards the anterior mitral leaflet must prompt extreme caution. Barbanti et al. found instead found that the site of LVOT calcifications most significantly associated with annular rupture was located below the right coronary cusp.[10]

The presence of asymmetrical calcifications therefore predisposes both to paravalvular leak and annular rupture; this poses a particular challenge in preoperative evaluation, as strategies intended to prevent one complication may actually facilitate the other. The use of a self-expanding device – because of the reduced radial force and the tendency to conform to the native annulus – is probably associated with a reduced risk of annular rupture, but, for the same reasons, may lead to a higher incidence of a significant paravalvular leak. This is reflected by the fact that the extent of calcification was shown to be a significant predictor of residual AR mainly in series where self-expanding devices were used.[12] Conversely, the use of a balloon-expandable valve tends to give the annulus a more rounded shape, possibly reducing the malapposition of the prosthesis but creating more trauma and therefore increasing the risk of annular rupture.

Grube and colleagues have shown that TAVI can be performed without balloon pre-dilatation.[14] This approach may be particularly useful in the setting of a calcific annulus, also considering that, if calcific nodules are mobile, there is a potential for embolization. Indeed, calcium represents the most common histological finding in debris captured with filter-based embolic protection devices during TAVI procedures.[15] Postdilatation of the valve may reduce leakage, but this manoeuvre may be traumatic to the annulus, so

that the operator must be prepared to accept a certain degree of regurgitation. The same considerations apply to valve sizing: it is recognized that an adequate valve oversizing is linked to less residual AR, but, again, oversizing is a risk-factor for annular rupture with balloon-expandable valves.[10,16] The use of a self-expanding valve may reduce the concern about oversizing the prosthesis: on the other hand, inadequate expansion of the valve may still result in paravalvular leakage and suboptimal functioning of the leaflets. Moreover, the presence of calcific spots along the circumference of the annulus also poses a technical problem in measuring the dimensions of the virtual basal ring itself, as there is no clear consensus if calcifications should be included or excluded from the perimeter measurements, particularly when they protrude inside the annulus. Our practical approach is to draw the perimeter so that half of the calcification is inside and half is outside the tracing.

So, when asymmetrical calcification is encountered, a more aggressive approach using an oversized balloon expandable prosthesis will possibly reduce the incidence of paravalvular leak, at the non-negligible expense of an increased risk of annular rupture. On the other hand, if a more conservative approach is adopted, a higher incidence of significant paravalvular regurgitation has to be expected, which in turn can lead to the necessity for postdilatation, again increasing the risk of damaging the annulus.

In conclusion, asymmetrical calcifications represent an important risk factor during TAVI; some general considerations to prevent complications are reported below:

1) Predilatation should be avoided whenever possible.

2) Postdilatation, when necessary, has to be performed with particular caution.

3) Self-expandable valves probably represent the safest option, particularly when significant LVOT calcification is present.

4) A reduced oversizing should be applied, particularly when using balloon-expandable prostheses: in this regard, the new SAPIEN 3 device allows the avoidance of excessive mismatch between annulus and prosthesis.

5) We still need to understand how the other new generation transcatheter prostheses will perform with this anatomy.

Clinical Cases

Case 1

An 80 year-old male with symptomatic severe aortic stenosis (AVA 0.8cm^2, mean gradient 56mmHg) and a high operative risk (logistic Euroscore 25%) was referred to our institution for transfemoral TAVI. Pre-procedural CT scan showed calcifications of the LVOT extending to the mitro-aortic junction (Figure 1). Aortic annulus measured 28x24mm, with a perimeter of 92mm. Accordingly,

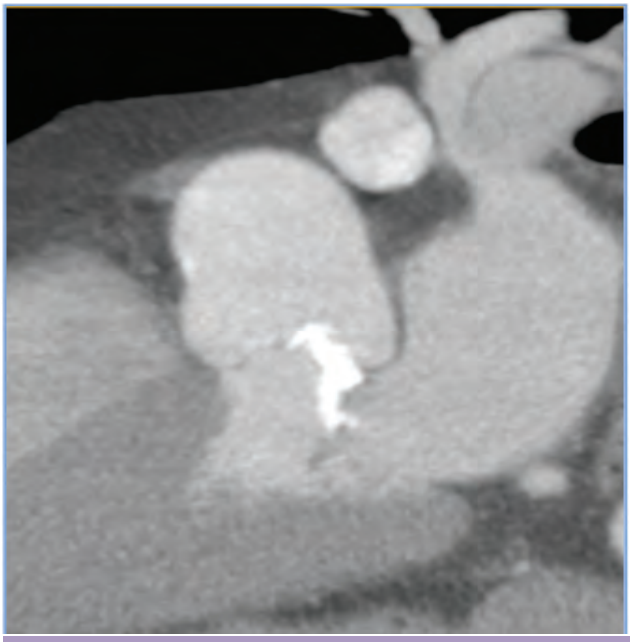

Figure 1. Extensive LVOT calcification extending to the anterior mitral leaflet.

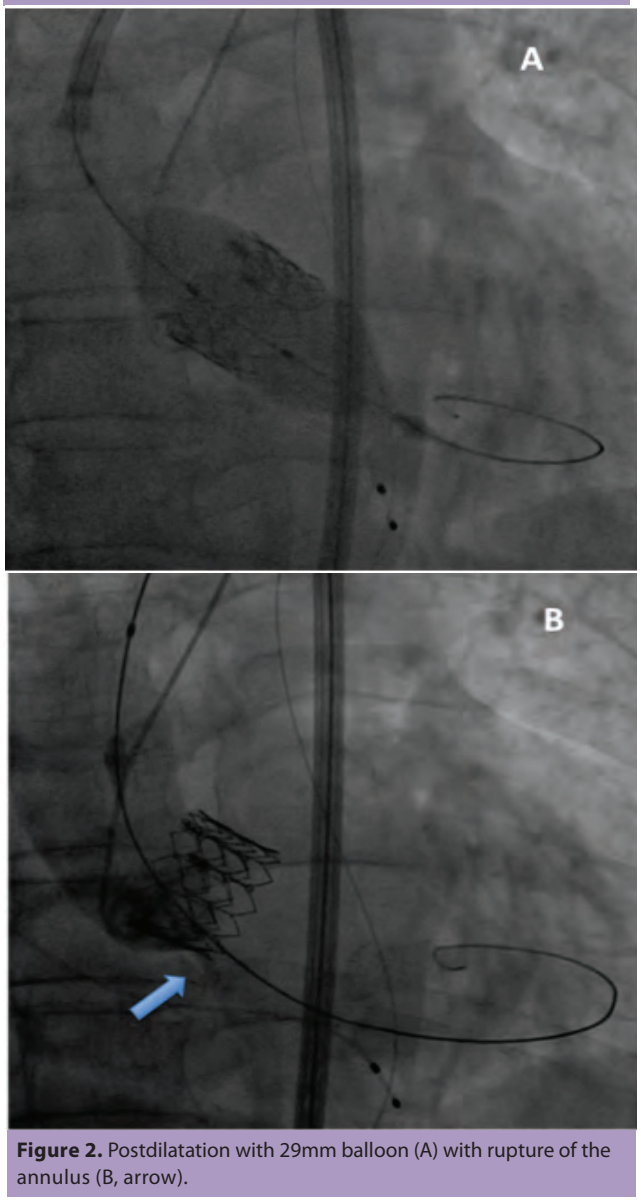

Figure 2. Postdilatation with 29mm balloon (A) with rupture of the annulus (B, arrow).

a 29mm Edwards SAPIEN XT was implanted via femoral access. After implantation, severe aortic regurgitation with hemodynamic instability was apparent, so that postdilatation with the balloon of the prosthesis was performed (Figure 2, panel A). However, annular rupture occurred (Figure 2, panel B) and the patient did not survive despite emergent surgery.

Case 2

Patient nr 2 is an 87-year-old male who presented with symptomatic severe aortic stenosis (AVA 0.4cm^2, mean gradient 66mmHg); he had previously undergone mitral valve replacement with a bioprosthesis and his estimated surgical risk by logistic Euroscore was 20%. He was therefore referred for TAVI; CT scan showed a small annulus (20x19mm, perimeter 63mm) with severe asymmetrical calcification extending into the LVOT (Figure 3). A 23 mm CoreValve was chosen; the valve was deliberately implanted in a high position to avoid interference with the calcific nodule and with the mitral prosthesis (Figure 4). Postprocedural angiography and echocardiography revealed a good result without significant paravalvular leakage.

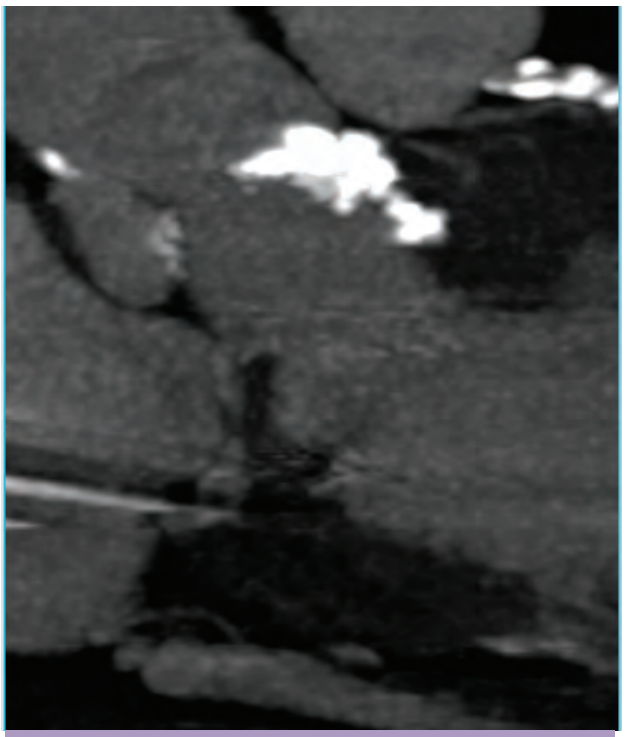

Figure 3. Pre-procedural CT scan.

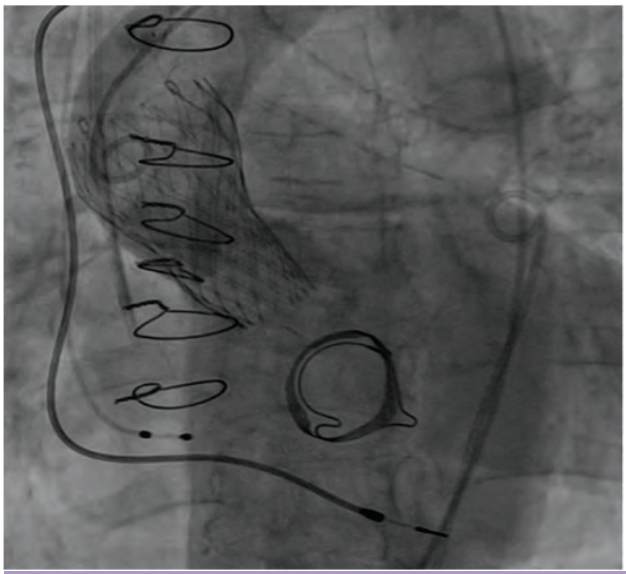

Figure 4. Final result after CoreValve 23mm implantation.

Case 3

An 82 year-old lady with ascending aorta calcification and a history of previous chest radiation because of lymphoma was referred to our hospital for percutaneous treatment of severe symptomatic aortic stenosis. CT scan showed a 24x22mm annulus with 74mm perimeter (Figure 5).

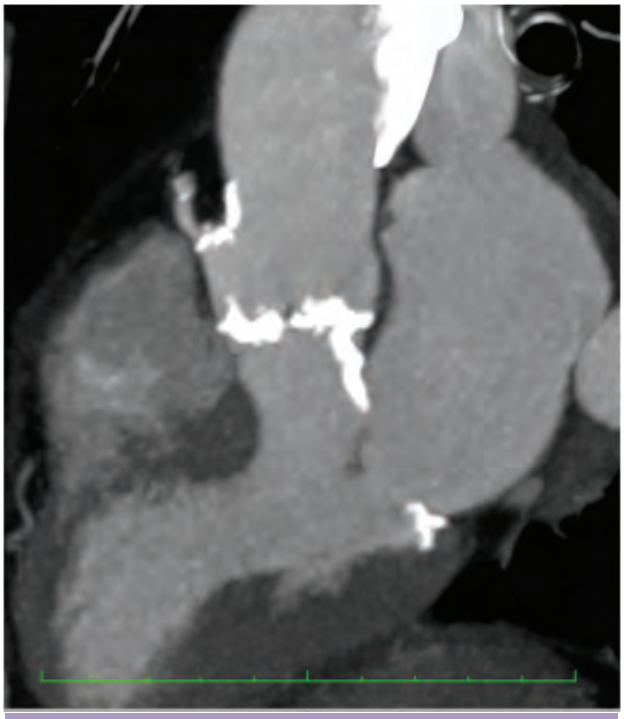

Figure 5.

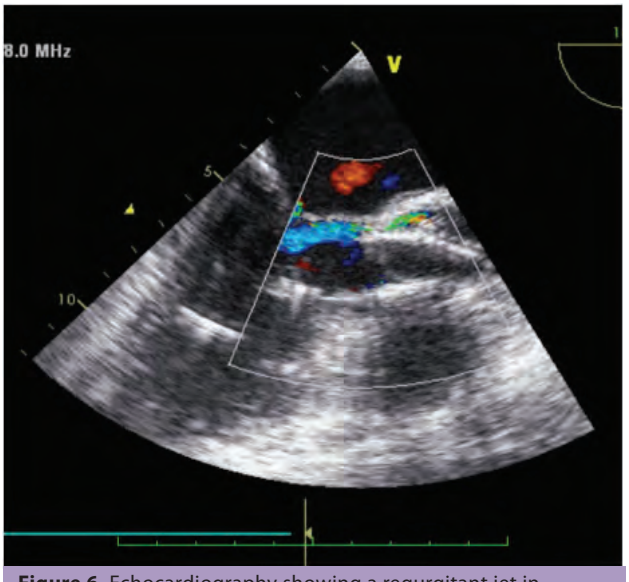

Figure 6. Echocardiography showing a regurgitant jet in correspondence of the mitro-aortic junction.

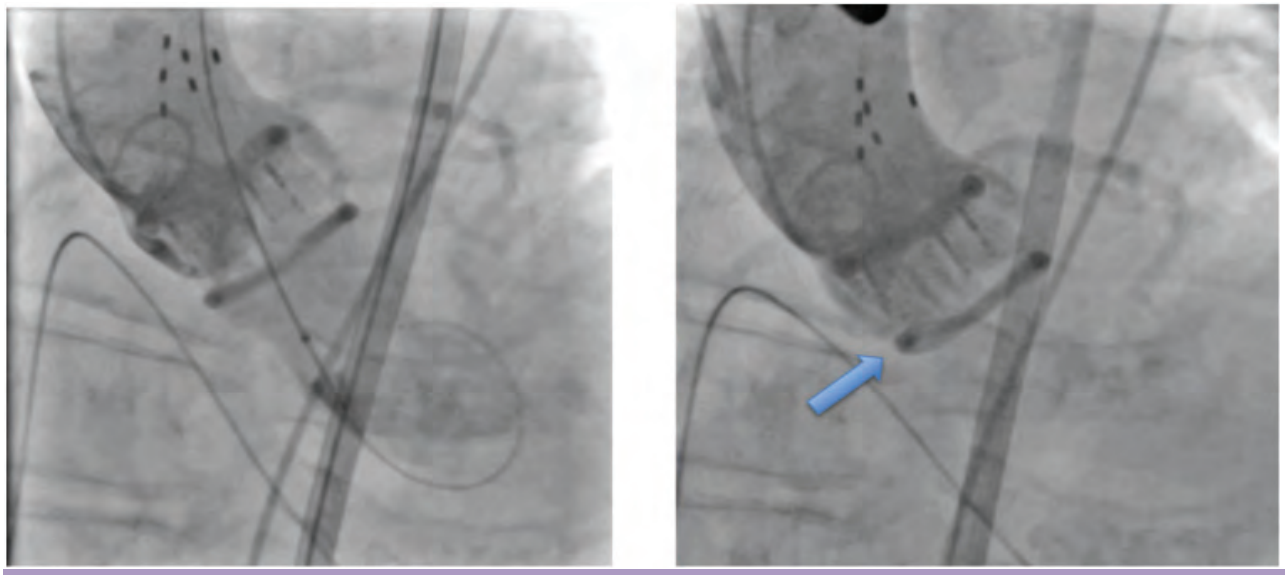

Figure 7. Adjustment of the valve positioning, particularly at the level of the non-coronary cusp (arrow).

A 25mm Direct Flow prosthesis was implanted despite the severe asymmetrical LVOT calcification, again extending towards the anterior mitral leaflet. After initial valve positioning, a moderate paravalvular regurgitation was evident due to a leak in correspondence with the LVOT calcification (Figure 6). The valve was therefore deflated and repositioned by raising the ventricular ring about 1mm higher, especially at the level of the non-coronary cusp (Figure 7). After valve repositioning, aortic regurgitation disappeared; the following clinical course was uneventful.

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