TREATMENT STRATEGIES
INTERVENTIONAL CARDIOLOGY

Volume 3 Issue 1

- Bifurcation and Left Main PCI
- Coronary Interventions
- Coronary Lesions
- Hypertension
- Percutaneous Coronary Interventions (PCI)

Articles include:

Aortic Stenosis and Pulmonary Hypertension

Drug-coated Balloons for Coronary Interventional Procedures

Optimising PCI Outcomes with Combined FFR and OCT Guidance

Understanding of the Transient Scaffolding: New Frontiers in Vascular Interventional Medicine for Atheroregression

Includes a review of the euroPCR 2013 Congress

TREATMENT STRATEGIES
Interventional Cardiology

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Welcome...

I am delighted to welcome you to the latest edition of *Treatment Strategies – Interventional Cardiology*. This edition will continue to address the key topical areas in the field of interventional cardiology, and will feature an exciting collection of papers from esteemed interventionalists on subjects such as bifurcation and left main PCI and coronary interventions.

This edition also features an in-depth, independent review of the latest developments and key findings from the euroPCR congress, held this year in Paris. 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. The event continues to be one of the most important and dynamic congresses for interventional cardiological medicine, and we are excited to bring the best of the show to you.

We hope that you find that content of this issue informative, and enjoy the range of interesting and thought-provoking perspectives on what is important in the field of interventional cardiology today. In order to maintain the high standards of the series, we would welcome your feedback on this edition. With your contributions, we will devour to ensure that the *Treatment Strategies* Series becomes one of the most useful publications in the healthcare industry.

We look forward to joining you next year in Paris for euroPCR 2014.

Hannah Corby, Chief Sub-editor

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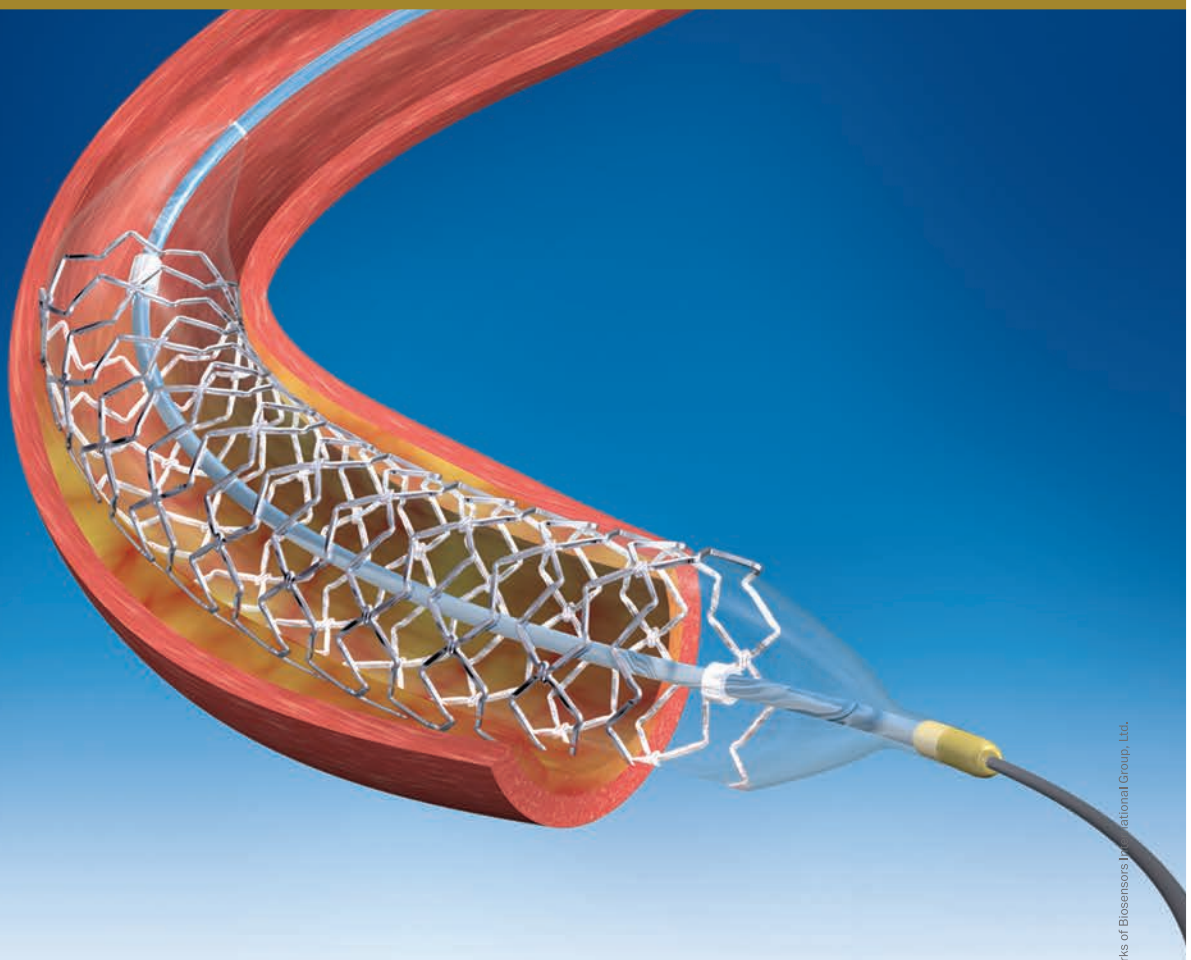

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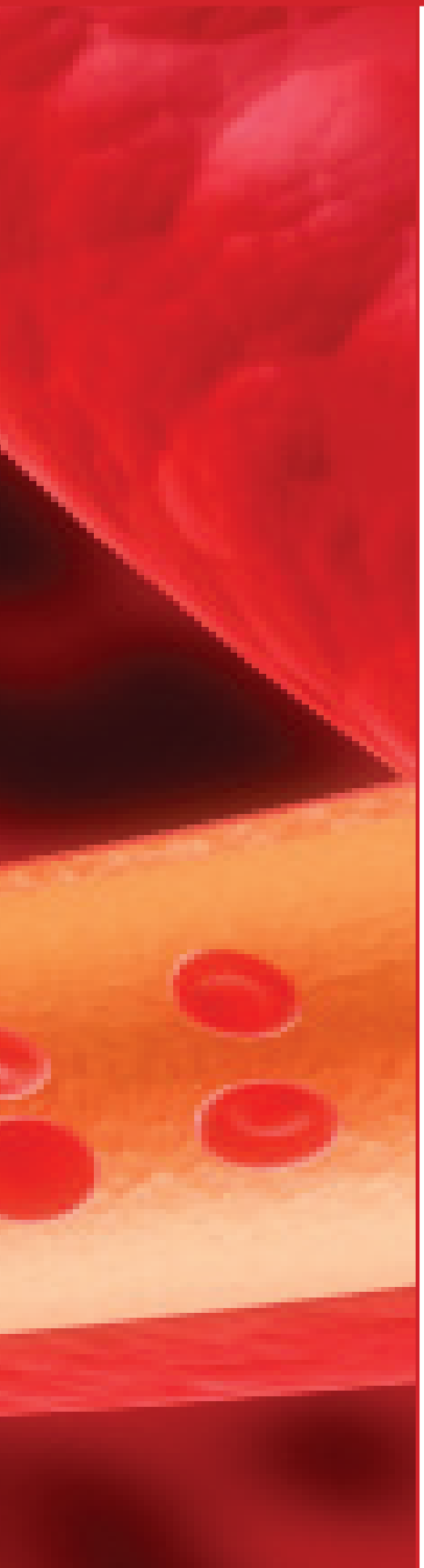

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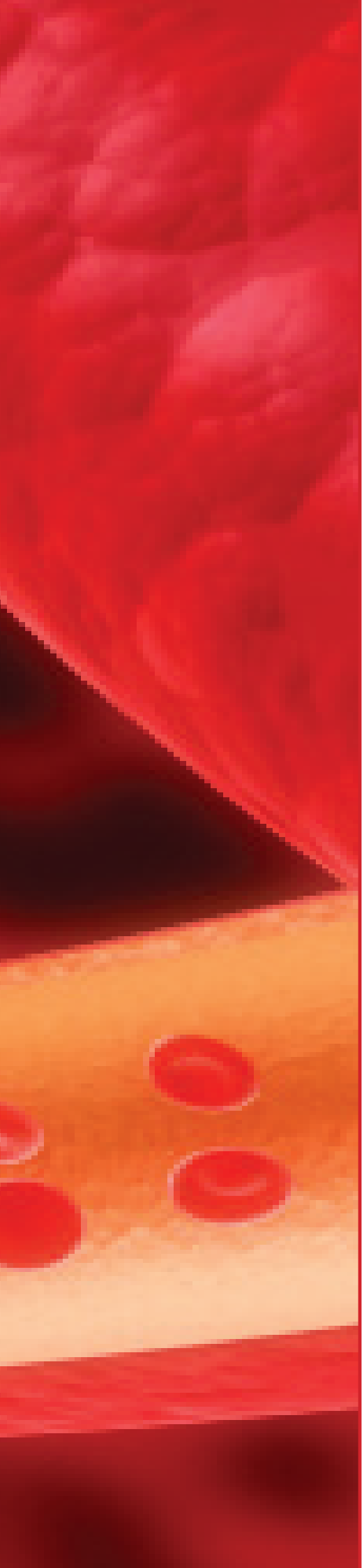

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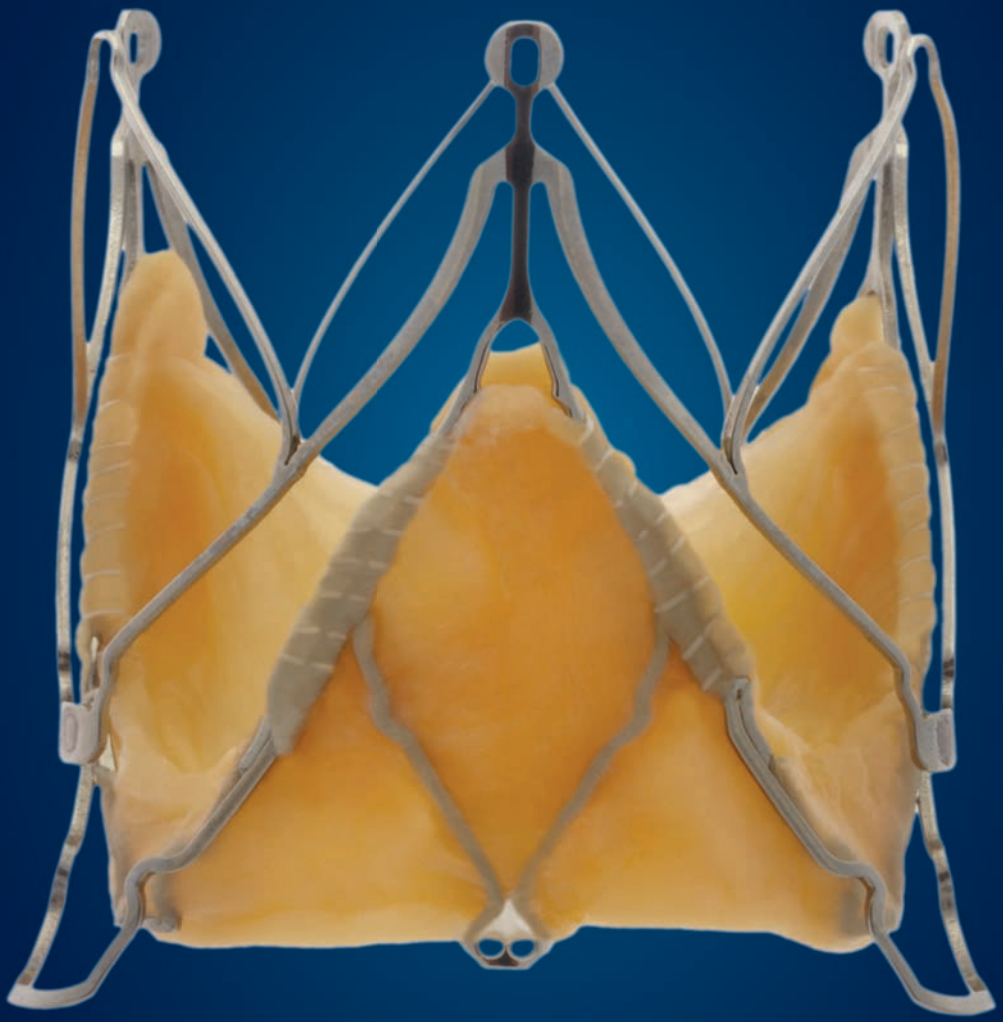

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Foreword

Nigel Lloyd
Managing Director, *Treatment Strategies*

Welcome to the latest issue of Treatment Strategies – Interventional Cardiology. We hope that this edition continues the resounding success of the last, and fulfils its aim of bringing healthcare professionals the latest updates and developments within the field of interventional cardiology.

This edition features a number of areas that the author's feel are of importance within the field of interventional cardiology, including coronary interventions. Alexander Kharlamov presents an in-depth discussion of transient scaffolding in his informative paper 'Understanding of the Transient Scaffolding: New Frontiers in Vascular Interventional Medicine for Atheroregression', while the role of coronary artery ectasia in acute myocardial infarction is explored by Usama Boles in his article 'Coronary Artery Ectasia as a Culprit for Acute Myocardial Infarction: Review of Pathophysiology and Management'. Optimising the outcomes of percutaneous coronary interventions is a further subject which is covered in the publication by Elvin Kedhi in his paper entitled 'Optimising PCI Outcomes with Combined FFR and OCT Guidance'.

Bifurcation and left main percutaneous coronary intervention has been identified as another key topic. Contemporary strategies in this area are discussed by Deb Aronson, Kleanthis Theodoropoulos, Nishar Kherada and Roxana Mehran in their article 'Unprotected Distal Left Main Bifurcation Percutaneous Coronary Intervention: Contemporary Strategies', while Tomasz Bochenek and Michał Lelek explore high risk PCI of left main. Additionally, the treatment techniques used to treat undilatable coronary lesions are considered by Tomasz Pawłowski in his paper ' Undilatable Coronary Lesions – Rotational Atherectomy and Other Techniques', and how drug-coated balloons can be used for coronary interventional precedures is discussed by Jochen Woehrle.

Hypertension is a further key area covered within this edition. Irene Lang and Christian Gerges explore the topic of aortic stenosis and pulmonary hypertension, while Martine Beeftink and Michil Voskuil present a compelling report on the subject of renal denervation in hypertension treatment. We feel that this range of papers will give the reader a well-rounded view into the key areas within interventional cardiology, and we hope that you enjoy these reports.

The publication also offers an extensive review of euroPCR 2013, which was held in Paris in May. This review includes two CEO interviews from Biosensors and JenaValve, in which we find out more about their products and their activities at the show.

We hope that you enjoy the latest edition of Treatment Strategies – Interventional Cardiology and the papers that have been included. Interventional cardiology is one of the most dynamic areas of medicine, in which new discoveries and developments are constantly being made. We hope that the publication gives an in-depth overview of some of the most important and interesting topics within the field today.

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euroPCR 2013 Course Review

21 - 24 May 2013 - Paris

Annual Meeting of the European Association of Percutaneous Cardivascular Interventions (EAPCI) - Review

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Sara Taheri, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the congress. We then follow with papers and reviews which give a brief insight from a number of sessions highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

euroPCR is the official congress of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), which aims to develop a platform for the exchange of clinical and scientific research and ideas, as well as reduce the burden of cardiovascular disease. The main attendees of the congress are interventional surgeons, valve specialists, nurses and technicians, residents, industry researchers and analysists, and it aims to contribute to the advancement of education and information on new and existing technologies in the field of cardiovascular intervention. The congress takes a multidisciplinary approach, and believes that this will provide the opportunity to work towards a consensus in action towards improving patient outcomes.

In addition to the wealth of symposiums and plenary lectures, this year the show had a greater focus upon interactivity, with a number of sessions focusing upon sharing ideas and sparking debate. These included the Interactive Case Corner, where open discussions on clinical cases were held in a friendly environment, and Forum Romanum, where attendees were encouraged to share their clinical experiences with their peers. Moderated Poster Sessions were also a new addition to the programme this year, and offered attendees the opportunity to discuss the posters on show with their authors, in order to gain a more in-depth understanding of the research. Live demonstrations were also prominently featured this year at the show, and were used in sessions such as the Cardiovascular Innovation Pipeline sessions, where inventors and innovative companies introduce themselves and their latest technologies, as well as in the Tools and Techniques sessions, in which clinical innovations and technical challenges

euroPCR 2013 in Paris.

encountered in daily practise were explored.

This year, the congress had over 12,000 attendees, up 5.54% from 2012. With 120 exhibitors and 560 sessions, 2013's Meeting was the biggest show yet. Course Directors Jean Fajadet and William Wijns highlighted the progress which has been made in the field of interventional cardiology, and the importance of the euoPCR in furthering these developments. 'This Course illustrates how both the width and the depth of our practices have expanded over two decades. Initially intended as less invasive, more patient friendly procedures, our interventions are indeed offering improved quality of life to many patients.'

Increased interactivity was at the heart of the Meeting, and attendees were encouraged to participate as much as possible in order to get the most out of the event. As William Wijns explained, 'Today, with all the knowledge and experience that is available across the globe, nobody can claim to have all of the answers. This year, it is very much about mutual exchange of knowledge and know-how and … delegates … are the source of that exchange.' React@PCR allowed attendees to post questions and comments via smartphone to session chairs in order to feed debate. Additionally, the topics for The Great Debate were chosen through an audience poll, with the content being solely constructed from attendee questions. For Active Participants programmes also allowed delegates to become more involved in the event by offering the opportunity to partake in informal discussions with euroPCR founder Jean Marco, amongst other world-renowned experts.

Another key focus of the conference was live case demonstrations. The opening session featured a case demonstration for each of the four tracks of euroPCR: coronary interventions, peripheral interventions, interventions for structural heart disease and interventions for hypertension and heart failure, and this emphasis was continued throughout the four day event.

This year, euroPCR returned to the Paris, the capital city of France. Paris is one of the world's leading business and cultural centres, which influences the world of politics, education, entertainment and science among others. Indeed, it has one of the highest GDP's in the world and is considered one of the best cities in the world for innovation.

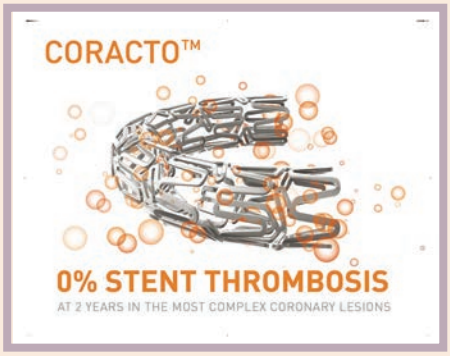
The city is seeped in rich history, and the city was the centre stage for the French revolution, in which the people of Paris rejected the divine right of monarchs in France. The city is also home to a wealth of Gothic architecture, including the Notre Dame cathedral and the church of Sainte-Chapelle. The Arc de Triomphe and the Eiffel Tower, which was originally built as a temporary structure for the 1889 Universal Exposition but was never dismantled, are also important architectural landmarks and key tourist attractions. Indeed, Paris is one of the world's leading tourist destinations, receiving around 28 million vistors per year. The city's monuments and museums are among the key tourist attractions including the Louvre which, with over 8 million visitors a year is the world's most visited art museum. Other notable museums include the Musée de Cluny and Musée d'Orsay.

Paris is also famous for its culture. Theatre has traditionaly occupied a place in Parisian culture, with some of the citiy's major theatres including Bobino, Théâtre Mogador and the Théâtre de la Gaîté-Montparnasse. Some theatres also double a concert halls. The city is also home to several yearly festivals, including Rock en Seine. French cinema is also an important industry in Paris, and it is home to a very large network of small cinemas. Paris also has an impressive culinary reputation, and over 9,000 restaurants exist in the capital. The country is famous for its cheeses, wines and patisseries. Additionally, Paris is famous for its sports, with the final stage of the Tour de France finishing on the Champs-Elysées, and the French Open Tennis tournament, which is held at the Roland Garros National tennis Centre near the Bois de Boulogne.

The conference was held in Le Palais des Congrès de Paris, a leading international venue for conferences, corporate events and shows, situated in the core of Paris' business activities. Boasting 41,000 square metres and four ampitheatres, as well as a hi-tech infrastructure, it is the perfect venue for this year's euroPCR conference.

CORACTO® for the Treatment Complex Cardiovascular Chronic Total Occlusions

Founded in 2007, Alvimedica is a company devoted to developing minimally-invasive medical technologies for medical professionals looking for the next level of innovation in the operating room. Alvimedica manufactures products using cutting-edge design and techniques to deliver world-class, quality products and services. With its world-class technology, Alvimedica manufactures coronary stents, balloon catheters and diagnostic and guiding catheters - all with the CE mark. Alvimedica's commitment to improving surgical procedures through innovative products is driven by their sincere care for patients' quality of life and goal to positively impact clinical outcomes. With an R&D facility based in Assen, the Netherlands, the company's current projects include renal and cranial intravascular stents amongst others. The company is also working on bioabsorbable stents, which are completely absorbed into the body.



As part of its wide product range, Alvimedica proudly presented the sirolimus (rapamycin)-eluting coronary stent CORACTO®, which has demonstrated excellent results in the PCI treatment of patients with complex cardiovascular Chronic Total Occlusions (CTO).*

The features of CORACTO® and the outstanding results achieved at 2 years with CORACTO® in a population composed at 100% of complex CTO cases were showcased during the presentation event.

Key features of CORACTO®; Lowest crossing profile 0,039; Only 4 µm of 100% biodegradable polymer thickness; Fast and Complete 100% drug (sirolimus) release in 10-12 weeks*; Late stent thrombosis was 0% at 24 months follow-up of patients with complex CTO lesions*; Overall significant relative risk reduction of restenosis with CORACTO® was 71% (p<0,0001) after 6 months. *

During the Alvimedica symposium, lectures were held on the latest research developments. Prof. dr. G. Sianos illustrated his extensive experience with CORACTO® by presenting 4 complex CTO cases. The presentation once again highlighted the clinical performance of CORACTO® proven by the significant results of our randomised multicentre CORACTO® trial.* Lively discussions were held and a very positive appreciation was expressed on the achievements and the performance of CORACTO®.

Ref: * Reifart N. *et al*. Eurointervention 6 (2010); 356-360

Medtronic CoreValve® System Gains First Approval for Transcatheter Valve-In-Valve Procedures

Replacing Degenerated Surgical Valves with CoreValve Results in Significant Haemodynamic Improvements for Patients

Medtronic, Inc. announced that it has received Conformité Européenne (CE) Mark for valve-in-valve (VIV) procedures using the CoreValve® and CoreValve® Evolut™ transcatheter aortic valve implantation (TAVI) systems in degenerated bioprosthetic surgical aortic valves. This is the first ever regulatory approval for VIV procedures, which provide a minimally invasive treatment option for patients whose surgical aortic valves have degenerated, and who are at extreme or high risk for surgery and would otherwise go untreated.

Results from the largest global VIV registry, published in *Circulation* in November (Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves: Results from the Global Valve-in-Valve Registry), showed the VIV approach resulted in considerable haemodynamic (blood flow) improvements, including a decrease in valve gradients (blood flow resistance). Positive procedural outcomes were maintained at 1-year follow-up (with 89 percent survival at one year), which was comparable with other non-VIV TAVI studies.[1]

"While surgical valves provide effective therapy for many patients, the replacement valves eventually degenerate over time, so valve-in-valve has become a topic of great clinical interest due to the needs of these patients," said Ran Kornowski, M.D., Chair of Cardiology at Rabin Medical Center and Tel-Aviv University in Tel-Aviv, Israel, and senior author of the Global Valve-in-Valve Registry. "European approval of the CoreValve® procedure is a very important advance in the treatment of severe aortic stenosis and enables an entirely new group of patients to benefit from this transcatheter valve."

The Global VIV registry evaluated the safety and efficacy of the VIV approach in 202 patients at 38 sites in Europe, North America, Australia, New Zealand and the Middle East,[1] with 124 patients receiving the CoreValve System. In the study, the CoreValve System demonstrated superior haemodynamic outcomes and high procedural success rates (96.8 percent).[1]

The valve-in-valve procedure, in which the CoreValve® System is placed inside the degenerated surgical aortic valve through a low-profile, 18Fr delivery catheter, is approved for use with all four CoreValve® sizes (23mm, 26mm, 29mm and 31mm), as well as three delivery approaches (transfemoral, subclavian and direct aortic access).

"We are pleased to now extend this safe and less-invasive, valve-in-valve procedure. This approach allows patients to avoid a second open-heart surgery to replace a failing surgical valve, which was originally performed to replace their own diseased valve." said John Liddicoat, M.D., Senior Vice President, Medtronic, and President of the Medtronic Structural Heart Business. "Furthermore, the impressive improvements in haemodynamic performance, due to CoreValve's supra-annular design, are showcased in the results of these valve-in-valve procedures."

Each year, approximately 200,000 people worldwide receive surgical aortic valves,[2] which typically last 15 years or more. When the surgical valves degenerate due to the aging process, patients require another valve replacement. However, some patients are not eligible for a second open-heart surgery, and the transcatheter VIV procedure may now provide them with a new treatment option.

The Medtronic CoreValve® System is available in the United States for investigational use only. In the Medtronic CoreValve® U.S. Expanded Use Study, the U.S. Food and Drug Administration has approved investigational VIV procedures in extreme-risk patients (part of the pivotal trial evaluating the CoreValve® System in the U.S.).

In collaboration with leading clinicians, researchers and scientists, Medtronic offers the broadest range of innovative medical technology for the interventional and surgical treatment of cardiovascular disease and cardiac arrhythmias. The company strives to offer products and services that deliver clinical and economic value to healthcare consumers and providers worldwide.

1 Dvir, D. *et al.* "Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves: Results From the Global Valve-in-Valve Registry." Circulation. October 2012
2 Brown JM *et al.*; The Journal of Thoracic and Cardiovascular Surger; V.137; No.1; 1/09; p82

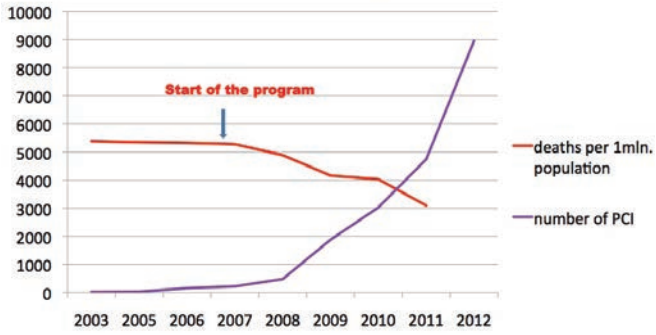
Development of Interventional Cardiology in Kazakhstan

Kazakhstan, officially the Republic of Kazakhstan, has the population of 17.000.000 people and territory 2,719,500 sq km, and is situated in the Central Asia. Thanks to the President of Kazakhstan Nursultan Nazarbayev's public policy for the integrated development of medicine in recent years, the industry has been developing rapidly.

In 2002, coronary angiography and PCI was performed in only 2 clinics in the country. The Government adopted a national program for the development of cardiology, interventional cardiology and cardiac surgery for 2007-2009, due to high morbidity and mortality from cardiovascular diseases. This programme has led to all major cities developing cardiac surgery centres and cath labs. In 2012, Kazakhstan had opened 40 catheterisation laboratories and coronary angiography was performed in 27739 patients, 58.4% of them for acute coronary syndromes. PCI was performed in 8958 patients, and 67.1% of them performed for acute coronary syndromes. Mortality from cardiovascular disease had decreased from 539 (for 100.000 населения) in 2003 to 309,1 in 2011.

In 2013, the Society of Interventional Cardiology of Kazakhstan for the first time had an opportunity to take part in the international arena - EuroPCR 2013. Only 9 countries, including Kazakhstan, have booths to present their society and national congresses.

Decline in deaths from cardiovascular disease in relation to the State program for developing Cardiology, Cardiac surgery and Interventional Cardiology 2007-2009



The scientific program of the Kazakhstan society consisted of three sessions:

- May 22 - Joint Session with Georgia "Acute myocardial infarction and multivessel disease. How should I treat?"
- May 23 - Session "Kazakhstan shares its most educational clinical cases."
- May 24 - Session: "Left main dissection during PCI."

Simeks Focus on Manufacturing and Developing Peripheral Interventional Products

Medical device company Simeks focuses on manufacturing and developing coronary and peripheral interventional products. The company started their activities in 2010 by manufacturing interventional cardiology products; PTCA balloon catheters, coronary stents and drug eluting stents; which have been commercially available in market since then. Simeks' innovative product portfolio has now been extended to also include interventional radiology products; PTA balloon catheters and peripheral stents for treatment of carotid, renal, iliac, SFA and BTK arterial disease. Furthermore, the company has initiated various projects focused on the development of innovative vascular technologies and devices as part of our mission.

Simeks is committed to developing interventional technologies and products for cardiovascular, peripheral vascular and neurovascular treatments. Simeks company policy is to work closely with physicians, study their needs and to meet their requirements.

Simeks will continue to focus on the production of disposable medical products. Indeed, they have started production on minimally invasive cardiology and radiology products such as balloon catheters and stent delivery systems, and nephrology products such as haemodialysis bloodline sets.

The company's main goal is to advance and diversify their products, and to push the boundaries of technology.

QualiMed GmbH Receive CE Approval for its Line of Peripheral Balloons for the Treatment of Peripheral Vascular Obstructions

The interventional peripheral market sector has been experiencing rapid growth in technological advancements as well as significant consolidation over the last 3 to 5 years. The mid cap consolidation is primarily the result of acquisitions by large multinationals looking to establish an entry into the peripheral markets, broaden their product portfolio, and expand their sales reach and expertise in this area.

Companies such as EV3 acquired by Covidien, Invatec by Medtronic, Atrium by Marquette, Clear Stream by Bard, as well as a number of others has left a void of peripheral vascular interventional technology companies in the mid cap market. Furthermore, the consolidation of the mid cap distribution channel into that of the acquirers has left an excess channel capacity of well-trained distributors that have significant relationship with existing clinicians, administrators, and support staff in the geographies they represent.

Qualimed believes the availability of its current line of peripheral stents, coupled with its new line of innovative PTA Balloons in .035, .018, and .014 guide wire compatibility up to 280 mm lengths that minimise inflation and deflation time as well as a line of AV Shunt balloons in .035 and .018 guider compatibility with high pressure to 22 RBP allows the company to provide one of the largest independent balloon production and product offerings globally. This advanced balloon technology is available for sale through Qualimeds OEM, Private Label, and Own Branded sales channels.

This new offering, coupled with the companies currently approved line of peripheral vascular stents, aspiration devices, as well as future peripheral technologies that will be launched in the first half of 2013, uniquely position Qualimed to take advantage of this channel opportunity and execute on its growth plans for in the Asian-Pacific and Middle East regions.

Eric Mangiardi, an Investor in Qualimed commented: "We are very pleased to announce this significant milestone and to further execute our strategy to expand our product offering and technological advancements in the areas of interventional cardiology, peripheral vascular, and non-vascular areas. This new balloon technology will be the platform the company utilises to complete its illuminating balloon platform that allows visibility under x-ray without the use of contrast media and its entrance into the drug eluting balloon space."

QualiMed was founded in 1997 in Winsen, Germany, where it develops, manufactures, and sells implantable medical devices in the cardiology, peripheral vascular, and non-vascular areas. The innovations are focused in the areas of Biodegradable Products, Drug Device Combination Technologies, Catheter, and Mechanical implant areas. Originally founded as an OEM, the company's products are now sold in over 50 countries worldwide through its OEM, Private Label, and Own Brand Networks.

For more information, please visit www.qualimed.de

Biodegradable Drug-eluting Stent: BUMA™ in China

SINOMED is an international company specialising in research, and the manufacture and production of interventional medical devices in the field of cardiology. They will soon be expanding their product line to include other fields of interventional devices, such as intracranial and peripheral stenting systems. Striving to produce cutting edge products they have collaborated internationally with AlchiMedics, a French technology company. Combining their own expertise and eG™ coating technology, SINOMED have introduced BUMA™ as the first domestic drug-eluting stent (DES), an original innovation.

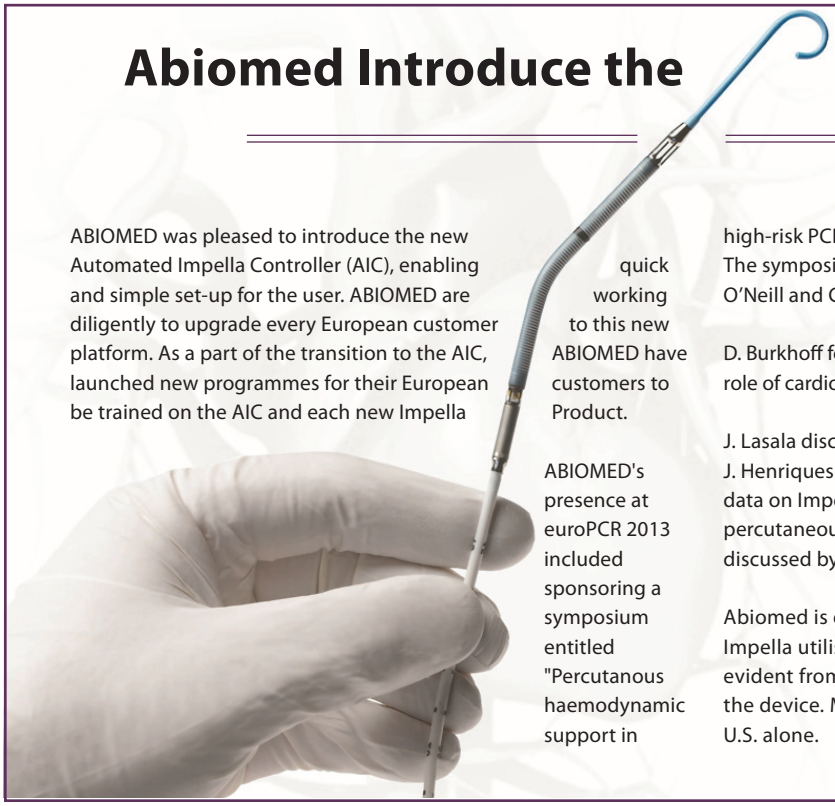
The patented eG™ technology creates a uniform nanometre scale coating with biodegradable coating technology, which lays a solid technical foundation for outstanding clinical performance.

On Wednesday 22 May, Sinomed gave a presentation entitled, 'First-in-man & novel DES and scaffolds', chaired by S. Verheye and R. Waksman. This presentation explored the The DEMONSTR8 study, which looked at the randomised comparison between a novel DES and a BMS to assess neointimal coverage by OCT evaluation. M. Webster also discussed the final 6-month results of the DIRECT (Direct-on-a-wire implantation of Rapamycin-eluting stent with bioabsorbable Carrier Technology) first-in-man study. Following these two speakers, J. Orminston explored the clinical, angiographic and IVUS outcomes of the NG PROMUS clinical trial evaluating the novel Promus PREMIER stent, and T. Kiviniemi talked in more detail about the HATTRICKOCT trial. J. Hou then went on to talk about a prospective randomised controlled 3- and 12-month OCT study to evaluate the endothelial healing between a novel sirolimus-eluting stent BuMA and an everolimus-eluting stent XIENCE V.

A wealth of other speakers also made this presentation particularly notable, including R. J. Gil who imparted his knowledge about the first-in-man study of the dedicated bifurcation sirolimus-eluting stent BiOSS Lim registry, E. Barbato's informative talk about the clinical evaluation of new drug-eluting coronary stent system in the treatment of patients with coronary artery disease, and D. Dudek's discussion of POLAR ACS, the multicentre registry in Poland. The pilot Absorb-STEMI registry and the first results of the EXPAND study were also discussed by P. Widimsky and R. J. Van Geuns respectively. Audience discussion and participation was encouraged at all stages of the presentation, and produced some interesting results.

SINOMED is engaged in various international projects to reach advanced technology and quality standards. SINOMED is stretching its sales and research opportunities in Europe from 2013. By conducting a multicentre RCT in Europe, SINOMED wishes to confirm its product efficacy and long-term safety.

Abiomed Introduce the Impella CP™



ABIOMED was pleased to introduce the new Automated Impella Controller (AIC), enabling quick and simple set-up for the user. ABIOMED are working diligently to upgrade every European customer to this new platform. As a part of the transition to the AIC, ABIOMED have launched new programmes for their European customers to be trained on the AIC and each new Impella Product.

ABIOMED's presence at euroPCR 2013 included sponsoring a symposium entitled "Percutanous haemodynamic support in high-risk PCI and cardiogenic shock: your safety net in the cath lab". The symposium was held on Tuesday 21 May, and was chaired by W. O'Neill and C. Spaulding.

D. Burkhoff focused on the science of haemodynamic support and the role of cardiovascular support in high-risk PCI and cardiogenic shock.

J. Lasala discussed the PROTECT II: 90-day results in high-risk PCI. J. Henriques presentation was concerned with the Current clinical data on Impella in cardiogenic shock. Finally, experiences with percutaneous haemodynamic support in cardiogenic shock was discussed by P. Hunziker.

Abiomed is enjoying a strong demand for its Impella products. Impella utilisation continues to grow at a healthy pace, as is evident from the increasing number of patients being treated with the device. More than 10,000 patients have been treated in the U.S. alone.

Natec Medical Ltd Receives 510(k) Clearance for its PTCA RX Dilatation Catheter

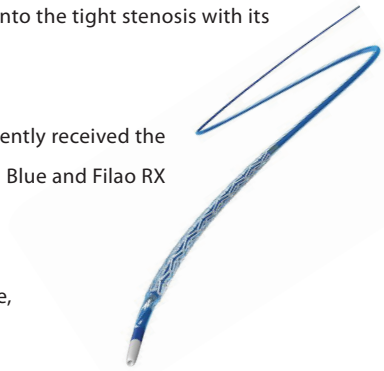
Natec Medical has announced that it has received US Food & Drug Administration 510(k) clearance to market its Tamarin Blue®.

A leader in coronary stent delivery systems, Tamarin Blue® is the ultimate platform for all current & future stent and drug-coated technologies.

Tamarin Blue® features exceptional trackability and pushability, and a unique crossability into the tight stenosis with its tapered tip.

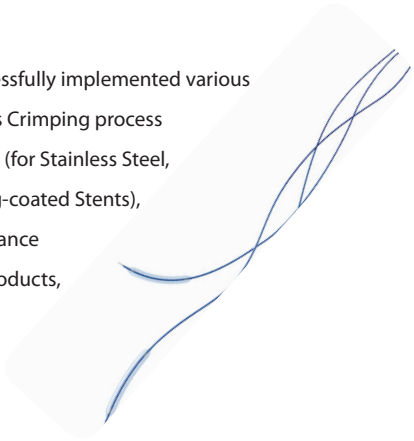
Natec Medical Ltd also recently received the Licence to market Tamarin Blue and Filao RX in Canada.

With 25 years of experience,



Natec Medical is your Global Partner for High Tech Medical Devices manufacturing and distribution with a full line of proven Coronary and Peripheral balloons catheters, and recently Urology and Gastrology balloons.

Natec Medical has successfully implemented various levels of services such as Crimping process improvement validation (for Stainless Steel, Bioabsorbable and Drug-coated Stents), Benchtesting & Performance reports, personalised products, Sterilisation and Regulatory filing.



Paieon Inc. Demonstrate C-THV for TAVI

At euroPCR 2013, Paieon Inc., a medical imaging company pioneering in the field of real-time imaging for cardiac navigation, gave live demonstrations of TAVI cases using the C-THV system from Clinique Pasteur, Toulouse, France.

Using a live recording from the Rabin Medical Center, Israel, A. Assali demonstrated the TAVI valve-in-valve case, with the intention of assisting the audience in understanding the occurrence, mechanism of action and impact of the post implant aortic regurgitation and how a self-expandable supra-annular valve can mitigate it.

Paieon's products maximise the use of images and data obtained from standard vascular angiography equipment, helping interventional cardiologists and radiologists optimise diagnosis, treatment and outcome. They offer two innovative imaging workstations that are designed to assist in all phases of the following procedures:

• C-THV for TAVI - a real-time angiography-based system, is designed to assist in Trans-catheter Aortic Valve Implantation/ Replacement (TAVI/TAVR). C-THV assists in all phases of the procedure from finding the optimal perpendicular projection through real-time positioning to post- deployment analysis. During delivery, while the physician navigates the device to its pre-inflation position, C-THV tracks both the aortic annulus and the device, in real time. This enables the physician to navigate the valve accurately to its optimal location.

• IC-PRO for PCI - a real-time imaging workstation designed to optimise performance and increase accuracy during challenging PCI procedures. The IC-PRO supports the physician in all stages of the PCI procedure, from diagnosis by 3D QCA through procedure planning, to the actual treatment using real-time navigation and post-deployment stent analysis.

• AF - presenting innovative technologies for Atrial Fibrillation procedures: 3D modeling over live fluoroscopy, CT / MRI image integration, circular ablation catheter positioning, balloon ablation and point ablation for re-do cases.

Tryton Medical Announces Successful Live Case Transmission With New Tryton Side Branch SHORT Stent

Data and Presentations at euroPCR Highlight Consistently Positive Clinical Results

Tryton Medical, Inc., the leading developer of stents designed to treat bifurcation lesions, transmitted a live satellite feed of a clinical case using the new Tryton Side Branch SHORT Stent to an audience of several hundred interventional cardiologists at uroPCR. The live procedure was performed 22nd May from the Erasmus Medical Center in Rotterdam, the Netherlands by Nicolas Van Mieghem, M.D. "This case was a real-world example of the benefits a dedicated bifurcated stent can offer in daily practice when treating a challenging lesion," said Maceij Lesiak, M.D., co-chairman of the session on "Complex Bifurcation Stenting".

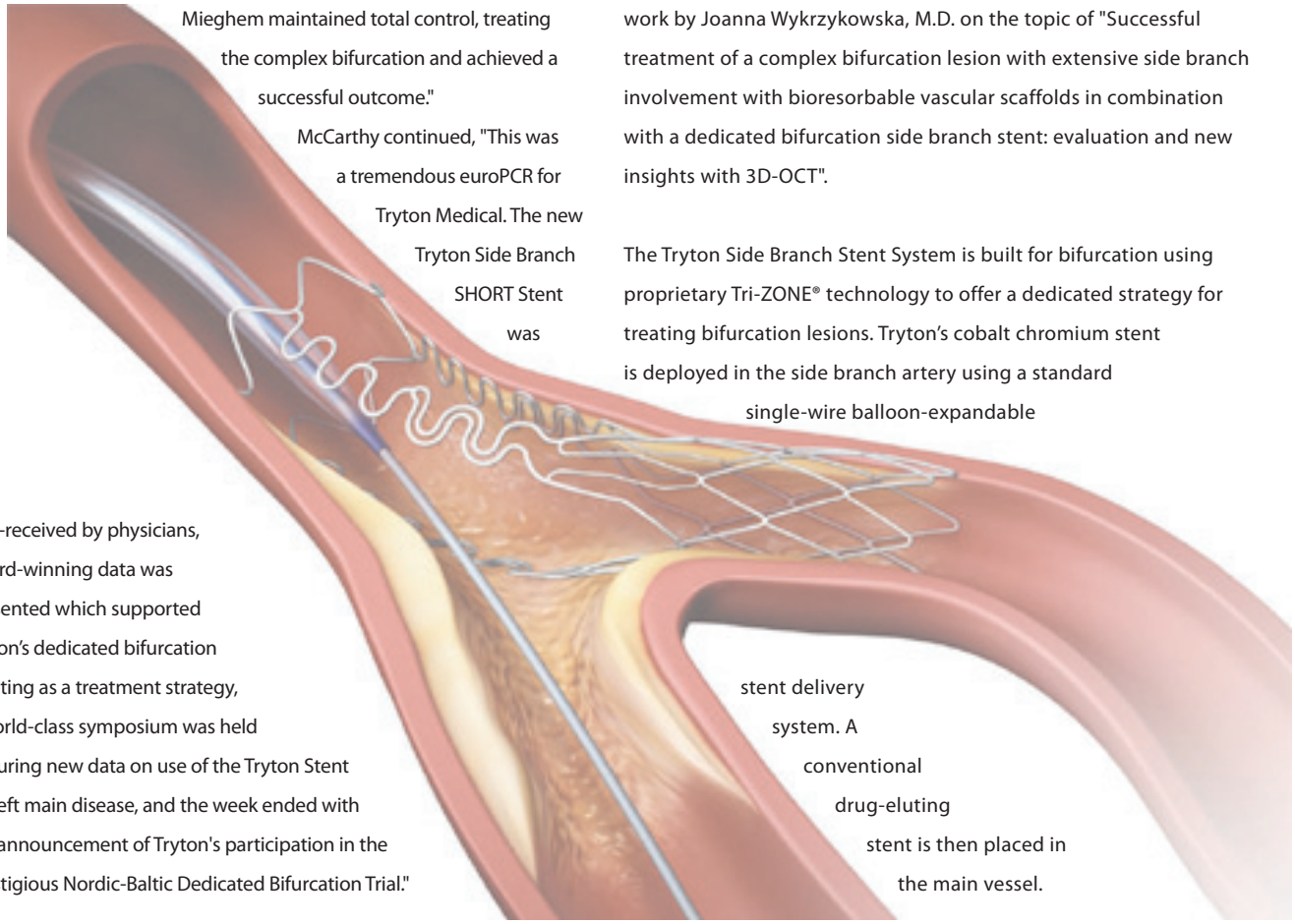
"The live case reinforced that the Tryton Side Branch Stent enables physicians to treat complex bifurcated coronary disease in a straightforward manner," said Shawn P. McCarthy, president and CEO of Tryton Medical. "Panelists commented that Dr. Van Mieghem maintained total control, treating the complex bifurcation and achieved a successful outcome."

McCarthy continued, "This was a tremendous euroPCR for Tryton Medical. The new Tryton Side Branch SHORT Stent was well-received by physicians, award-winning data was presented which supported Tryton's dedicated bifurcation stenting as a treatment strategy, a world-class symposium was held featuring new data on use of the Tryton Stent for left main disease, and the week ended with the announcement of Tryton's participation in the prestigious Nordic-Baltic Dedicated Bifurcation Trial."

Further presentations confirmed consistent clinical results with the Tryton Side Branch Stent:

• A clinical symposium featured a comprehensive overview of Tryton Side Branch Stent clinical evidence, and highlighted the Tryton IDE study as a landmark study in the treatment of coronary bifurcation disease.
• Robert-Jans van Geuns, M.D. presented the one month clinical follow-up data of 30 patients in the prospective clinical 'first in human' registry treating patients with left main disease, and concluded that "the newly CE-marked Tryton Side Branch SHORT Stent will broaden the treatment options in patients with a short main branch landing zone."
• A clinical case using a Tryton Side Branch Stent was awarded the "Best Clinical Case of euroPCR 2013". The award was presented for work by Joanna Wykrzykowska, M.D. on the topic of "Successful treatment of a complex bifurcation lesion with extensive side branch involvement with bioresorbable vascular scaffolds in combination with a dedicated bifurcation side branch stent: evaluation and new insights with 3D-OCT".

The Tryton Side Branch Stent System is built for bifurcation using proprietary Tri-ZONE® technology to offer a dedicated strategy for treating bifurcation lesions. Tryton's cobalt chromium stent is deployed in the side branch artery using a standard single-wire balloon-expandable stent delivery system. A conventional drug-eluting stent is then placed in the main vessel.



For more information, please visit www.trytonmedical.com

St. Jude Medical EnligHTNment Study Highlighted at euroPCR During Trials That May Change Clinical Practice Session

St. Jude Medical, Inc., a global medical device company, announced the start of its landmark EnligHTNment clinical study. This is the largest randomised, prospective trial to determine whether renal denervation and medication offers additional health benefits beyond lowering blood pressure in patients with uncontrolled hypertension. The EnligHTNment study will evaluate the EnligHTN™ Multi-Electrode Renal Denervation System and its ability to reduce the risk of major cardiovascular events such as heart attack, stroke, heart failure and cardiovascular death.

Prior to the EnligHTNment trial, the majority of renal denervation studies have only tested the safety and efficacy of this technology in patients with drug-resistant hypertension, which is defined as systolic blood pressure above 160 mmHg, despite taking three or more anti-hypertensive medications including a diuretic.

"The EnligHTNment trial will provide a key insight into whether renal denervation therapy can reduce common cardiovascular complications of high blood pressure that often leave patients disabled or, in some cases, can even be fatal," said Professor Thomas Lüscher, Chairman, Cardiology and Cardiovascular Center at the University Hospital in Zurich, Switzerland, a principal investigator for the trial. "Learning more about renal denervation's impact on major cardiovascular diseases will provide critical information on the health effects and potential benefits of the therapy in patients who currently don't have an adequate treatment option."

Renal denervation represents an important area of research in the management of hypertension for the estimated one billion people globally who live with this life-threatening condition. Hypertension occurs when blood pressure in the arteries is elevated, requiring the heart to work harder than normal to circulate blood through the body.

The EnligHTNment study is a prospective, randomised, controlled study of approximately 4,000 patients with a systolic blood pressure greater than 160 mmHg. Patients enrolled around the world at up to 150 sites will be randomised to medical therapy plus renal denervation or medical therapy alone. All patients will be followed for five years under an event-driven trial design. Primary endpoints for the study include major cardiovascular events such as heart attack, stroke, heart failure with hospitalisation and cardiovascular death. Secondary endpoints include the reduction of in-office and ambulatory blood pressure and changes in renal function.

Renal denervation therapy in the EnligHTNment study will use the EnligHTN Renal Denervation System. Prior studies of this system have demonstrated that patients with drug-resistant hypertension had a safe, rapid and sustained drop in blood pressure. After thirty days, systolic blood pressure was rapidly reduced by an average of 28 mmHg. At six months, it remained stable with an average reduction of 26 mmHg. It is important to note that the risk of cardiovascular death is cut in half with every 20 mmHg decrease in systolic blood pressure.

"St. Jude Medical is pleased to start the landmark EnligHTNment trial to learn more about the long-term effects of uncontrolled hypertension and to see how we can better assists physicians in treating at-risk patients," said Frank J. Callaghan, President of the St. Jude Medical Cardiovascular and Ablation Technologies Division. "We are committed to being a leader in clinical research and have put in place a team of highly respected thought leaders to run this trial. We look forward to working with the steering committee and study investigators in the coming years."

The EnligHTN system is a multi-electrode ablation technology that features a unique, non-occlusive basket design that delivers a predictable pattern of four evenly-spaced ablations with each catheter placement. This allows for continuous blood flow to the kidney during the procedure. Compared to single-electrode ablation systems, the multi-electrode EnligHTN system has the potential to improve consistency and save time, which may result in improved workflow and cost efficiencies.

The EnligHTN technology includes a guiding catheter, ablation catheter and ablation generator. The generator uses a proprietary, temperature-controlled algorithm to produce effective lesions. Additionally, minimal catheter repositioning may result in a reduction of contrast and fluoroscopic (X-ray) exposure.

In 2012, the EnligHTN Renal Denervation System earned European CE Mark approval and was launched in several markets. It is not yet approved for use in the U.S.

For more information please visit www.sjm.com

ZOLL Medical Corporation Showcase Lifevest® and AutoPulse® at euroPCR

ZOLL Medical Corporation, a manufacturer of medical devices and related software solutions, showcased the LifeVest® Wearable Defibrillator and the AutoPulse® at euroPCR 2013.

Heart failure affects an estimated 15 million people in Europe. Patients with heart failure are at high risk of sudden cardiac arrest (SCA), especially immediately following an acute event such as hospitalisation for heart failure decompensation or myocardial infarction.

The LifeVest® is worn by patients at risk for SCA, including patients with cardiomyopathy or congestive heart failure that places them at particular risk. The LifeVest® provides protection during their changing condition and while permanent SCA risk has not been established, allowing a patient's physician time to assess his or her long-term arrhythmic risk and make appropriate plans. It is lightweight and easy to wear, and continuously monitors the patient's heart. If a life-threatening heart rhythm is detected, the device delivers a treatment shock to restore normal heart rhythm.

The LifeVest® is used for a wide range of conditions or situations, including following a heart attack, and before or after bypass surgery or stent placement, as well as cardiomyopathy or congestive heart failure that places patients at particular risk.

The AutoPulse®

AutoPulse maintains perfusion, allows vascular access, and supports end organ perfusion. The AutoPulse® Non-invasive Cardiac Support Pump can also run codes for as long as necessary while professionals work to get the patient warm. And, as a recent case in London showed, cold and comatose need not mean warm and dead—even after three hours if there is sufficient perfusion to maintain major organ viability.[1]

The AutoPulse delivers a complete thoracic compression, wrapping a band around the chest. This allows the compression force to squeeze the entire chest cavity rather than a point on the sternum, driving perfusion to near-normal levels while maintaining a safe compression.[2] AutoPulse is the only mechanical CPR system to show significant clinical benefits in comparative human trials. Multiple comparative studies have demonstrated that vital signs improve in humans because the AutoPulse drives superior blood flow. And AutoPulse consistently shows improved ROSC (return of spontaneous circulation) rates compared to sternal compressions. By distributing the compression force over the thoracic cavity, the pressure at any one point on the chest is about one-tenth that experienced at the sternum with a manual compression. Studies show that distributing the force over a wide area drives perfusion to near-normal levels while maintaining safe compression forces well below the threshold for injury. Although infrequent, there are times when mechanical CPR is needed during in-hospital cardiac arrest. When that need arises, the AutoPulse is sure, smart, and safe.

References

1. Daily Mirror, Jan. 14, 2011.
2. Halperin HR, *et al*. J Am Coll Cardiol. 2004;44(11):2214–20.

Learn more at www.zoll.com

Benefits of the Symetis ACURATE TA™

Post-Market Registry Data Confirm High Success Rate, Superior Safety Profile and Patient Benefit with the Symetis ACURATE TA™

At euroPCR 2013 Symetis' presented the 30 Day outcomes of their SAVI (Symetis Acurate Transapical Valve Implantation) Registry. They also arranged a Tool and Technique Session, where a LIVE ACURATE TA case from Hamburg and a LIVE ACURATE TF case from Bad Nauheim were showcased. This was the first time that the company had presented their new transfemoral technology in Europe.

The Symetis ACURATE TA™ valve is at the forefront of second-generation Tavi. The self-seating, self-sealing valve is designed to ensure a simple and intuitive implantation technique with tactile feedback and minimal paravalvular (pv) leak. Now, the short-term clinical benefit and safety of the ACURATE TA™ have been proven in "real world" usage by data from the Symetis ACURATE TA™ valve implantation (savi) Registry.

Savi is comprised of the first 250 implanted patients following market approval of the ACURATE TA™ and represents the results of everyday clinical use of the device. Real-world use of data are key to prove whether a Tavi device lives up to its pre-market data in a highly selected population.

The savi Registry followed 250 patients who received ACURATE TA™ between November 2011 and November 2012 at 17 centres in Germany, Switzerland, Argentina and Italy. It collected data at 30 days and at 1 year after implant. 'The discharge/30-day follow up data from the full 250-patient population in SAVI were presented at the 2013 PCR Congress in Paris and these results confirmed high procedure success rates, superior safety profile and patient benefit after treatment with the ACURATE TA™.'

ACURATE TA ™ was designed to deliver a unique two-step implantation technique facilitating simple intuitive positioning with tactile feedback and a favourable learning curve. In the savi registry the design delivered on these promises. In the SAVI Registry, ACURATE TA ™ reinforced its superior safety profile as shown throughout First-In-Man trials through product approval. Post-market use echoes these same results.

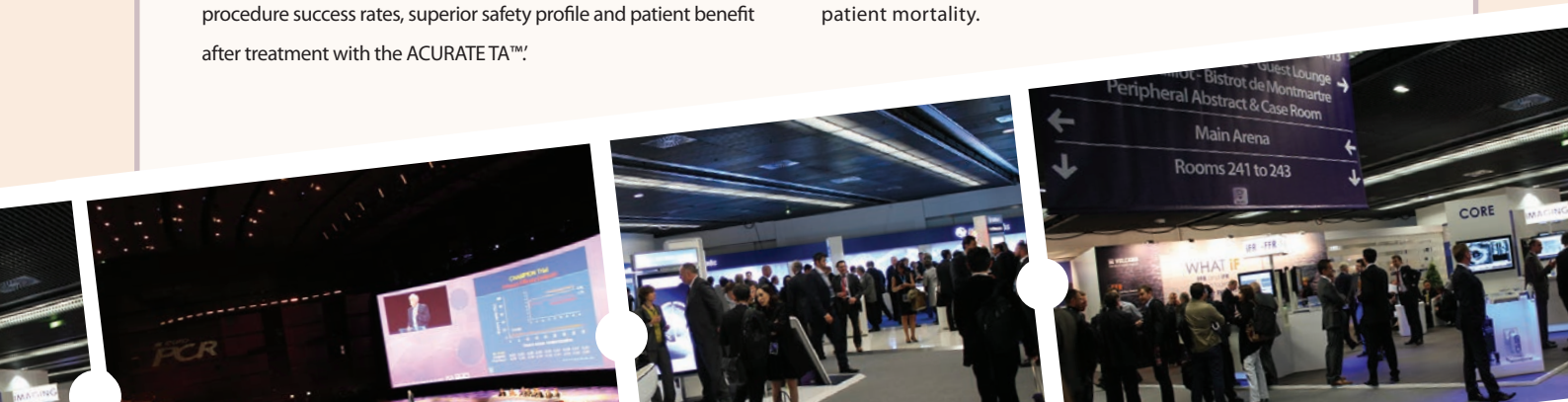
Low Mortality at 30 Days

With its low rate of PV leak and exemplary ease of use, the low mortality rate after treatment with the ACURATE TA ™ were expected as confirmed in SAVI . Again, the device delivered on its promises: Mortality rates at 30 days, 6.8%, were lower than comparable populations in other registries and half of those in SENTINEL. This is highly relevant as the SAVI Registry shows rates from use in actual clinical practice, not from clinical studies in highly controlled conditions.

The Future

The implant and follow-up data from the SAVI Registry demonstrate that ACURATE TA ™ has lived up to the high expectations of ease of use, compelling clinical results with excellent safety and minimal leak.

Data at one year post-implant are being collected will be presented in early 2014. These data will show whether the innovative valve design will translate into improved long-term patient mortality.



COMBO Dual Therapy Stent™

OrbusNeich, a global company that designs, develops, manufactures and markets innovative medical devices for the treatment of vascular diseases, have announced clinical results for the COMBO Dual Therapy Stent during euroPCR 2013.

Results from REMEDEE (Randomized Evaluation of an abluMinal sirolimus coatED bio-Engineered stEnt), a randomised clinical trial of the COMBO Dual Therapy Stent versus a drug eluting stent (DES) were presented by Michael Haude, M.D., of Medical Clinic at the Lukaskrankenhaus in Neuss, Germany, during a symposium titled "Clinical value of anti-restenosis and pro-healing COMBO Stent".

The symposium, which was chaired by Prof. Haude and Sigmund Silber, M.D., Ph.D., of the Heart Center at the Isar, Munich, Germany, featured other case-based presentations that explored the differences between monotherapy DES and the COMBO Dual Therapy Stent. Symposium presentations included:

- Where are we with monotherapy DES? – Renu Virmani, M.D., of the CVPath Institute Inc. in Gaithersburg, Md.
- What are the true unmet needs? With case-based discussions – Roxana Mehran, M.D., Mount Sinai Medical Center, New York
- How do we design clinical studies beyond DES to show incremental benefits of dual therapy stents? – Robbert de Winter, M.D., Ph.D., of the Academic Medical Center, Amsterdam
- Where are we with the dual therapy stent? EGO-COMBO serial OCT assessment at nine and 24 months – Stephen W.L. Lee, M.D., Queen Mary Hospital, University of Hong Kong

Prof. Haude also presented "Sirolimus released from a bioresorbable polymer with endothelial cell capturing capability – REMEDEE" during the session "Bioresorbable versus durable polymer coatings for DES" on Friday, May 24 at the Palais des Congrès de Paris.

Other Scientific Sessions of note include:

Cardiovascular Innovation Pipeline Session: New stents, scaffolds and drug-eluting balloons.
- "OrbusNeich absorbable programme update." presented by Robert Cottone, vice president, intellectual property and technologies at OrbusNeich.
- Glimpse into the future: Preclinical studies of upcoming bioresorbable scaffolds.
- Robert Cottone also presented "Preclinical evaluation of drug-eluting CD34 antibody-coated bioresorbable scaffold made of a mixed polymer."
- Prof. Lee presented the following: "The first establishment of early healing profile, 9-month neointimal growth, and 24 months outcomes of the dual therapy endothelial progenitor cell capturing sirolimus-eluting stent as assessed by longitudinal sequential OCT: the EGO-COMBO study." (POS060M)

The COMBO Dual Therapy Stent 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. OrbusNeich's patented endothelial progenitor cell (EPC) capture technology promotes the accelerated natural healing of the vessel wall after the implantation of blood-contact devices such as stents. The technology consists of an antibody surface coating that captures EPCs circulating in the blood to the device to form an endothelial layer that provides protection against thrombosis and modulates restenosis.

For more information, visit
www.OrbusNeich.com

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Drug-Eluting Stent Utilising Bioabsorbable Drug Coating

Svelte Drug-Eluting Stent Utilising New Class of Bioabsorbable Drug Coating Attains 0% Clinically-Driven Events Through 12-Months in First-In-Man Study

At the late-breaking clinical trials session at euroPCR 2013, principal study investigator Dr. Mark Webster presented final 6 and 12-month results of the DIRECT first-in-man clinical study. No patients experienced clinically-driven TLR, TVR or MACE at 6-months, with results sustained through 12-months. It is believed the Svelte drug-eluting stent is the first ever to achieve 0% clinically-driven MACE through 12-months in a independent core-lab and DSMB adjudicated clinical study.

The Svelte drug-eluting stent utilises a new class of drug coating composed of a fully bioabsorbable, amino acid-based drug carrier mixed with the well-known anti-proliferative compound sirolimus. Amino acids occur naturally in the human body, providing a non-inflammatory and inherently bio-friendly drug-eluting platform. Unlike current-generation bioabsorbable coatings relying on hydrolysis for absorption, amino acids undergo gradual enzyme-based surface erosion with no bulk degradation or pH change activating an inflammatory response.

Invasive imaging at 6-months in the DIRECT study corroborates these clinical outcomes, revealing stent volume obstruction of 2.7%, approximately one-half that observed in current-generation, market-leading drug-eluting stent first-in-man studies. Optical coherence tomography revealed 98% of stent struts were fully covered, indicative of low inflammation and consistent vessel healing.

"We could not be more pleased with the outstanding and unmatched clinical outcomes observed in the DIRECT study," said Jack Darby, President and CEO of Svelte Medical Systems. "Having no clinically-driven events through 12-months is indicative of the bio-friendly nature of our drug coating, strength of our stent design and precision of our stent delivery system. We congratulate the study investigators, all of whom were first-time users of our IDS, for achieving these results in a challenging first-in-man patient population."

The DIRECT (Direct Implantation of Rapamycin-eluting stent with bio-Eroding Carrier Technology) study evaluated the Svelte drug-eluting stent mounted on a fixed-wire Integrated Delivery System (IDS) in 30 patients at 4 sites in New Zealand. Providing the lowest crimped stent profile on the market, the Svelte system facilitates use of the trans-radial approach and general downsizing of the access site, while allowing access to more difficult to cross and distal lesions. The IDS also incorporates proprietary Balloon Control Band (BCB) technology providing uniform and controlled balloon growth, even at high pressures, to safely perform direct stenting as well as high-pressure post-dilatation, thereby minimising procedure time and cost. This balloon technology will also be available with a rapid-exchange delivery system at commercial launch.

Approximately one-fifth of patients in the study were diabetic while one-half presented with Type B2 or C lesions. Procedural success was 100% and device success was 97%. Study results are published in the current issue of EuroIntervention, the official journal of euroPCR and the European Association of Percutaneous Cardiovascular Interventions (EAPCI).

The Svelte drug-eluting stent is currently under evaluation in the DIRECT II study. DIRECT II is a prospective, randomised, multi-centre clinical study comparing the safety and efficacy of the Svelte drug-eluting coronary stent mounted on the IDS to Medtronic's Resolute Integrity™ drug-eluting stent. The DIRECT II study will enroll 159 patients at up to 20 clinical sites in Europe and Brazil to assess the primary endpoints of Target Vessel Failure (TVF) and in-stent Late Loss (LL). All patients are scheduled to receive 6-month clinical and angiographic follow-up, with clinical follow-up through 5-years. A subset of patients will receive optical coherence tomography (OCT) imaging at 6-months.

For more information please visit www.sveltemedical.com

CEO Interview: Helmut Straubinger, JenaValve™ Technology

JenaValve™ Technology is a medical device company focused on developing transcatheter aortic valve implantation (TAVI) systems to treat patients suffering from aortic valve disease. The company's vision is to develop second-generation transcatheter aortic valve implantation (TAVI) systems for transapical and transfemoral implantation to address the needs of the cardiac surgeon and cardiologist, respectively.

At euroPCR 2013, *Treatment Strategies*' Sara Taheri speaks to JenaValve CEO Helmut Straubinger to find out more about the company's activities at the congress.

Q. Tell me a little bit about your role at JenaValve and JenaValve's activities?

A. I am the CEO of JenaValve, we are based in Munich. I started the company back in 2006 and built it up from zero to about 40 people now in the company. We are developing and already selling TAVI (Transcatheter Aortic Valve Implantation) devices so we are on the market for transapical TAVI device, and the transfemoral device will be on the market next year

Q. euroPCR is the most significant event in terms of interventional cardiology, so what is euroPCR to JenaValve?

A. PCR is one of the most important places where we can present our product, where we meet potential customers and doctors. It is where we can present our data, and we just presented our latest data of the post market trail here. We are a growing company, and we have started distributing our product in other countries as well so it's a good place to meet potential distributors and to make arrangements, that's basically why we are here.

Q. What is JenaValve's focus at euroPCR this week?

A. We are focusing basically on demonstrating our product and showing it to potential users, to potential cardiologists and also surgeons, the features of the product, the differentiation of our device compared to the other existing products on the market and to convince these people to use our product basically. And, as I said before, to also show our data, to be on the podiums and get the chance to present our company to the world of cardiologists and surgeons.

Q. What is the competitive advantage of the JenaValve?

A. Our device is a second-generation TAVI device; our differentiators are based on the customer's needs and also on the patient's needs.

So what is important here is paravalvular leakage, and this is given by the positioning feature that we have with our device, positioning and sealing so that it is perfectly placed in the annulus. This is the most important request on a second-generation TAVI product. We achieved this with our device, and started very early on with these new features so we have so called positioning feelers on this device; it can be repositioned and it can be retracted before it is placed in the annulus. You could say it's a kind of airbag, so you don't need it mostly, but it is good to have.

A second-generation product like ours has to have benefits compared to the first-generation, and we strongly believe that we have that with our device

Q. What is the message that you would like the visitors to take away from JenaValve and euroPCR 2013?

A. The message they should take away is that there is a new product on the market already with the transapical device, and that there will soon be a transfemoral product which has exactly the same features that we have proven with our transapical device, which is already in the market in European countries, and it will come next year.

And we had the chance here to demonstrate our product and to show it and how it works, to demonstrate the features of the device and that's basically what we need to do to get these people motivated and excited about our product. That is basically the purpose of why we are here.

CID SpA Sponsor Major Symposium on Cre8™

CID SpA Sponsored a major Symposium at euroPCR 2013 entitled 'Cre8™: Welcome back confidence in short dual antiplatelet therapy with effective DES', which discussed the clinical impact of the Demonstr8 striking data related to Cre8 polymer-free Drug Eluting Stent (DES).

The Chairpersons of the symposium were Dr. Mehran, Director of Interventional Cardiovascular Research and Clinical Trials at The Mount Sinai School of Medicine in New York (USA), and Dr. Pachinger, Chair of the Department of Cardiology at Medical University of Innsbruck (Austria).

Dr. Pachinger, briefly detailed Cre8™'s unique features and recent trial results, while Dr. Valgimigli showed, through the latest evidences, that 'longer than 6-8 months of DAPT duration with latest polymeric DES results in excess of bleedings including disabling and potentially fatal events'. This opens the possibility for the new polymer-free DES in a further shortening of DAPT duration to provide an extra added safety margin compared to polymeric DES.

In a following lecture Dr. Stella detailed the latest Demonstr8 trial results, also presented during the Late Breaking Trials, which have for the first time shown that Cre8™ polymer-free DES coverage at 3 months is non-inferior to the BMS coverage at 1 month (RUTTS score <30%; 99.75% CRE8™ vs. 99.55% BMS; p<0.0001). With these findings it is possible to assess that Cre8™ could allow three months DAPT duration since at this time point it's a BMS; and its endothelisation is comparable to a standard BMS for which the guidelines recommend 1 month DAPT.

The clinical impact of the above remarkable data has been extended by the OCT case study presented immediately after by Dr. Romaguera, in which a complex case of a diabetic patient who was insulin dependent presenting a complex CTO of the right coronary artery resulted in the same striking Cre8™ strut coverage empowering the Demonstr8 randomised study results.

The chairs recieved much positive feedback in the open discussion session, which has led the symposium's attendees to identify Cre8™ as the most appealing DES that could be able to allow physicians to address DAPT duration to patient's clinical conditions and not to the specific DES implanted.

Interview: Jeffrey Jump, Biosensors

The Treatment Strategies team caught up with Jeffrey Jump, President of the Cardiovascular Business Unit at Biosensors, at the company's stand to learn more about what they were looking to achieve at euroPCR.

Q. Tell me a little about Biosensors?

A. We've been involved for about 12 years in interventional cardiology, but it's really been in the last 5 years with Biomatrix and the publication of LEADERS that we've really come into the forefront and are now a major force in interventional cardiology and a major part of PCR.

Q. So PCR is the world's largest interventional cardiology event. What does PCR mean to Biosensors?

A. We share a common philosophy. The whole PCR idea from John Marco in the very beginning was patient benefit and education, and dissemination of educational clinical studies that help patients, and that's exactly the same philosophy that we have. This year we have 32 presentations, and so I think that the relationship between PCR and Biosensors is that we share a common philosophy.

In addition to this, both companies are really focused outside the United States. We're focused in Europe, Asia, the Middle East and Latin America, and that is the same as PCR. So we not only share a philosophical agenda, we also share a geographical agenda.

Q. Specifically what are biosensors activities here this week at euroPCR?

A. Well this week our theme is raising the standard. Last year we presented the five-year data on the LEADERS study on BioMatrix, showing it as the gold standard in DES stents. This year we're raising that standard. We have a follow-up publication to LEADERS, which showed that in a subset of CTO patients, and these are complicated patients, an even larger benefits than we demonstrated in the original study.

..."this week has really allowed us to demonstrate clinical evidence that shows that our products help patients."

We also have a study with COMFORTABLE AMI. COMFORTABLE was a study last year that was presented here, where we showed that in STEMI patients, these are emergency patients, a DES was safer and more effective than a bare metal stent. Before that, the common knowledge was that a bare stent would be better to use in these patients. However, this study proved for the first time that a DES was safer and more effective in these patients, and that took the percentage in the market that was DES from 50% to 60%, just because we could treat all of these emergency patients, so certainly that was important.

This week we also had our first release of the E-BioMatrix registry, and the important thing about that is that you always get a different

result from a registry than you do from a perspective randomised study. Well actually, we demonstrated that you don't, and that the results are the same. So we validated the randomised study with the registry, and we were able to show in a large patient population that you get the same good results. I think this week has really allowed us to demonstrate this clinical evidence that shows that our products help patients.

Q. Biosensors are sponsoring several sessions and symposiums this week at euroPCR, can you give us a brief insight into some of these?

A. I think as you say we have many symposiums that we are sponsoring this week. I guess the main one would be the DIVERGE five year data which we presented in our TNT (Tools and Techniques) symposium. This was the first time that you had five-year data on over 500 patients on a bifurcated stent. This was the largest body of data that anybody has been able to collect and it is extremely positive data, so I think that was a very good session. I think the whole theme of all of our sessions is that we're making them very interactive, so we left more time than usual for questions, of which there were many because it's a complicated procedure.

I think that our focus this year has been to try and make it as interactive as possible, because we are at the point now were we dealing with complicated issues: duration of Dual Anti-Platelet Therapy – a complicated issue of where you use bifurcated dedicated stents and where you don't, and bleeding. I think in our symposium we talked about the global LEADERS, which was focusing on bleeding from the perspective of changing the drug. We also have LEADERS FREE, which is another study looking at bleeding from changing the stent and the duration of Dual Anti-Platelet Therapy. So I think interactivity and raising the standard of interaction between physicians and industry.

Q. What is the message that you would the attendees to take away from the symposium, Biosensors and euroPCR 2013?

A. I think the main message is that we're very bullish on the interventional cardiology space and we're investing in it. We're investing in many aspects; we're launching a product here at the meeting this week, the NeoFlex, which is basically based on the data that we collected in LEADERS and published in the *Lancet*, but in a more deliverable package. We've improved the delivery system so that the patient can benefit from this biodegradable technology and abluminal coating and the biolimus drug of course. So I think the biggest thing we're launching this week is the NeoFlex, which is the BioMatrix in a more deliverable package.

I think the other thing is, when I mention that we're investing in interventional cardiology, is that we have just bought a company last week that we have been partnering with for several years, and that company is called Spectrum Dynamics. They have a really interesting technology that is now ours, that could change the way that interventional cardiology is practiced. Today the big problem with interventional cardiology is that 50% of the time a patient goes onto the cath lab table and they don't need to be there. Unfortunately we don't know which 50% until we get them there. What this technology will do in a minimally invasive way is that you sit in a chair, a screen comes over your chest and it tells you whether you need to go to the cath lab or not. Not only that, but the same image tell you which vessel needs a stent but also how many stents you need. So this allows us to help choose patients that get on the table, to treat them better once they are on the table, and then six months, a year or two years later, we can also go back in a minimally invasive way, a screen comes over the chest and we can say how effective that procedure that we did six months to a year ago was. So we're really vertically integrating the whole patient treatment process in interventional cardiology.

Q. Finally, as the President of Biosensors Cardiovascular Division tell us a little bit about your focus for the future?

A. We're very excited about the future; I think that you can expect a lot more of the same in terms of supporting clinical studies that demonstrate patient benefit, big studies like global LEADERS that focus on the benefits of Dual Anti-Platelet Therapy and bleeding, GLOBAL LEADERS, which also focuses on bleeding but from a different angle, from shortening the Dual Anti-Platelet Therapy, COMFORTABLE which shows advantages in STEMI patients, and DIVERGE which shows advantages in patients that have bifurcated lesions. I think you'll continue to see us bringing realistic meaningful scientific data based on clinical best evidence that show patient benefit.

We're also investing in new technologies that can help patients. I mentioned Spectrum Dynamics, which will allow us, in a minimally invasive way, to find out which patients need to be on the cath table, exactly how to treat them in the most effective manner and then afterwards how to measure that we did the right thing when we treated them and that it worked. So certainly we'll continue to invest in those technologies. In addition, we have internal programmes that are very exciting with drug-eluting balloons, and new areas of intervention that I cant really discuss yet because they are so innovative. Also we'll continue to acquire companies. We've made five acquisitions in the last few years, the latest being Spectrum. I think that you can expect us to continue to find complimentary technologies and acquire these companies and integrate them into the Biosensors portfolio. So we're very excited about the future.

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Unprotected Distal Left Main Bifurcation Percutaneous Coronary Intervention: Contemporary Strategies

Kleanthis Theodoropoulos,[1] Nisharahmed Kherada,[1] Usman Baber,[1] and **Roxana Mehran[1, 2]**

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Introduction

Left main coronary artery (LMCA) disease occurs in 4-9% of patients undergoing percutaneous coronary intervention (PCI) and in 10-30% of patients undergoing coronary artery bypass grafting (CABG).[1-3] Although current guidelines recommend CABG as a class I indication for a significant LMCA disease with level B evidence, several contemporary studies suggest a clinical equipoise between drug eluting stent (DES) implantation and CABG surgery for this coronary lesion.[4] Recommendations for LMCA treatment have advanced to either a class IIa or IIb indication with a level of evidence B for patients with low PCI risk and high surgical risk.[5,6] It is important to note that the guidelines are not uniform with respect to unprotected distal left main bifurcation (uDLMB) disease management. Most LMCA plaques (40-60%) develop on distally, which is associated with worse clinical outcomes.[7-9] The uDLMB lesions are associated with more downstream lesions and multivessel disease patterns than with non-bifurcated lesions (63.5% vs. 27.4%, P<0.001).[9] Lesion complexity makes percutaneous intervention for uDLMB technically challenging, which can result in higher rates of restenosis, incomplete revascularisation, and less favourable clinical outcomes.[9,10] These challenges have historically made coronary artery bypass grafting (CABG) the first line of treatment.[11] Although there is still room for PCI to be selected with precedence over CABG, the advancement in PCI techniques (Intravascular ultrasound [IVUS] guided PCI, fractional flow reserve (FFR) guided PCI, presenting atherectomy and final kissing balloon (FKB)) and stent design (1st and 2nd generation drug-eluting stents [DES]) have paved the way for PCI to become a viable alternative to CABG for management of uDLMB in contemporary interventional practice. Several studies have found that, except for higher target vessel revascularisation (TVR) in the PCI group,[12-15] there is a comparable safety and efficacy profile when compared to CABG for endpoints including death, myocardial infarction (MI), and stroke.

Distal LM bifurcation outcomes are affected by both lesion complexity and the bifurcation stenting strategy.[16] The anatomical complexity involved with LM bifurcation has given rise to diverse stenting techniques ranging from simple 1-stent (1S) provisional stenting to complex dedicated 2-stent (2S) approaches, primarily as T-stenting, V-stenting, simultaneous kissing stenting (SKS), crush technique, culotte technique, T and protrusion (TAP) technique and importantly DKCRUSH (Double-Kissing and Double-Crush) technique. The majority of bifurcation PCI studies excluding uDLMB have shown that a provisional 1S technique results in more favourable outcomes than using 2S complex techniques.[17] The randomised CACTUS (Coronary Bifurcations: Application of the Crushing Technique Using Sirolimus-Eluting Stents) study found that the 1S technique was effective in bifurcation lesions with diseased dual branches with one-third the crossover rate. Similarly, in a pooled analysis of two large studies (Nordic Bifurcation Study and British Bifurcation Coronary Study - BBC ONE Study) it was shown that a provisional T-stenting (considered 1S) technique was associated with lower rates of the 9-month composite of death, MI, and TVR than 2S strategies.[17,18] Data supporting the various bifurcation techniques for use with uDLMB are controversial and should be carefully interpreted in that the studies were either retrospective, non-randomised, or subgroup analyses of underpowered studies that utilised a wide variety of 2S strategies.

An initial feasibility and safety assessment of uDLMB stenting techniques was performed by Kim *et al*., with 116 patients using sirolimus-eluting stent (SES). They found that the 1S technique

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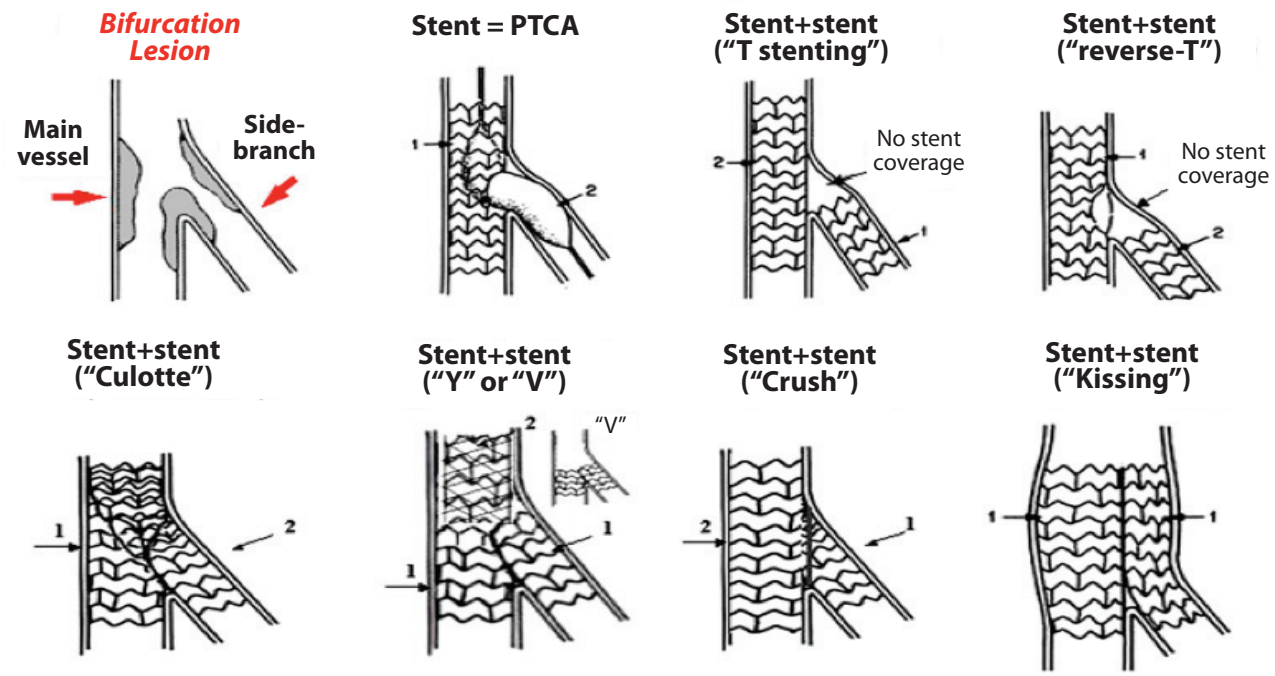

Figure 1. Various stenting techniques used for bifurcation lesions. Adapted from Sharma SK *et al*. Coronary bifurcation lesions. Cardiol Clin 2006;24:233–46.

entailed lower technical complexity and resulted in better clinical outcomes than the crush or SKS techniques.[19] Conversely, Valgimigli *et al*. found similar angiographic performance and MACE rates with the 1S versus 2S technique.[20] A long-term study by Chang *et al*. compared 1S (n=360) to 2S (n=196) including T-, crush, culotte, and kissing stenting, and found similar long-term outcomes (4.2-year follow-up) between both techniques (HR 0.91, 95% CI 0.47 -1.76, P=0.78) except for higher TVR rates in the complex group (HR 1.95, 95% CI: 1.20 to 3.17, P=0.001).[21] Taken together, complex 2S techniques are associated with higher rates of TLR and consequently less favourable clinical outcomes.[17-19] Conversely, there are several exceptional cases where a complex 2S approach is preferred, as with cases of better anatomy for the 2S technique such as with left circumflex disease extending >5 mm from the carina, a challenging re-access to the left circumflex or an impending collapse of left circumflex.[22] Additionally, which 2S technique is applied depends upon the operator's comfort and whether the anatomy is favourable. In this way, similarly sized left circumflex and anterior descending arteries favours the culotte technique, whereas disproportionate sizes may signal the operator to apply the crush technique, and a bifurcation with a very steep angle is better addressed with either the T- or TAP techniques[23] (Figure 1).

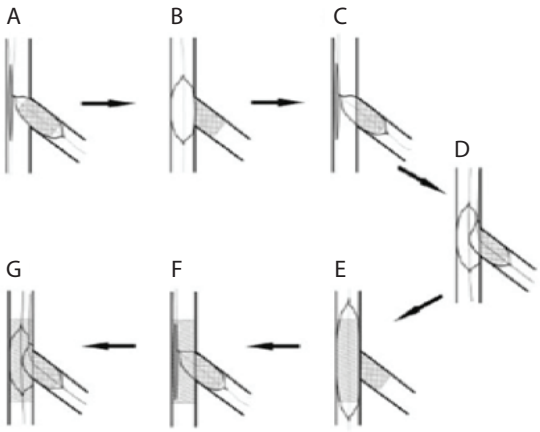

Figure 2. DKCRUSH Bifurcation Stenting Technique. (A) Stenting SB (3-5 mm protrusion in MV) (B, C) Balloon Crush of SB stent, (D) First Kissing Balloon inflation, (E, F) Stenting MV, (G) Final Kissing Balloon Inflation.

Adapted from Jim MH *et al*. Catheterization and Cardiovascular Interventions 2007;69:969–975

In an effort to improve LM bifurcation PCI outcomes, the use of the FKB technique after complex 2S procedures was developed and has been studied extensively, with favourable results. The FKB technique was suggested as required in most recent bifurcation trials (BBC ONE, CACTUS trial) after using a complex 2S approach. Ge *et al*. studied the role of FKB in crush stenting in overall bifurcation lesions and they found decreased restenosis rate in side branch (SB) (11.1% vs. 37.9%, P<0.001), and considered the crush procedure without FKB as a predictor of TLR.[24] Additionally, the recent randomised Nordic bifurcation III study for overall bifurcation PCI showed a significant reduction in the angiographic SB restenosis rate in true bifurcation lesions (7.9% for FKB versus 20% for the non-FKB group), but showed no improvement in clinical outcomes with FKB use.[25] However, unsatisfactory FKB inflation can lead to worse outcomes due to increased TLR. Thus, to improve the rate of FKB inflation and immediate procedural outcomes, the double kissing (DK) crush technique was introduced by Chen *et al*., (Figure 2) and was shown to improve MACE

(11.4% vs. 24.4%, P=0.02) and TLR free survival (89.5% vs. 75.4%, P=0.002) compared to the classic crush technique.[26] In comparison to a provisional 1S technique, the DK crush technique showed improvement in TLR and TVR without any significant benefits over MACE rate in a randomised Double Kissing Crush versus Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions (DKCRUSH-II) trial.[27] A recent prospective study of 633 patients with uLMCA bifurcation lesions who underwent DES PCI compared the 5-year safety and efficacy among various bifurcation stenting techniques including the 1S provisional, 2S complex (culotte, T-stenting, kissing stenting and classical crush) and DK crush techniques.[28] They demonstrated that the cumulative incidence of MACE at 5 years were similar for both the 1S and 2S groups, whereas when DK crush was compared to 1S and 2S techniques the 5-year MACE incidence (DK crush: 14.8% vs. 2S: 37.0% and 1S: 28.0%, P<0.001) had significantly decreased. Interestingly, they also found that most of the 2S approaches (except for the DK crush technique) may be independent predictors of MACE in patients with uDLMB. The recent DKCRUSH-III study by Chen *et al*. showed a comparison between DK crush to the culotte techniques among 419 patients undergoing uDLMB PCI. The DK crush technique was associated with lower incidence of MACE (6.2% vs. 16.3%, P<0.05) and TVR (4.3% vs. 11%, P<0.05) at 1 year follow up, while in-stent restenosis in the side branch at 8 month angiographic follow-up was significantly lower in the DK crush group (6.8% vs. 12.6%, P=0.037) compared to the culotte.[29]

Further advancement in PCI technologies, such as using IVUS guided or fractional flow reserve (FFR) guided physiological assessment of epicardial coronary lesions before PCI, are rapidly gaining popularity due to the associated improvement in angiographic and clinical outcomes[30, 31] In the multicentre ESTROFA-LM Registry, De La and colleagues found that IVUS use enabled better outcome prediction in uDLMB lesion PCI independently (HR 0.5, 95% CI 0.23-0.99, P=0.04), and resulted in beneficial effects in distal left main PCI.[8] In uLMCA disease IVUS use may aid the decision of the type of intervention and also post intervention determination of proper stent implantation. Similarly, an IVUS guided plaque debulking via atherectomy prior to LM bifurcation stenting was shown to be associated with lower LCx restenosis rates.[32] Specifically, 101 patients with uDLMB lesions treated with the 1S technique were divided into two groups based on whether they underwent directional coronary atherectomy (DCA) prior to stenting. The severity of the diameter stenosis in LCx was significantly less in the DCA group (n=46) than in the non DCA group (n=60) at 9 months post PCI (20.8±12.3% vs. 31.9±21.4%, P=0.007), and likewise the restenosis rates in the LCx was higher in the non-DCA (0% vs 10.2%, P=0.048). The FFR technique may contribute to the selection of the optimal revascularisation strategy (CABG vs. PCI), to the assessment of the SB stenosis post-procedurally, and to appropriateness/necessity of SB stenting.[33, 34] To date, the data on FFR are conclusively in favour of using it in cases of indeterminate uDLMCA disease severity by angiography, with specific caution in cases of heavily diseased downstream vessels.[35] The results of the highly anticipated EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation) trial are expected to provide definitive data on whether on IVUS guided PCI should be used in cases of uDLMCA disease.

No significant differences have been found amongst 1st generation DESs and between 1st and 2nd generation DES. Specifically, the MAIN-Compare (Revascularisation for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularisation) and SP-DELFT (The Sirolimus vs Paclitaxel Drug-Eluting Stent for Left Main) registries comparing PES to SES in PCI for uLMCA lesions, showed no difference in long-term clinical outcomes at the 1- and 3-year follow-ups.[36-38] In the large, multicentre, retrospective ESTROFA-LM Registry of 770 patients with uLMCA disease, there was no difference in the outcome of death, MI, and revascularisation (83.6% vs. 82%, P=0.60), and stent thrombosis (1.6% vs. 1.4%, P=0.80) between PES and everolimus-eluting stents (EES).[8] Thus, there is a need for a large prospective study to evaluate the effect of newer generation DES on uDLMB PCI compared to CABG, and thus again results from EXCEL trial are highly awaited in this context.

Conclusively, in the current PCI era, CABG is still the preferred revascularisation strategy for uDLMB bifurcation lesions, however PCI is increasingly considered a safe and reasonable alternative in patients with high surgical risks. The complexity of these techniques requires a high level of operational expertise and continued improvements in available stents and stenting procedures. A careful patient selection demands a holistic assessment of periprocedural risk factors, patient's adherence to antiplatelet therapy and a close interaction between surgeons and interventionists is also crucial. The guidelines highly recommend the establishment of a heart team approach for revascularisation of uLMCA disease and calculation of the SYNTAX and Society of Thoracic Surgeons Score (STS) in high risk patients. Importantly, in comparison to CABG the growing technical PCI advancement may help improve the periprocedural complication rate and improve long-term outcomes. Among the available PCI methods, the vast majority of interventionalists prefer the provisional 1S technique to treat LM bifurcation. The stenting strategy should be based on anatomic, functional, haemodynamic criteria which must be matched with the patient's health status and the operator's comfort. An emerging dedicated DK crush technique is complex but attractive and has shown significantly improved clinical outcome in uDLMB PCI, which also needs a larger randomised comparative trial for better evidence. The ongoing EXCEL trial using the latest generation DES may provide more informative safety and efficacy data that can be used to elucidate the optimal treatment for unprotected distal left main bifurcation and aid in updating current guidelines.

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High Risk PCI of Left Main

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Introduction

Significant narrowing of the Left Main Coronary Artery (LMCA), defined angiographically as stenosis severity > 50%, occurs in 4 to 6 percent of patients who undergo angiography,[1] and is rarely isolated. ST segment elevation ≥ 1 mm in lead aVR on admission electrocardiogram may be suggestive of severe Left Main (LM) disease in patients with Acute Coronary Syndrome (ACS).[2] LMCA is responsible for the blood supply to 80% of the left ventricular wall, apex and interventricular septum.[3] Patients with Unprotected Left Main (ULM) disease have a 3 year mortality rate of around 50% when treated medically.[4] Angiography is a subjective tool to asses the severity and quality of artery narrowing, and newer methods such as Intravascular Ultrasound (IVUS), Optical Coherence Tomography (OCT) or Fractional Flow Reserve (FFR) may be necessary to objectively assess the lesion in the cathlab. Historically, the main treatment of LMCA has been cardiac surgery. The series of papers on LM treatment was started in 1975 by Gorlin *et al*. For many years, the superiority of surgery over medical therapy and Percutaneous Coronary Intervention (PCI) has been evident in the majority of studies. However, the introduction of Drug Eluting Stents (DES), new techniques and tools have led to a wider acceptance of PCI.

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Furthermore, newer studies such as Le Mans, Taxus or SYNTAX have been more optimistic about LMCA stenting. PCI with DES has emerged as a useful alternative to Coronary Artery Bypass Grafting (CABG), mainly for patients with isolated unprotected LM disease or LM and single coronary vessel disease. Currently, unprotected left main PCI is considered in patients with low to intermediate anatomic complexity who are at an increased surgical risk.[5]

By its nature, every percutaneous intervention within LMCA is a high risk procedure, because once complications occur they are potentially life threatening, especially as the majority of patients who undergo PCI of LM have many co-morbidities and a high EUROSCORE which could have potentially disqualified them from CABG. It is extremely important to find the group of patients who have highest risk of angioplasty among PCIs of LM, and to adequately prepare for the treatment of this specific subgroup. ULM PCI should be performed by operators with experience in the management of the anatomic complexities of left main and multivessel disease, specifically in issues relating to bifurcation disease, calcification, and haemodynamic support.[6] In studies on PCI of ULMCA it was found that distal location is one of the most important predictors of repeated revascularisation and overall Major Adverse Cardiac Events (MACE).[7]

For patients with the highest complexity unprotected LMCA, represented by a SYNTAX score ≥ 33, PCI is also associated with a higher MACE. Moreover, LM may have different sizes or lengths, and can be either heavily calcified or not, which creates a technically difficult PCI that makes results less favourable. Also ULMCA PCI in the acute setting, including cardiogenic shock, is a high risk left main PCI.

Table 1 summarises clinical scenarios of high risk angioplasty of LM.

Distal Lesion of LM

Percutaneous intervention of distal left main is always challenging. In contradiction to patients with ostial or midshaft lesions, patients with distal bifurcation lesions are more difficult to treat and have less favourable long-term outcomes.[5] Figure 1 shows distal LM lesion.

High risk PCI of Left Main
Distal lesion of LM
Calcifications and narrow artery
Presence of a clot
SYNTAX score ≥ 33
Acute coronary syndrome
Cardiogenic shock
LV dysfunction

Table 1. Summary of clinical scenarios of high risk angioplasty of Left Main.

Distal LM coronary disease is a major predictor of outcome in patients undergoing percutaneous intervention in the drug-eluting stent era.[8] In the French study, distal LM interventions were associated with an increased risk of adverse outcomes.[9] Multiple stenting techniques for distal LM disease are used including culotte, crush, T-stenting and etc. Indeed, a consensus on the best technique has not been reached. Within the literature there are only a few data regarding long-term results associated with those stenting techniques. In a recent study, which looked at an unselected series of 70 patients undergoing PCI for distal LM, a single-vessel stenting strategy was associated with superior long-term outcomes after accounting for angiographic characteristics[10] of the bifurcation. A study in 2012 demonstrated that with distal LM bifurcations, the two-stent technique (excluding Double Kissing (DK) crush) is an independent predictor of long-term MACE. DK crush was the technique with most favourable outcomes if 2 stents were needed.[11] Figures 2-6 represent the consecutive steps of mini crush - one of PCI techniques for distal LM bifurcation disease.

Acute Coronary Syndrome (ACS) and Cardiogenic Shock

Patients with acute myocardial infarction and culprit lesion in the left main are relatively rare. This group constituted only 4% of the GRACE population. Following the results of a subgroup in the GRACE registry, it was stated that coincidence of ACS and unprotected LMCA is associated with high mortality, especially in patients with ST Elevation Myocardial Infarction (STEMI) and/or haemodynamic or arrhythmic instability.[12] Figure 7 shows an example of primary PCI of occluded LM in a patient being resuscitated.

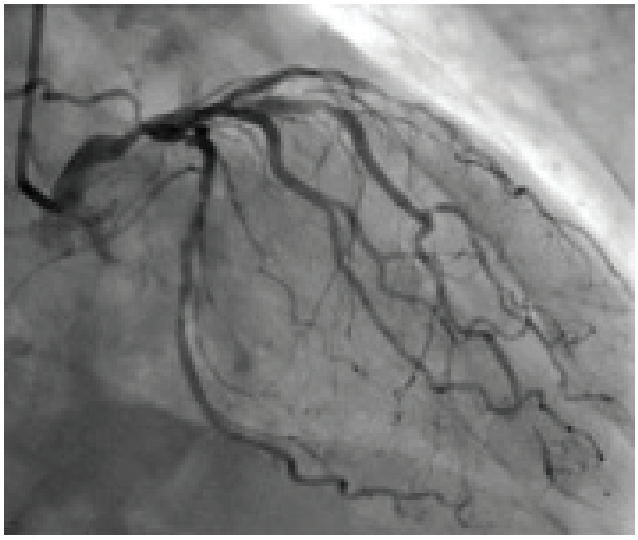

Figure 1. Distal LM lesion

In this study, in-hospital mortality was 7.7%, which rose to 11% in patients who presented with STEMI or new Left Bundle Branch Block (LBBB), and was 34% in patients with cardiogenic shock and/or cardiac arrest. The authors emphasised that LM PCI in ACS is performed in patients with a higher risk than those treated with CABG, and this assertion could justify a better outcome of CABG long term. It was stated that CABG and PCI should be complimentary. In a study by Buszman *et al*., PCI was found to be a reasonable alternative to CABG in patients with NSTE-ACS and ULMCA stenosis.[13] In another study, the analysis of 348 LM PCIs in ACS found that LM PCI in the context of acute myocardial infarction appears to have a remarkably high (89%) in-hospital survival, even with the inclusion of 12% patients with cardiogenic shock. Concurrent LM and non-LM PCI was shown to have worse outcomes than isolated LM PCI.[14] Acute left main occlusion is a rare but devastating presentation of myocardial infarction, invariably with cardiogenic shock. The cohort of patients with LM occlusion was described by the Canadian group. They concluded that emergent PCI may be an effective method to acutely revascularise this subset of patients; however, aggressive post-PCI care including ECMO and ventricular support may be required to improve patient survival.[15] It has already been proven that PCI of LM in an acute setting is a prognostic factor of unfavourable outcome. To prevent haemodynamic instability, cardiac support devices such as Intra Aortic Balloon Pump (IABP) are recommended. The Impella is an alternative for circulatory support during high risk PCI.

Heavy Calcifications, Presence of a Clot

More than 50% of LM lesions are calcified (Figure 8). Surgery is usually preferred over PCI for heavily calcified LM lesions. LM calcification has been shown to be an independent predictor of mortality. Intravascular ultrasound (IVUS) is the ideal method for confirming the presence of significant left main disease as well as for assessing the presence of calcification[16] (Figures 9 and 10).

Rotational atherectomy (RA) may be beneficial in this setting to facilitate stent placement.[17] In a group of patients with high surgical risk, RA on severely calcified left main stenosis is feasible and, in spite of high

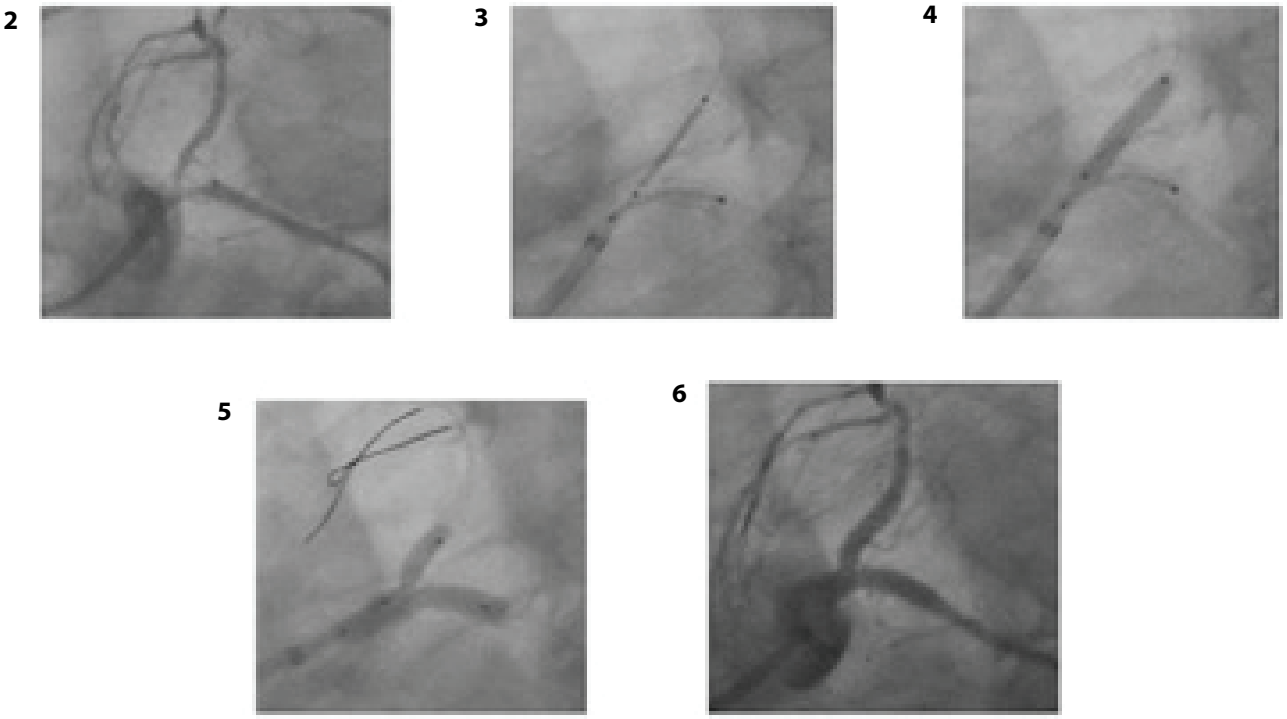

Figure 2. Wire placement in both branches; **Figure 3**. Simultaneous stent positioning; **Figure 4**. LAD stent is implanted with minimal protrusion to LM; **Figure 5**. After CX stent implantation - Kissing balloon inflation is performed; **Figure 6**. Final result.

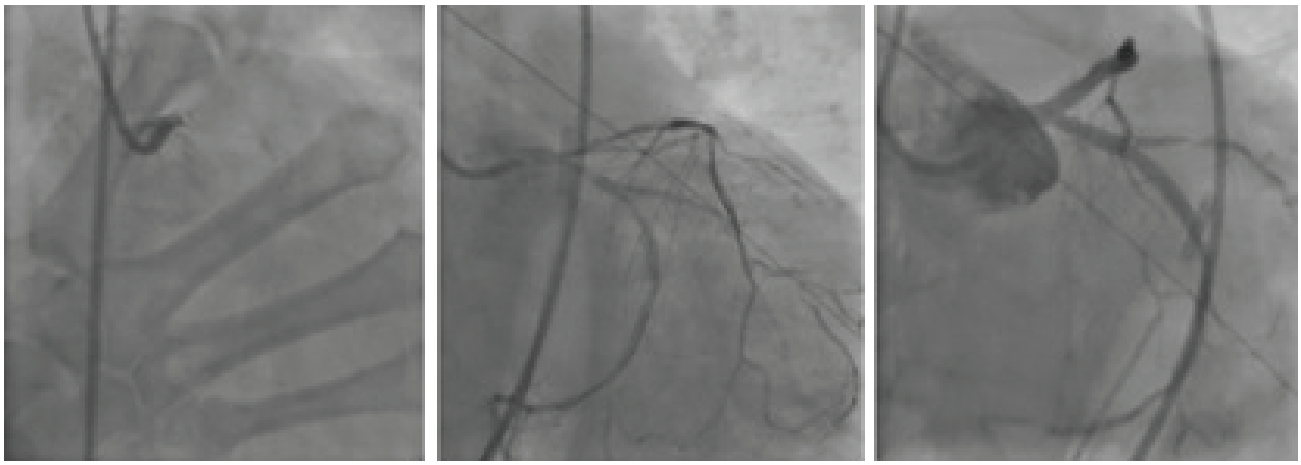

Figure 7. Occluded LM – Rescue PCI – Patient is resuscitated (cardiologist's hand seen), next angiography after balooon dilatation is shown, finally post PCI result.

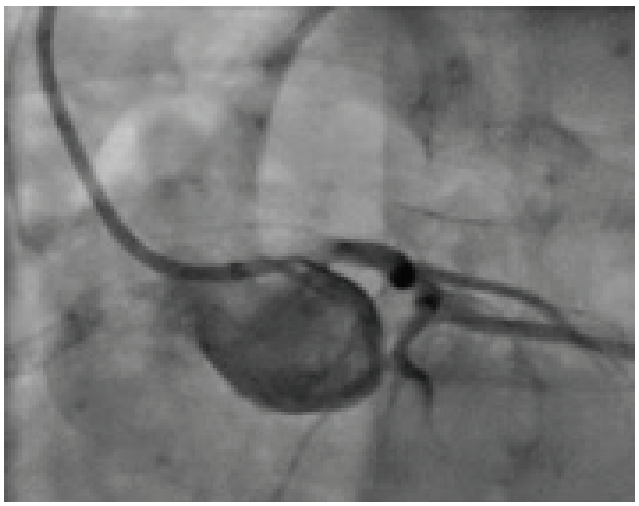

Figure 8. Porcelain aorta and heavily calcified ostial LM stenosis.

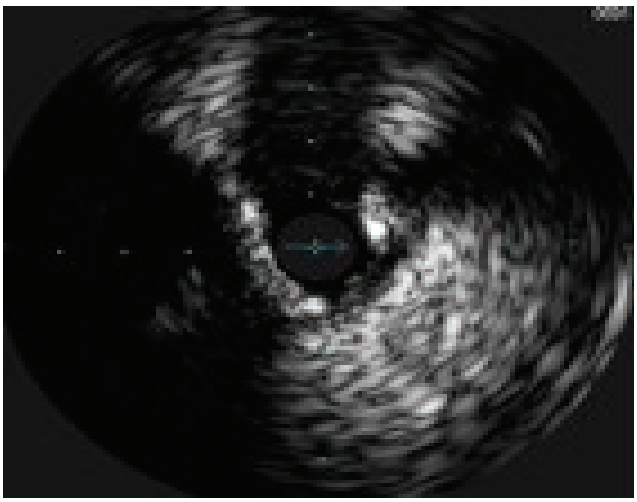

Figure 9. Distal LM calcified lesion. CX Take off at 12 o'clock.

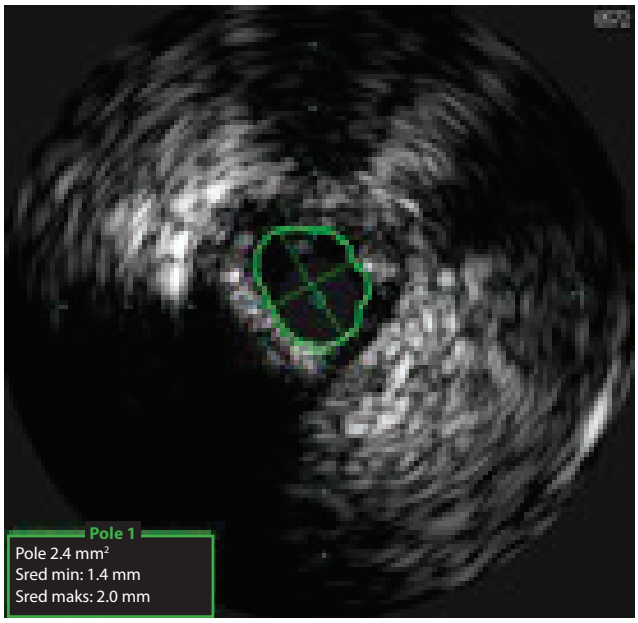

Figure 10. Significant distal LM stenosis. MLA 2.4 mm. MLD 1.4 mm.

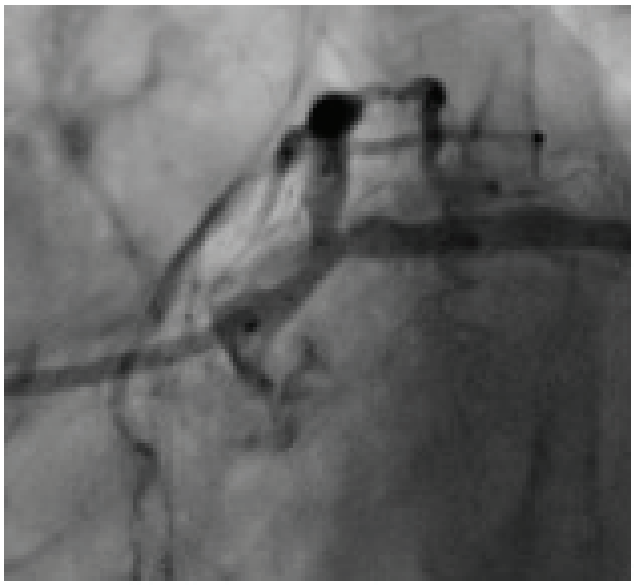

Figure 12. Acceptable residual stenosis after stenting.

mortality rates, could pose the only possible effective treatment.[18] In our experience, repetitive high pressure noncompliant balloon inflations, starting from smaller to larger diameter balloons, can create enough space for stent placement. However, in most cases a perfect angiographic result will not be achieved (Figures 11 and 12).

Left main thrombosis with occlusion of LM is a relatively rare condition, with a high risk of mortality. LM thrombectomy can be performed using guiding catheter, or in the case of long LM and distal thrombus location,

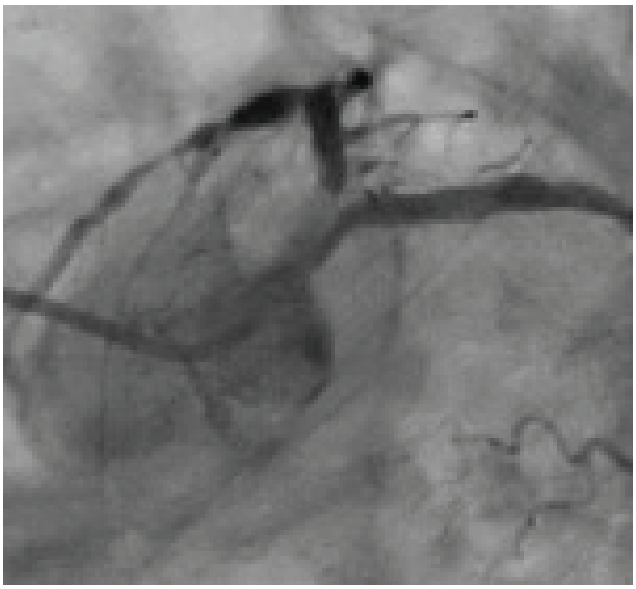

Figure 11. Calcified LM stenosis.

standard thrombectomy catheters may be used. Infusion of IIb/IIIa inhibitors should be started as soon as possible.

Left Ventricle Dysfunction

The outcomes of PCI in patients with diminished Left Ventricle (LV) function are difficult to summarise because the main trials have relatively low rates of patients with LV dysfunction. In the GRACE Registry, post-discharge six-month mortality was 14% in patients with heart failure who underwent revascularisation, mainly by PCI. The mortality for patients with LM disease and poor LV function is still high, even using current standards.[19] In the large Chinese study, among the patients undergoing PCI for multivessel coronary artery disease or LM, left ventricular dysfunction remains associated with further risk of cardiac death in-hospital and during long-term follow-up.[20] In a study published in *Circulation*, in patients with reduced EF who underwent PCI with an IABP support, the 5 year all cause mortality was 4.2% lower than those without IABP support (a 34% significant relative risk reduction).[2] In our opinion, IABP should always be considered in the case of PCI of LM in patients with severely impaired LV function.

Conclusion

To conclude, PCI of left main coronary artery in the high risk group of patients is feasible, and the outcomes are promising. The interventional cardiology community is looking forward to new trials which will give further answers on the optimal treatment of LM disease, including the high risk group of patients.

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Coronary Artery Ectasia as a Culprit for Acute Myocardial Infarction: Review of Pathophysiology and Management

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Introduction

Coronary artery ectasia (CAE) is the abnormal dilatation of coronary arteries such that the ectatic segment exceeds the diameter of the normal adjacent segments or the diameter of the patient's largest coronary vessel by 1.5 times. CAE may be diffuse or segmental, and in approximately 20-30% of patients it is believed to be congenital in origin. However, the pathophysiology of CAE remains unclear. Despite its close relationship with atherosclerosis, especially in the West, the histological variances and conflicting reports of the role of traditional cardiovascular risk factors weakens the significance of such association.[1] CAE was first described over 40 years ago as an association with atherosclerosis, and since then anticoagulants have been considered as a treatment option.[2] However this remains controversial.

Despite this controversy, the relationship between CAE and atherosclerosis remains only modestly established. Demopoulos *et al.* reported better prognosis of pure, non-atherosclerotic, CAE compared to atherosclerotic obstructive CAE.[3] This was contradicted by a Japanese group[4] and others, who claimed that CAE is not a simple condition but rather that it has an adverse clinical course.[5] Aside from a direct relationship between CAE and atherosclerosis, there is a risk of slow flow phenomenon and CAE as described by Markis *et al.*[6] Slow flow phenomena may lead to ischaemia and thrombosis, but this mechanism has never been fully elucidated.[7] Such variety of mechanisms creates significant uncertainty as to the best treatment strategy for patients with CAE in order to minimise potential complications. We report three cases of CAE presented with ST-Elevation Myocardial Infarction (STEMI), which demonstrate the variety of presentation and clinical challenges that exist when managing this condition. This review is unique in critically presenting the available controversial evidence upon management plans.

Usama Boles achieved his MB, BCH and MRCP at the Royal College of Physicians, Ireland, as well as his MSc in Cardiology. Additionally, he achieved a PhD at Umea University, Sweden. Dr. Boles' research interest is coronary artery ectasia, and previous work includes a study focused on Ventricular Activation Time in Diastolic Dysfunction.

Case 1

A 70-year-old man with no prior medical history presented with inferior ST-elevation myocardial infarction (STEMI), based on an acutely recorded ECG by the attending paramedics. ST segments elevation had resolved by the time the patient had arrived at the Heart Attack Centre. He underwent a coronary angiogram which revealed diffuse CAE involving the proximal left circumflex and mid right coronary artery (RCA). Subsequently, he underwent percutaneous coronary intervention (PCI) to the culprit athermanous lesion at the mid RCA using a clot aspiration device, but with no great success. This proved to be a difficult lesion, which required stent deployment using a high pressure-endurance balloon to overcome the well-organised atheroma and thrombus, with good final results (Figure 1).

Case 2

A 55-year-old man was playing tennis when he developed severe chest tightness. A resting ECG showed left bundle branch block so he underwent urgent coronary angiography, which demonstrated diffusely ectatic coronary arteries with minor atherosclerosis. However, it was noted that there was slow flow and stagnation of the contrast in some of the ectatic segments in the absence of any flow obstructing lesions (Figure 2). No coronary intervention was required and the patient was discharged from the medical unit the following day on β-blocker therapy.

Case 3

A 64-year-old female presented with an inferior STEMI and had PCI to the proximal RCA with one stent inserted. The culprit lesion was within an area of CAE. A week later, intravascular ultrasound (IVUS) revealed a clot beneath the stent in the ectatic area with no evidence of atherosclerosis in this segment (Figure 3).

The patient was continued on dual antiplatelet and oral anticoagulation was added in view of the spontaneous thrombus formation. Clopidogrel was stopped after 6 weeks and she remained on aspirin and oral anticoagulation long term.

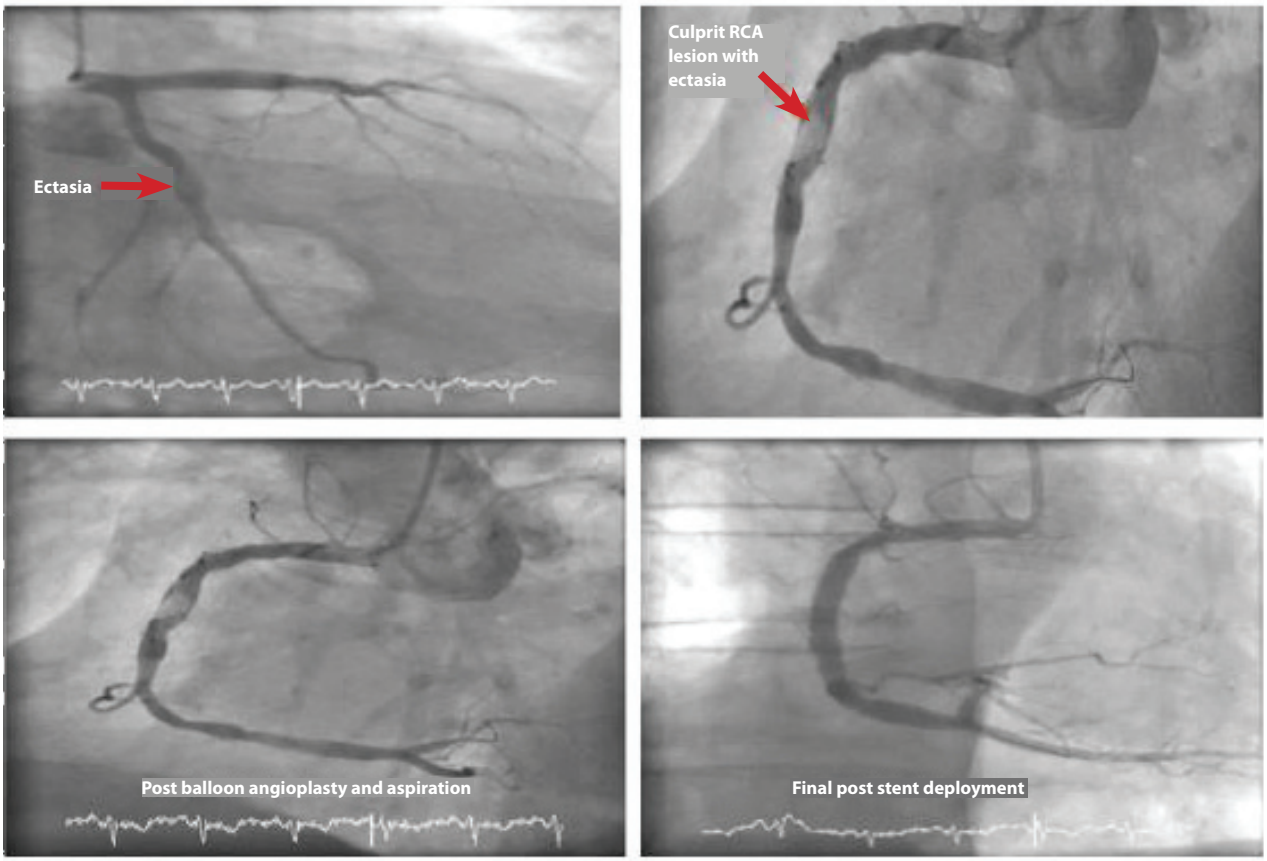

Figure 1. Culprit lesion in ectatic RCA before and after angioplasty. RCA= Right Coronary Artery. CAE= Coronary Artery Ectasia.

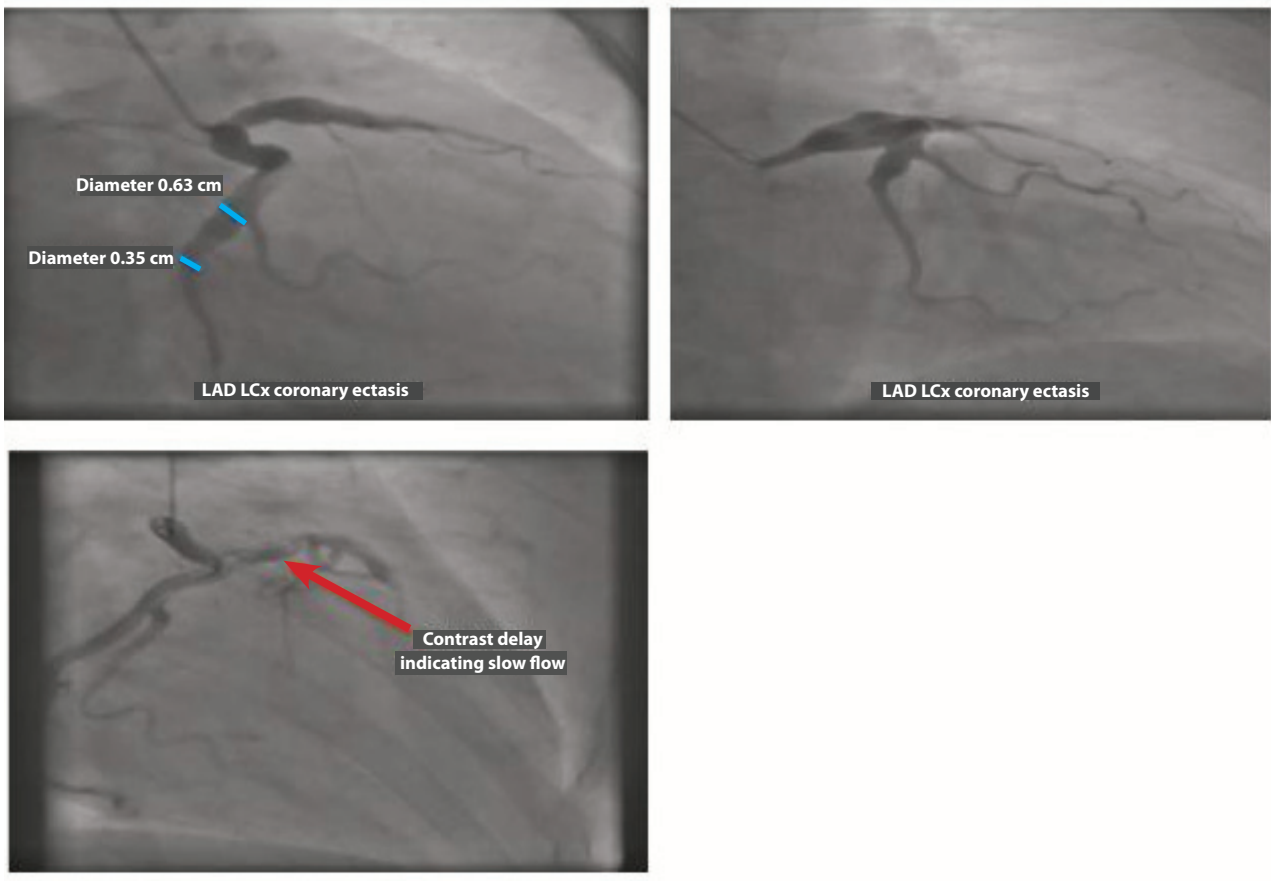

Figure 2. Demonstrating coronary slow flow in coronary artery ectasia.

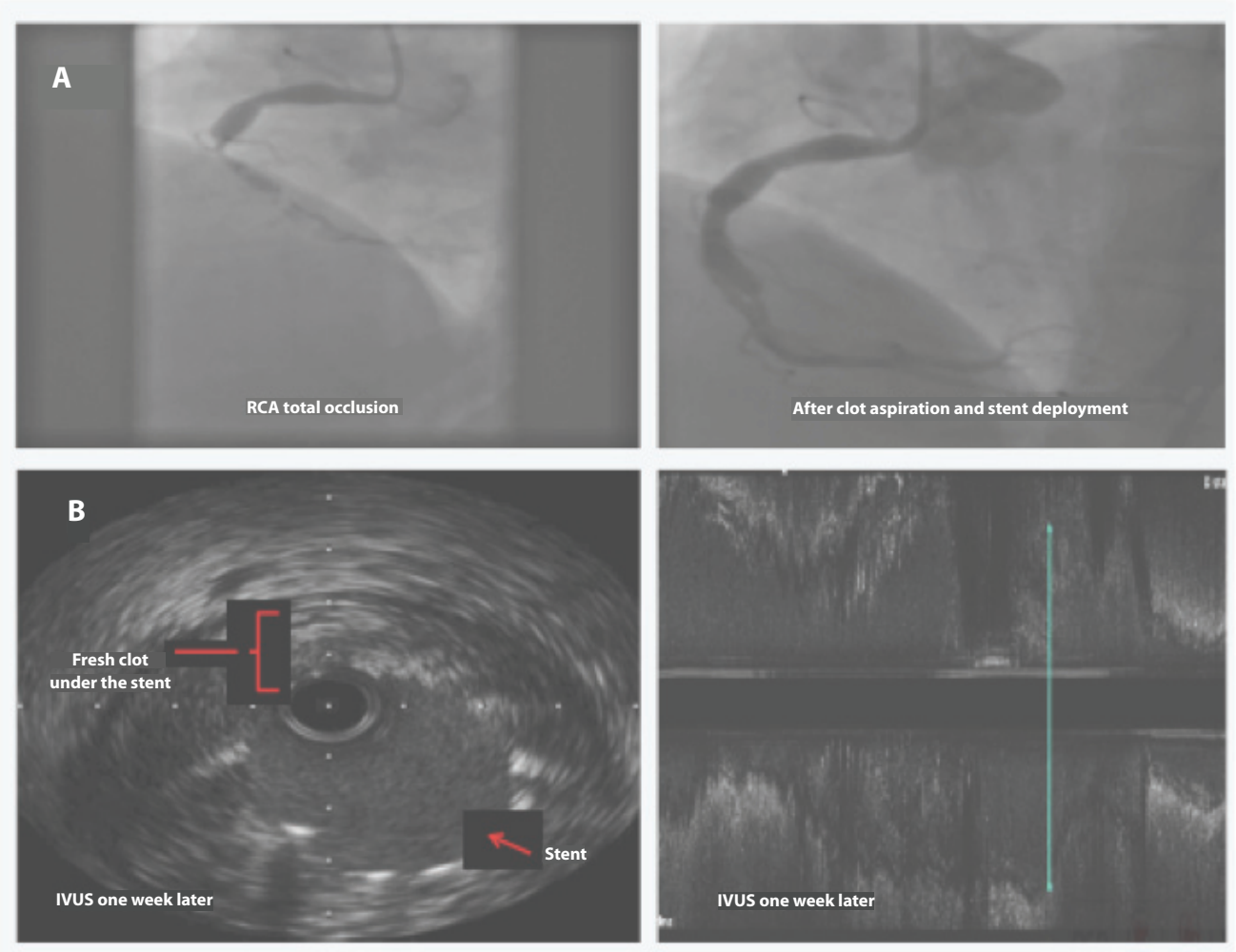

Figure 3. A) Coronary Angiography revealing subtotal RCA occlusion pre and post intervention. B) Intravascular Ultrasound (IVUS) of the RCA one week after PCI showing thrombus underneath stent struts.

Discussion

Pathogenesis of Coronary Artery Ectasia

Studies of coronary arterial wall pathology highlighted the lack of uniformity in CAE. In patients with mixed CAE, Swanton *et al.* reported similar histological appearance to that of atherosclerosis, with marked destruction and reduction of the medial elastic fibers with disruption of the internal and external elastic laminae.[8] However, the pure form of CAE showed smooth muscle hyalinisation of the coronary fibro-muscular media leaving the intima intact.[9] These finding were taken further by Fukuda *et al.*[10] and Johanning *et al.*,[11] who related the hyalinisation process to excessive nitric oxide (NO) production. This was supported by reports in the early 1980s, which investigated the association between CAE and excessive herbicide exposure. The herbicides themselves were shown to increase nitric oxide productions that lead to hyalinisation by indirect acetylcholine production.[12]

A distinct morphological pattern of CAE is the aneurysmal dilatation and slow flow, which causes angina, in the absence of any flow limiting lesions. This was thought to be related to coronary endothelial dysfunction, assessed by plasma asymmetric dimethyl arginine (ADMA) levels and endothelium-dependent flow-mediated dilatation (FMD), having excluded the inflammatory response as a potential contributor to this phenomenon.[13] Moreover, Ackay *et al.*, found a direct relationship between CAE and erectile dysfunction, suggesting that endothelial dysfunction in CAE may manifest in two different forms,[14] thus adding to the already existing pathophysiological confusion.

Another pathological explanation for CAE is coronary artery remodeling, which was first described by Glagove *et al.*[15] His theory of remodeling was based on the finding that early compensatory enlargement of human atherosclerotic coronary arteries occurs even before noticeable luminal narrowing, simulating CAE appearance. This arterial enlargement mainly occurs in the external elastic lamina with positive adaptation of the internal elastic lamina.[16] If this mechanism holds, it may then increase the risk for arterial wall vulnerability with potential progress to an acute coronary syndrome. In contrast, negative remodeling of coronary inner elastic lamina is expected to have a more benign and stable prognosis.[17] Although these theories appear reasonably sound, they are unable to explain many of the features that distinguish CAE

from atherosclerosis.

Clinical Challenges in Coronary Artery Ectasia

Coronary Slow Flow (CSF)

This angiographic phenomenon is frequently referred to as a potential mechanism for explaining angina in CAE in the absence of flow limiting lesions. CSF is characterised by delayed distal vessel opacification in the absence of significant epicardial coronary artery disease. CSF was reported in a number of cases and has been shown to predispose patients to inducible myocardial ischaemia, even myocardial injury, during stress particularly in those with diffuses disease.[18, 19] CSF can be assessed by the TIMI frame count method (TFC), an index of coronary flow velocity along the entire epicardial coronary artery. CAE is usually associated with a higher TFC (slower flow).[20] Magnetic resonance based peak flow velocity (PFV) is another method for assessing CSF which carries the advantage of being non-invasive.[21] In view of this finding, the exercise related ischaemia in CAE could be explained on the basis of a volumetric discrepancy between epicardial and peripheral microcirculatory vessels.[22]

However, from eyeballing we see CSF in the ectatic segment and it seems out of proportion to the increased diameter. Yet, it is not easy to cite in usual clinical practice with the current routine investigation. A new pathway has to develop in order to have more facts about this phenomena and the superlative way of investigation.

Pre-infarction Angina (PA)

This phenomenon has beneficial effects attributed to the development of ischaemic preconditioning (with more collateralisation of the microcirculation) resulting in reduced infarct size in patients with acute myocardial infarction receiving thrombolysis.[23] This effect is even better demonstrated in patients receiving primary angioplasty.[24] Patients with atherosclerotic CAE and PA have been shown to achieve an equally good outcome when treated with primary PCI compared to atherosclerotic CAD with PA.[25] However, further details on culprit lesions (CAE related), extent of disease, and coronary anatomy should assist in better differentiation between CAE and CAD and hence strategic management plans.

Mean Platelet Volume

Mean platelet volume (MPV) is another mechanism behind thrombosis in CAE. High MPV is associated with major adverse cardiac events including the combination of cardiac death, nonfatal myocardial infarction and recurrent hospitalisation.[26] MPV was found to be larger in CAE compared with classic atheromatous CAD, hence it has been suggested as a potential follow-up marker in patients with CAE, irrespective of CAD.[16] In addition to MPV, patients with isolated CAE (non-stenotic) have been found to have abnormally raised plasma P-selectin, beta-TG and PF4, which suggests increased platelet activation, hence the higher tendency to thrombosis.[27]

Thrombus Load

TIMI frame count measurement has been found to be significantly increased according to the ectasia size and ratio. This suggests a clear predisposition to thrombus formation in the ectatic segments.[28] This is further evident by the relationship between the severity of CAE and the acute presentation of STEMI.[29] However, treating such a condition might result in distal embolisation, micro vascular obstruction and the 'no-reflow' phenomenon. This is the basis for the development of the combined mechanical and pharmacological treatment approach.[30] Oral anticoagulant has been well prescribed in this scenario with satisfactory follow-up results.[31] Mechanical thrombectomy on the other hand may have a role in selected PPCI patients with large caliber vessels and heavy thrombus burden.[32] Thrombectomy devices vary from mechanical atherectomy devices for large caliber devices to aspiration atherectomy in acute fresh thrombus. No special devices have yet been produced to meet with the need for atherectomy in coronary ectasia.

Myocardial Function

Left ventricular (LV) function has been shown to be abnormal in CAE with raised myocardial performance index (MPI), suggesting dyssynchronous contraction. MPI has been reported to be abnormally high in segments subtended by the ectatic coronary arteries.[33] The relevance of these findings in the absence of other evidence supporting ischaemia remains to be determined.

Therapeutic Strategies

With the widespread availability of coronary angiographic investigations, both invasive and non-invasive, it is expected that more patients with CAE are likely to be identified with Major Acute Cardiac Events.[5] As such, the management of patients using an evidence-based approach needs to be established. The available treatment options include anticoagulants, anti-platelets, coronary vasodilators, angioplasty and CABG in certain cases, but medical management is widely accepted as the treatment of choice for non-obstructive CAE.

Oral Anticoagulation and Antiplatelet Agents

In patients with pure CAE (diffuse with no flow limiting lesions) treatment aims at minimising thrombosis risk. Oral anticoagulation may be an appropriate strategy[4] however, increased platelet activity and MPV remains a limitation when considering single oral anticoagulant use. In patients with mixed CAE, Demplouse *et al.*, refuted the need for additional oral anticoagulation.[3] This conflicting opinion on anticoagulation should not hamper the use of aspirin[34] in the presence of underlying atheroma. Dual antiplatelet therapy (DAPT) should also be instituted if PCI is performed.

Vasodilators

Coronary artery spasm is considered one of the main reasons for ischaemic symptoms in CAE patients with atherosclerosis. While nitrates are widely accepted as a coronary vasodilators, for symptomatic relief of obstructive CAD, they may exacerbate stress-induced ischaemia in isolated CAE,[35] so are generally avoided. Instead, calcium channel blockers and β blockers might be considered as the main stay of vasodilator therapy for patients with CAE. Stronger evidence for the benefit of vasodilatation in CAE remains to be determined.

Surgical Intervention

The presence of a thrombus within CAE and the necessity to remove large aneurysms has led to the introduction of a variety of operative procedures, including proximal and distal ligation, and even aneurysm resection. These interventions have yielded good results.[36, 37] Other procedures including CABG, aneurysmectomy and thrombectomy have been used for many years in CAE with CAD. Currently, the main indication for surgery is largely the extent of atherosclerotic CAD and obstructive lesions, but CAE without obstructive CAD is generally managed medically.

Stent Deployment

Ochiai *et al.* reported excellent early and long-term results of balloon angioplasty in lesions adjacent to CAE segment. An important consideration is the need for adequate stent expansion and wall apposition. This, at times, can be accomplished with IVUS.[38] Stent deployment is currently considered the treatment of choice in symptomatic CAE patients with obstructive CAD. However, rationalising stent deployment as a treatment for large CAE segment with high predisposition to clot formation, and therefore acute myocardial injury remains to be determined.

Conclusion

The previously described firm link between CAE and atherosclerotic CAD might limit lateral consideration of other underlying pathophysiology for CAE, particularly the pure form, and its effect on the myocardium and ventricular function. CAE may have serious effects from the high thrombosis probability leading to major acute cardiac events with related challenging plans. Treatment strategies are not rationalised as they are based on a small number of individual reports with conflicting opinion on oral anticoagulation, conservative and/or interventional therapeutic options.

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Understanding of the Transient Scaffolding: New Frontiers in Vascular Interventional Medicine for Atheroregression

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The Glagov Remodeling: A Key Mechanism to Maintain Lumen Patency

Prevention of atherosclerosis and treatment of its complications remain a clinical challenge.[1] HMGCoA reductase inhibitors have an outstanding track record of lowering cholesterol and improving outcomes. Clinical trials such as MIRACLE (2001), REVERSAL (2004), NORMALIZE (2004), PROVE IT (2004), ESTABLISH (2004), ASTEROID (2006),[1] JUPITER (2008), and SATURN (2011)[2] have demonstrated that lowering LDL levels through intensive statin therapy can slow progression, or even partially reduce the total atheroma volume (up to 6.38 mm^3) in coronary arteries. Of note, plaque regression was associated with only a 30% relative reduction in events.

Current percutaneous coronary intervention (PCI) using drug-eluting stents (DES) is associated with a small, though sizeable risk of delayed healing, late stent thrombosis,[3] abnormal vasomotion[4] and neoatherosclerosis[5] (Figure 1). New devices such as bioresorbable scaffolds (BRS) have been tested in more than 1,000 humans (Absorb BVS – bioresorbable vascular scaffold, Abbott Vascular, Santa Clara, CA).[3, 6] These devices scaffold the diseased coronary artery and elute an anti-proliferative drug that counteracts constrictive remodeling,[7] and excessive neointimal hyperplasia.[5, 8] Until now, the BRS platform has been used in selected lesions partly due to the nature of patient selection in these first-in-human trials.[6, 9, 10] BRS may represent a new era in cardiovascular medicine, since interventions will not only address the obstructive component of atherosclerotic disease, but also the biologic and functional properties of the vessel. BRS may thus be viewed as platforms upon which bioactive compounds are added to act as disease-modifying agents.

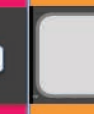
New generations of devices may help us to fulfill our ultimate goal of atheroregression below the *Glagov threshold* by reversing atherogenesis, slowing the ageing process and triggering repair of diseased arteries. Glagov's observation[11] in 1987 suggests that vascular remodeling maintains the artery lumen dimensions[12] as long as the plaque burden threshold of 40% is not trespassed; a stage where the growth of the plaque can no longer be accommodated by external elastic membrane (EEM) enlargement. This process of EEM enlargement in accommodating the plaque and maintaining the lumen dimensions is referred to as the *Glagov phenomenon,* which is a cornerstone issue in atheroprotective strategies.[13] Therefore, plaque reduction below the *Glagov threshold* would imply some kind of atherosclerosis reversal setting back a lesion.

BRS technologies have been tested in some clinical studies (see Figure 1). Among the first polymeric devices to be studied was the PLLA bioabsorbable stent designed and tested by Stack *et al.*, which was reported to hold up to 1,000 mmHg crush pressure and maintain its radial strength for 1 month.[14] The pioneering experimental studies using a non-biodegradable polyethylene-terephthalate braided mesh stents in porcine animal models were published by our group in 1992.[10, 14, 15]

The first two publications on Absorb BVS eluting everolimus in patients have reported three seminal observations made respectively at 6-month and 24-month follow-up: a) complete resorption documented indirectly by optical coherence tomography (OCT), intravascular ultrasound (IVUS) grey scale and IVUS radiofrequency backscattering; b) physiologically or pharmacologically induced restoration of vasomotion in the scaffolded area; c) late luminal enlargement with plaque/ media regression documented by IVUS and OCT between 6 and 24 months.[1, 6, 9, 10, 15, 16]

Alexander N. Kharlamov received his M.D. *cum laude* in 2005 and Ph.D. in 2011 from Ural State Medical Academy (Yekaterinburg, Russia). In 2008 he started his career as a Physician and Translational Researcher at the Department of Interventional Cardiology, Acute Care Unit, and founded a Department of Science in the Ural Institute of Cardiology (Yekaterinburg, Russia) working in the field of novel nanobiotechnologies (plasmonic photothermal therapy, near-infrared lasers) in cardiology. Since 2007 he has worked as a Scientific Assistant to C.E.O. Ural Institute of Cardiology and Chief-cardiologist of the Ural Federal District (Russia) Prof. Jan Gabinsky. Since 2009 he has been working as a Research Fellow in a number of institutes in the Netherlands, including supervision of Prof. Patrick W. Serruys (Erasmus MC, Rotterdam, The Netherlands). He is an author of more than 55 articles and some grant proposals (NANOPLASTY, REVOLUTION, NIRVANA, REVERIE, DREAM and HEARTCORE projects) for the European Commission, and has received national and international awards for his research work.

A

	Durable polymer coating		Biodegradable polymer coating		Polymer-free drug delivery, reservoir, micropores, or nanotechnologies							
	Abbott Vascular	Meril Life Science	Micell technologies	Orbus Neich	Envision Scientific	Conor Medsystems	Lepu Medical	CID	Biosensors Inc.	Translumina	MIVT	Meril Life Science	Abbott Vascular
	Xience V	BioMime	MiStent	Genous	Focus NP	Conor	Lepu Nano+	Cre8	Bio Freedom	YUKON Choice	VESTA Sync	Mitsu	**BVS**
													
Composition	Stainless steel	Cobalt-chromium	Cobalt-chromium	Stainless steel	Cobalt-chromium	Stainless Steel	Stainless Steel	Stainless Steel	Stainless Steel	Stainless Steel	Stainless Steel	Cobalt chromium	PLLA
Strut thickness, µm	81	65	64	90x100	73	127	100	80	119	87	65	40	150
Coating thickness, µm	7.6	2	< 10	<0.5	0.1-0.3	None	None	iCarbofilm <0.3	None	None	None	< 2	6
Coating polymer, µm	Fluoro	PLLA + PLGA	PLGA	Biomatrix	Lipo-based nano-carriers	Nitra-srtut wells with erodable polymer	Nanopores 0.4x0.15	Pyrolytic carbon with drug reservoir	Micro-structured abluminla surface	Modified micro-porous	Microporous hydroxy-apatite	Solid lipid nanoparticle < 0.3	PLLA + PLGA
Coating drug, µm/mm²	Everolimus 1.0	Sirolimus 1.25	Sirolimus 2.44	Anti-hCD34 antibody	Sirolimus 2.0	Paclitaxel 1.0 or 3.0	Sirolimus 2.2	Amphilimus (sirolimus), 0.9	Biolimus9 (dose under investig.)	Sirolimus 1.2	Sirolimus 2.9	Merilimus 0.45-2	Everolimus 1.0
	2nd Gen	3rd Gen	3rd Gen	4th Gen	4th Gen	4th Gen	4th Gen	4th Gen	4th Gen	4th Gen	4th Gen	4th Gen	BRS

B

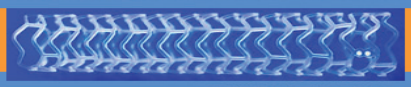
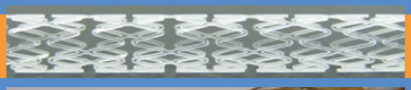
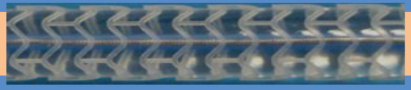
Company	Picture	Thickness of struts, µm	Polymer/drug	Features	Absorption time, months	LLL, mm (months)
Igaki-Tamai (2000)		170	PLLA PLLA plus Tranilast	Deployed with a heated balloon	24	0.48 (6)
Biotronik (2006)		125	Mg alloy with paclitaxel (AMS-2)	Balloon expandable	4-6	0.46 (6)
Abbott (2006)		150	PLLA with everolimus	Balloon expandable	24	0.19 (6)
Reva Medical (2008)		200	Tyrosine poly carbonate with iodine	Ratchet links for deployment	24	1.81 (6)
BTI (2008)		200	Salicylic acid into polymer (PLA or adipic acid) with sirolimus	Balloon expandable	6	NA
Elixir (2011)		150	PLLA with novolimus	Balloon expandable	12-24	0.19 (6)
Huaan Biotech (2011)		160	PLLA with novolimus	Balloon expandable	12-24	NA
Regranion (2011)		300	PLLA (60%)-PLGA (15%) – caprolactone (10%) – lovastatin (15%)	Balloon expandable	12	NA
Amaranth (2012)		150	PLLA in a 'raw' resin phase without drug	Balloon or self-expandable with shape-memory	36-48	NA

Figure 1: Comparative analysis of DES and BRS platforms currently available. **Panel A** demonstrates different generations of stents and BRS. In addition, some representatives of the new fourth generation are shown, utilising polymer-free technologies with drug-loading in micro- and nanopores (LepuNano+), micro-reservoirs (Cre8), stents coated with CD34+ cells-catching system (Genous), stents with lipid-based nanocarriers (Focus NP) and ultra-thin nanoplatforms (Mitsu). **Panel B** presents the main characteristics of nine bioresorbable scaffolds (BRS), which are currently in clinical trials. NA – information is non-applicable or not available. Figure adapted from references [2, 5, 7].

However, analysis of the first-generation Absorb BVS revealed unwanted late scaffold recoil which was fully remediated by a second-generation design and process that showed an unchanged scaffold area at 6 months follow-up. Further evaluation at 12 and 24 months follow-up as well as analysis by OCT and IVUS confirmed the persistence of an unchanged scaffold area without substantial loss in lumen area, while vasomotion became detectable. These observations brought the evidences of the ongoing yielding process[15] and mechanical integrity of the scaffold to the vessel.[2, 3, 5, 15] A 3-year follow-up of this second generation is currently under way to refine these observations and to confirm whether the first signs of late lumen enlargement are detectable.

To date, Absorb BVS is the first device which has shown phenomena such as late lumen enlargement without pathological remodeling and wall thinning with reduction of plaque burden. Thus, Absorb BVS in combination with other state-of-the-art approaches could pave the way for a new era of atheroregression and vascular reparative therapy.

Transient Scaffolding as the Optimal Tool for Atheroregression

In general, preclinical studies of BRS eluting mTOR (mammalian target of rapamycin) inhibitor everolimus in the porcine coronary model have shown that polymeric struts completely disappeared and remnants were fully incorporated into the vessel wall within 4 years, becoming indiscernible by histology, OCT and VH-IVUS.[2, 3, 6, 15, 17] Moreover, a circumferential evaluation of the healing process by OCT after BRS implantation showed a minimal amount of neointima forming a neocap of 170 µm, which potentially contributes to plaque stability.[5] As in the porcine model, late lumen enlargement, and plaque-media reduction (12.7%) with wall thinning were also observed in humans using IVUS. By comparison, in the most recent study of plaque regression in patients receiving atorvastatin, the relative reduction in plaque-media volume was 8.5% over a period of 2 years.[1, 4]

Optimising BRS: Targeting Key Molecular and Cellular Pathways

mTOR inhibitors remain the key compound of BRS. mTOR is a key mediator of growth, metabolism, and inflammation. mTOR is a part of two distinct multiprotein complexes, of which only mTOR complex 1 (mTORC1) is sensitive to cyclic macrolides, whereas mTOR complex 2 (mTORC2) is not. Preclinical systemic application of mTOR inhibitors decreases atherosclerotic plaque formation in both apolipoprotein E knockout ($ApoE^{-/-}$) and low-density lipoprotein-receptor knockout ($LDL\text{-}R^{-/-}$) mice.[18] Systemic mTOR inhibitors also increase plasma triglycerides and LDL cholesterol levels which may be mediated, at least in part by decreased levels of hepatic LDL-R and increased PCSK9.[18] Very recent findings imply a novel role of mTOR in the ageing process.[19] Chronic rapamycin treatment prolongs life span in *C. elegans*,[19] drosophila and mice.[18, 19] At the molecular level the following questions on mTORC1 inhibition remain unanswered: what are the effects of mTOR inhibitors on vascular healing, foam cell formation, autophagy, cholesterol metabolism and reverse cholesterol transport as well as their effects on vascular ageing.

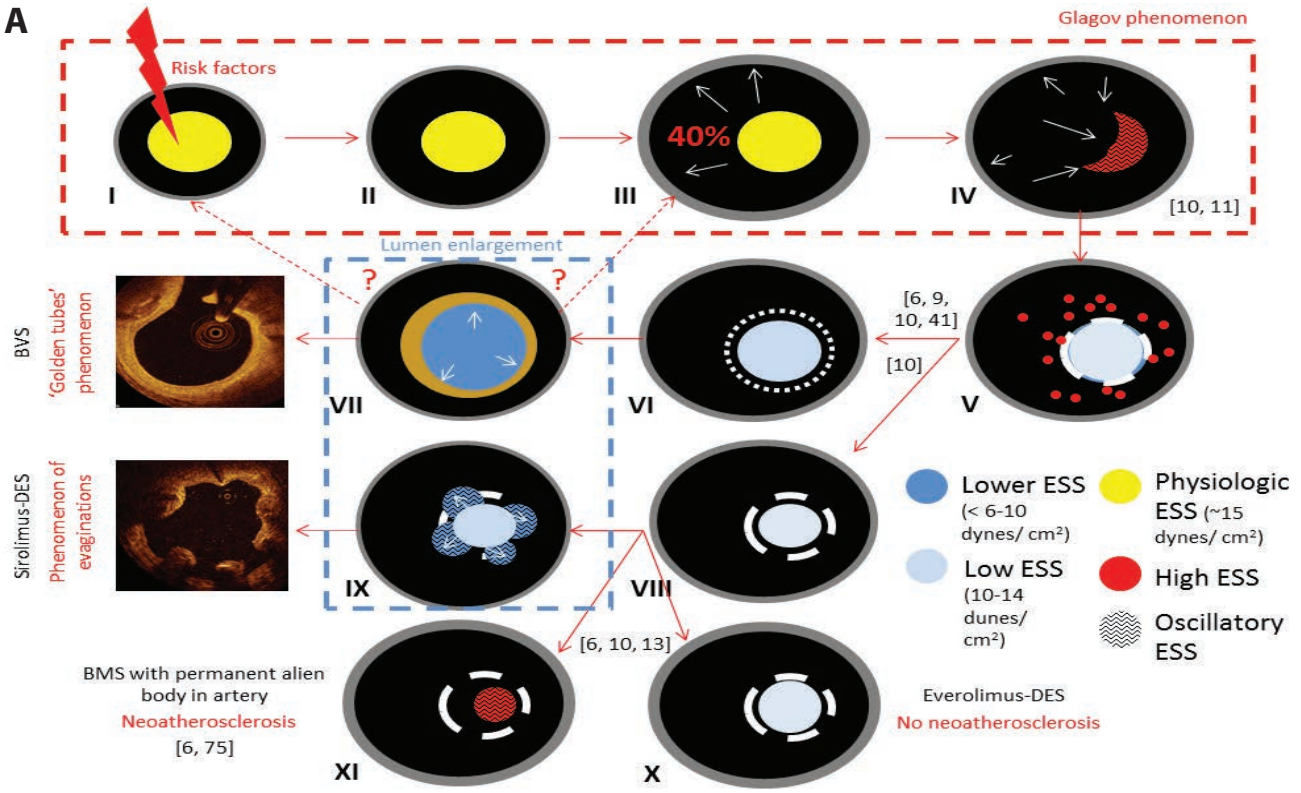
Our previous bench and bedside findings support the concept that BRS could set the stage for 'physiological reversal' of atherosclerosis (72 articles, 2006-2013, collected in the ABSORB Publication Compendium, Erasmus University Medical Center Library, Rotterdam, The Netherlands).[6, 10] New treatment such as systemic mTORC1-inhibitor administration, advanced statins (such as rosuvastatin),[1, 2] Lp-PLA2 inhibitor darapladib,[17] ApoA-I Milano, PCSK918, other drug agents, and tailored physical exercises may improve clinical results after BRS implantation.

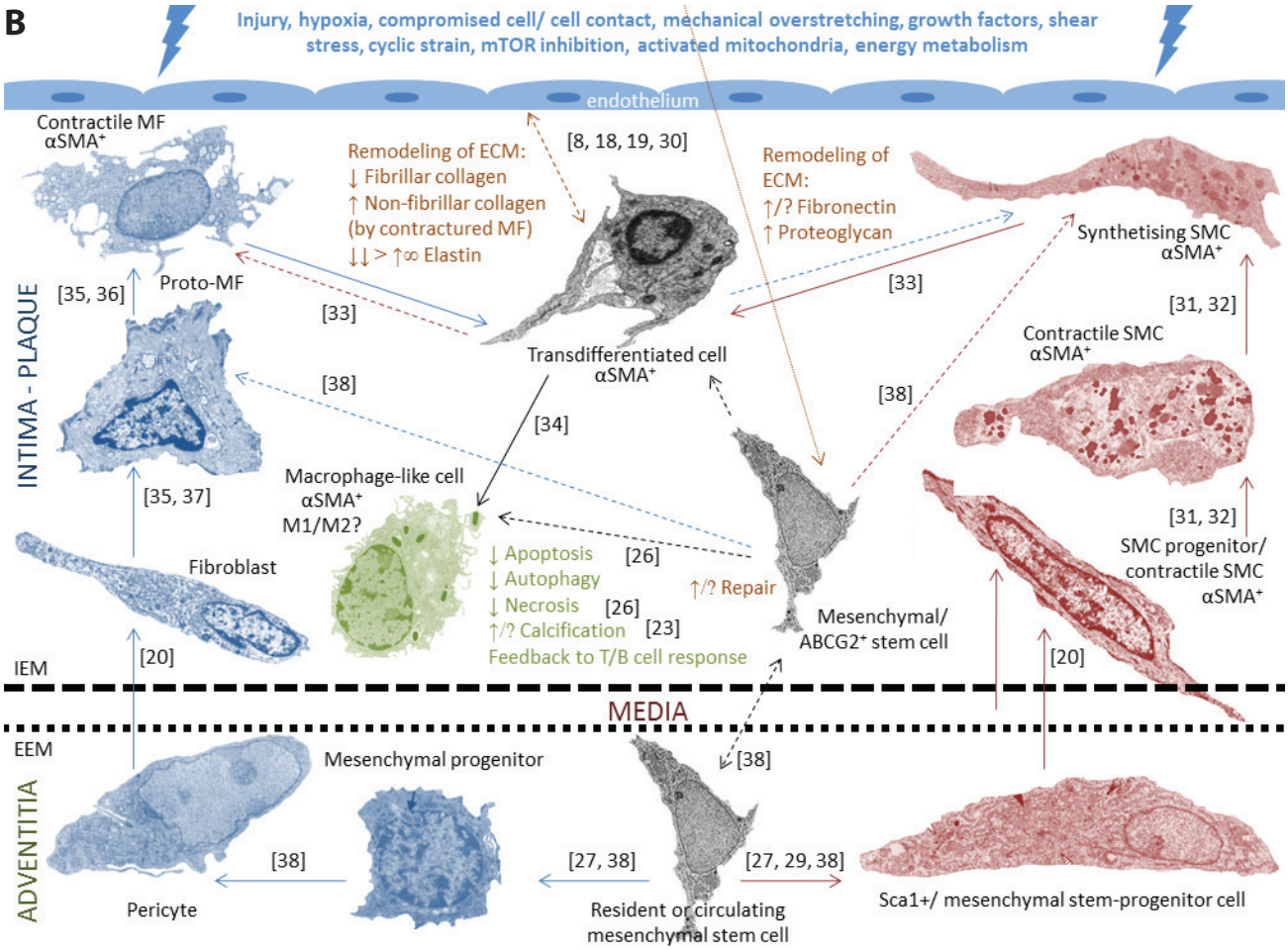
BRS/mTOR-inhibitor-associated reversal of atherosclerosis (see Figure 2) is mediated by late wall thinning with putative atheroregression, and late lumen enlargement with unmodified or even expanded EEM, resulting in a dilated 'overcompensated'[12] vessel.[13] It has been hypothesised that the reversal of atherosclerosis is a result of reorganisation of the extracellular matrix (ECM) by non-fibrillar collagen, elastin and entire connective tissue, with mobilisation and reduction of the necrotic core, in conjunction with a change in macrophage, myofibroblast (MF) and vascular smooth muscle cell (VSMC) phenotypes and pools. It is unknown whether this 'plaque and media regression' on IVUS[16, 20] is a true atherosclerotic regression, with change in vessel wall composition and plaque morphology or a pseudo-regression due to resorption of the polymeric struts,[20] remodeling of the provisional matrix left behind, or shrinking of new tissue.[21, 22]

True atherosclerotic regression will be only confirmed and understood when the unresolved mechanistic questions are answered *in vitro* and *in vivo*, assuming that mTOR inhibitors durably affect central pathways in progression of atherosclerosis.[10] The restoration of vasomotion[23] and the recapping of lesions[4] in patients with Absorb BVS implantation open a new page in the history of the intravascular treatment already dubbed 'vascular reparative therapy' by some investigators.[4, 9, 14]

BRS may potentially stimulate specific molecular pathways promoting vascular remodeling, innate[7, 24] and adaptive immunity, and trigger mechanisms including re-endothelialisation, cellular reorganisation, and resorption of calcium by osteoclast-like cells.[25] The rebuilding of the vessel wall via de- and transdifferentiation of the resident and other stem or progenitor cells is regulated by shear stress or mechanical tension and growth factors such as TGFβ, extra domain A fibronectin (ED-A FN) and other cytokines.[26, 27]

The mobilisation and subsequent reduction of the necrotic core is a cornerstone target for BRS, halting macrophage-dependent pathways with impact on prolonged endoplasmic reticulum stress, phenotype and activity as well as primary and secondary necrosis.[28] The activity of the adventitia[27] as a niche for stem and progenitor cells, source of myofibroblasts, and a gate for inflammatory cells including B and T cells[29, 30] is a pivotal element of the vessel wall homeostasis, which might also be affected by BRS. Furthermore, the turnover of endothelium and optimal re-endothelialisation with engraftment of circulating


A
Glagov phenomenon
Risk factors
I
II
III
40%
IV
[10, 11]
Lumen enlargement
?
?
BVS
'Golden tubes' phenomenon
VII
VI
V
[6, 9, 10, 41]
[10]
Sirolimus-DES
Phenomenon of evaginations
IX
VIII
Lower ESS (< 6-10 dynes/ cm²)
Physiologic ESS (~15 dynes/ cm²)
Low ESS (10-14 dunes/ cm²)
High ESS
Oscillatory ESS
[6, 10, 13]
BMS with permanent alien body in artery
Neoatherosclerosis
[6, 75]
Everolimus-DES
No neoatherosclerosis
XI
X


B
Injury, hypoxia, compromised cell/ cell contact, mechanical overstretching, growth factors, shear stress, cyclic strain, mTOR inhibition, activated mitochondria, energy metabolism
endothelium
Contractile MF αSMA+
[8, 18, 19, 30]
Remodeling of ECM:
↓ Fibrillar collagen
↑ Non-fibrillar collagen (by contractured MF)
↓↓ > ↑∞ Elastin
Remodeling of ECM:
↑/? Fibronectin
↑ Proteoglycan
Synthetising SMC αSMA+
[35, 36]
Proto-MF
[33]
[33]
[31, 32]
Contractile SMC αSMA+
INTIMA - PLAQUE
[38]
[38]
Transdifferentiated cell αSMA+
[34]
[35, 37]
Macrophage-like cell αSMA+ M1/M2?
[31, 32]
SMC progenitor/ contractile SMC αSMA+
Fibroblast
↓ Apoptosis [26]
↓ Autophagy
↓ Necrosis [26]
↑/? Calcification [23]
Feedback to T/B cell response
↑/? Repair
Mesenchymal/ ABCG2+ stem cell
[20]
[20]
IEM
MEDIA
EEM
Mesenchymal progenitor
[38]
ADVENTITIA
[38]
[27, 38]
[27, 29, 38]
Pericyte
Resident or circulating mesenchymal stem cell
Sca1+/ mesenchymal stem-progenitor cell

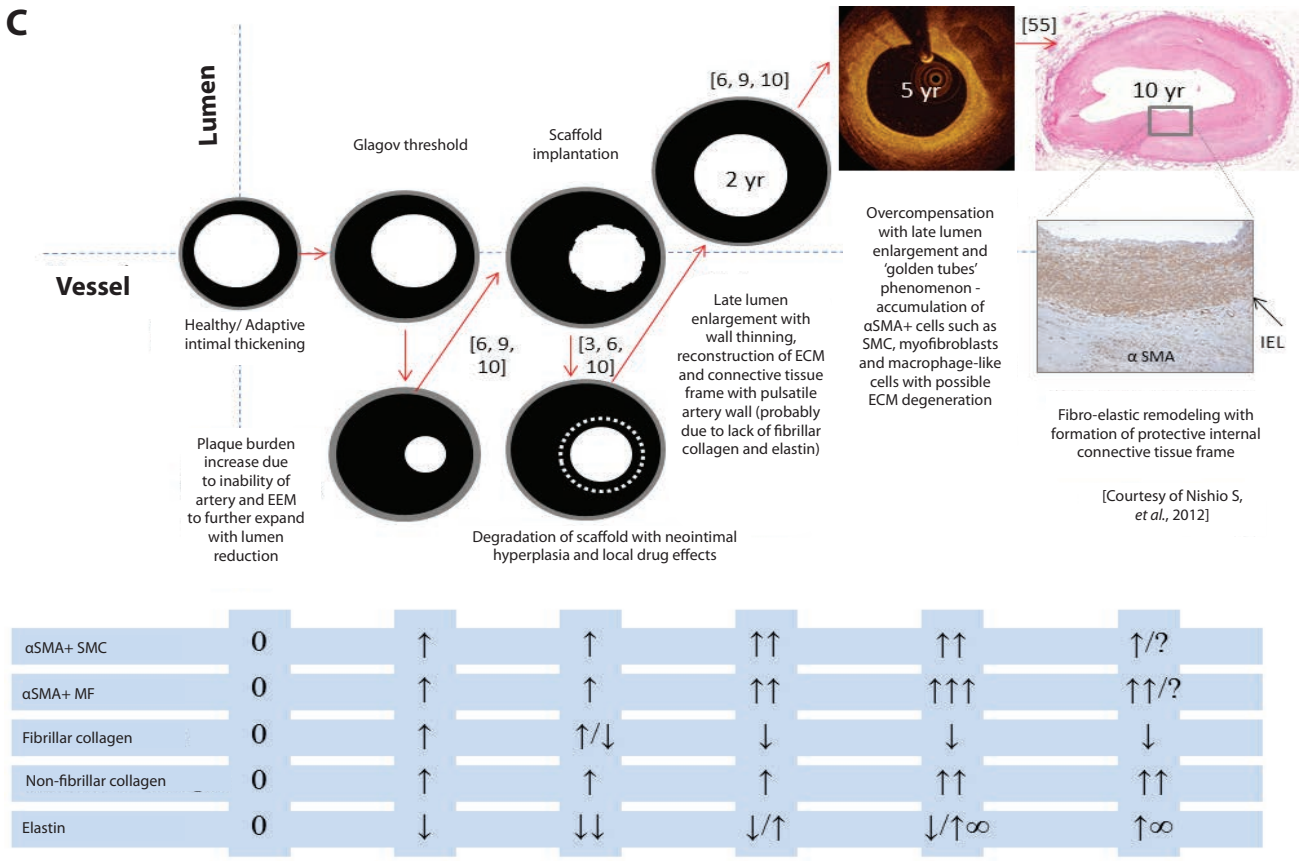


Figure 2: Glagov phenomenon as target for reversal of atherosclerosis. **Panel A** shows the general concept of the Glagov phenomenon (frames I-IV), and of the BRS-mediated reversal (frames V-VII). After BRS implantation, an artery undergoes the remodeling process with lumen enlargement, vessel wall thinning (plaque-media reduction) and pseudo-atheroregression (with OCT-visible 'golden tube'), which can be regarded as a kind of vascular reparative therapy. At 24 months, most struts of BVS 1.0 ABSORB are no longer detectable. In contrast to BRS, a metal cage (usually sirolimus-DES or BMS; see frames V, VIII, XI) provokes chronic irritation of tissue with progressive neoatherosclerosis, or can prevent neoatherosclerosis (DES; see frames V, VIII, IX, X) with OCT-detectable coronary evaginations – defined as outward bulges in the luminal contour between struts (sirolimus-DES; see frame IX) fixed to the struts, limiting further artery wall expansion. Endothelial shear stress (ESS) adjusts to artery remodeling and transient scaffolding. **Panel B** demonstrates the hypothetical cellular biology (animal data-based) of artery remodeling after the implantation of BVS/mTOR inhibitor platform. There are depicted: the role of phenotypic switch of smooth muscle cells (SMC) and fibroblasts/myofibroblasts (MF), migration (from the circulation, perivascular adipose tissue and resident sites – internal layers of adventitia) and action of different stem-progenitor cells (Sca1+, mesenchymal, circulating, bone marrow-derived) as well as activation of α-smooth muscle actin (+) (α-SMA) cells (MF, SMC, macrophages) with reconstruction of extracellular matrix (ECM) frame. IEM – internal elastic membrane, EEM – external elastic membrane. Pathways of α-SMA cell activation are considered as potential targets for the management of artery remodeling. **Panel C** schematically represents the reorganisation of the ECM and related artery remodeling after BVS implantation with analysis of the vessel/lumen ratio over time. Accumulation of α-SMA(+) cells with degradation of fibrillar collagen and deposition of elastin with non-fibrillar collagen play a major role in late lumen enlargement. IEL – internal elastic lamina. Figure adapted from reference [2, 5, 7, 20].

progenitors[30, 31] as well as neovascularisation[8, 32, 33] and switch over VSMC or myofibroblasts[21, 22] are other factors determining the restoration of the vessel wall and optimal artery remodeling after Absorb BVS implantation.

BRS is also able to potentially modulate biologic effects of shear stress and mechano-transduction with a slow adaptive response of the vessel wall to the mechanical degradation of the BRS, facilitating restoration of cyclic strain by affecting the arterial stiffness as well as rearrangement of collagen/elastin density and the connective tissue frame.[22] The degradation of fibrillar and accumulation of non-fibrillar 'hyaline-like' collagen maintains the balance of the fiber density between different sublayers, thereby probably changing the mechanics of the artery and ensuring the 'conservation' or 'cementation' of ECM particularly between necrotic core and lumen. This degradation, accompanied by continuous slow increase of production of elastic constituents with turnover of collagen, provokes overcompensated extension of the vessel wall.

The cellular mechanisms of the above-mentioned arterial remodeling remain unclear due to the limited interpretation of some histology studies.[3, 4, 6] The Russell-Movat pentachrome staining does not allow distinction between the synthetising phenotype of VSMC and MF. Both types of cells synthesise smooth muscle alpha-actin and vimentin as well as collagen and proteoglycans, and have their distinction mostly in the transcriptional mechanism of protein expression.[33] The only difference between these cell types is expression of myosin (lacking in MF) and desmin (absent in VSMC).[33]

Accumulation of ECM, α-smooth muscle actin-expressing cells (see Figure 2) such as VSMC, MF and macrophage subsets (along the M1 - M2 spectrum) may play a major role in the overcompensated remodeling and formation of the so called OCT (optical coherence tomography)-documented phenomenon of 'golden tubes' (novel optically-bright homogenous internal layer) observed after Absorb BVS implantation with

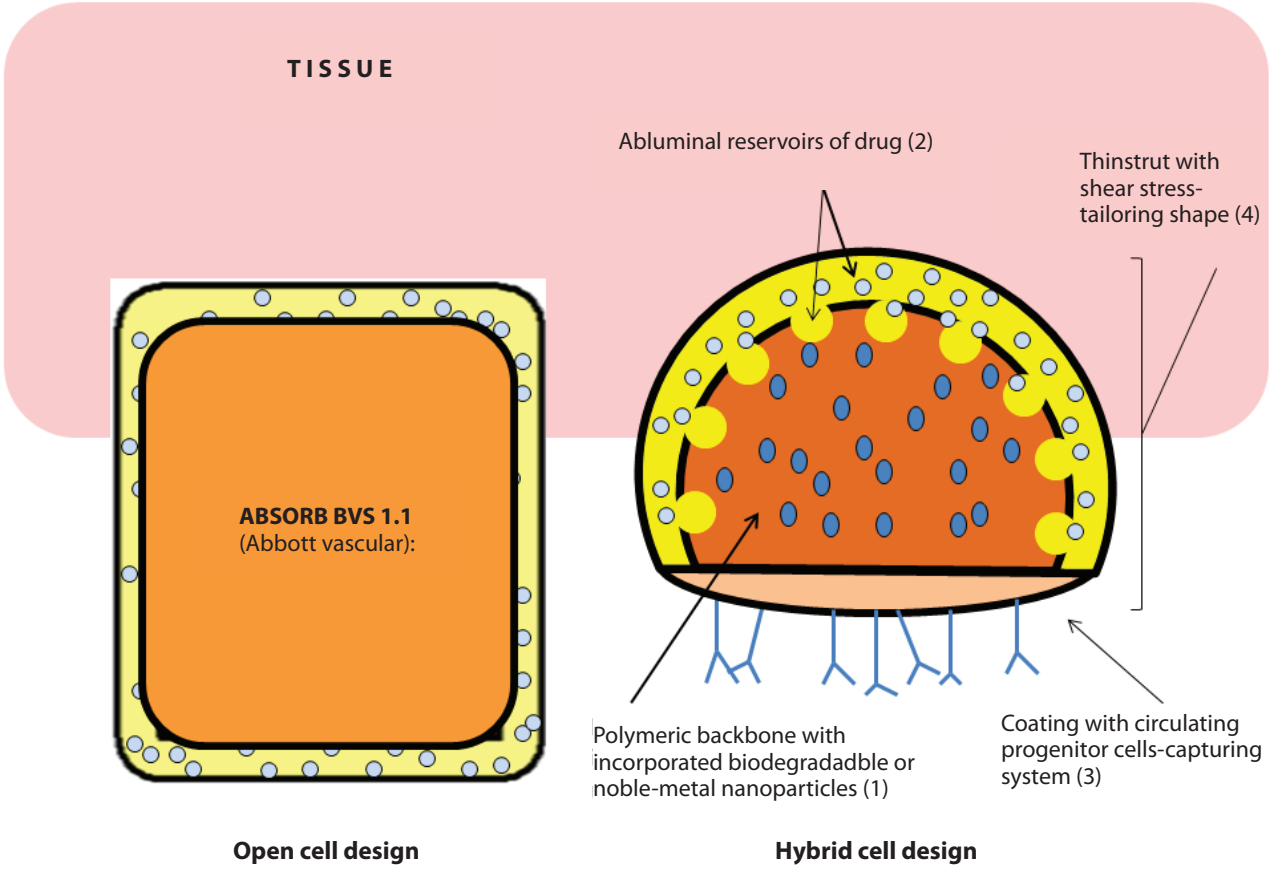


Figure 3. The optimal implantable platform: BRS or nanotechnologies? The panel demonstrates a cross-sectional appearance of BRS (thick struts with weak mechanical properties, eluting mTOR inhibitor (one month release) and proposed optimal scaffold. The structure of the ultimate platform includes: 1. A polymeric backbone with incorporated biodegradable nanoparticles (for example, lipid and calcium-phosphate-based with better mechanical properties), carrying mTOR inhibitor/ drug (long-term drug-release and optimal local metabolism), 2. Abluminal reservoir of mTOR inhibitor/ drug in lipid-based nanoparticles, acting acutely, 3. Coating with antibodies to CD73+, CD105+ or CD133+ in order to capture progenitor cells for optimal re-endothelialisation and immune or repair responses.

fibro-elastic reconstruction.[33-38]

The polylactate of BRS is highly biocompatible and promotes normal metabolism with degradation up to products of the Krebs cycle.[39] Metabolic turnover of lactate could be a key factor in the mitochondria- and ROS-mediated response to the exhaustion of energy and cell respiration. This approach is of significant value in designing new therapeutic strategies for alleviation of mitochondrial dysfunction and bioenergetics failure observed in atherosclerosis.

During the first 1-3 months after implantation local or systemic (long-term) mTORC1 inhibition using everolimus could modify parameters such as endothelial function (reduce eNOS expression at high shear stress); apoptosis/autophagy (stimulate innate immunity);[40] matrix generation (inhibit collagen synthesis);[40] VSMC proliferation and migration;[41] cholesterol efflux (due to increased ABCA1);[41] cholesterol uptake (suppression of scavenger receptors SR-A, SR-BII, CD68, CD36, LOX-1);[40,41] monocyte chemotaxis (decrease in MCP-1 and SDF-1),[40,41] promoting a favourable immune and repair response with the reduction of the necrotic core and atheroregression.

Taken together, BRS and mTORC1 inhibition may tip the balance in favour of scaffolding-mediated atheroprotection, and provide means to induce regression of atheroma below the *Glagov threshold*.

Optimising BRS: In Search of the Ideal Platform

The optimal design of BRS (see Figure 3) should confer excellent mechanical properties, timely release of appropriate drugs and defined duration of resorption. The currently available BRS platform (Absorb BVS, Abbott Vascular, Santa Clara, CA) is a balloon expandable open-cell design device consisting of a polymer backbone of poly-L-lactide (PLLA) coated with a thin layer of 1:1 mixture of an amorphous matrix of poly-D, L-lactide (PDLLA), and 1.0 µg/mm^2 of the antiproliferative drug everolimus.[15]

A novel optimal BRS platform could have a hybrid-cell design (open cells in the middle and closed cells at the edges) with thinner struts (40-80 µm) and stronger mechanical properties (radial strength at least 900-990 mmHg) with extra benefits such as slow drug releasing system for:

1. mTOR and mPTP (mitochondrial permeability transition pore) inhibitors which suppress cytochrome C and apoptosis as well as provide anti-

proliferative effects via the peripheral benzodiazepine receptor, or other drugs, for example, regulators of immune-inflammatory response such as new generations of limus in stable formulation – micro-crystalline or in a lipid envelope,
2. lipid metabolism modulators, for instance, rosuvastatin, lipoprotein-associated phospholipase A2 inhibitor, new substances such as PCSK9 inhibitors, ApoA1-Milano, monoclonal antibodies against oxLDL, and
3. reparative therapy of vasomotion and artery remodeling,
4. agents against 'spontaneous' and necrotic-core-mediated calcification such as calcitriol and paricalcitol,
5. components of ECM, including components (powders) of adipose tissue, or recombinant with minimal concentration of platelet-reactive substances,
6. anti-platelet drugs with minimal local toxicity, atheroprotective and reparative potential.

The abluminal nanocoating (thickness of no more than 100-150 nm) with bioresorbable polymer or nano-pores, and incorporation of nanoparticles, which are able to carry any drug could be helpful for the management of the vessel wall immediately after implantation and prevention of enhanced atherogenesis, atherothrombosis or detrimental and perverted biological feedback to the intervention. Local (drug-carrying nanoparticles within the backbone) or systemic administration (for example, low-dose chronic prescription of everolimus up to 2 mg each 2 days, or pulse therapy by 7.5 mg x 3 days, 5 mg x 2 days)[42] of mTOR inhibitor enhances optimal re-endothelialisation and the local cellular milieu's response and also provides general atheroprotective effects. Applying a drug-coated balloon[42] for pre-dilatation might be another solution for the local anti-proliferative therapy.

Calcium-phosphate[42, 43] or magnesium bioresorbable nanoparticles in the backbone and sophisticated management of the polymer structure ('raw' and rubber resin, shape memory technologies, solid freeform fabrication with micro-filamentation) with alterations of carbon bonds are able to substantially alter mechanical properties of the scaffold (such as conformability, recoil, eccentricity or asymmetry) and allow reduction of strut thickness. Moreover, the PDLLA-luminal layer can be coated with antibodies to capture progenitor cells selectively, such as against CD73, CD105 (cells with pro-mesenchymal phenotype) or CD34 (bone marrow-derived cells) and CD133 (endothelial cells). Cell-capturing approaches involve different progenitor cell types with unpredictable local inflammatory and immune response and require sophisticated selection of capture antibodies.

Conclusions

The adoption of transient scaffolding using bioresorbable platforms and the progress of new technologies have created an attractive field for device design in interventional cardiology and an important tool for treatment of atherosclerosis. This is largely due to the ability to guide artery remodeling, to generate multifunctional nanoagents bearing combinations of targeting, diagnostic, and therapeutic moieties. These approaches have the potential to achieve the goal of atheroregression below the *Glagov threshold*, thereby targeting restoration of vessel integrity.

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Undilatable Coronary Lesions – Rotational Atherectomy and Other Techniques

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Introduction

Several comorbilities, such as diabetes, hypertension and renal failure as well as smoking, have been identified as risk factors for coronary calcification.[1] This is a natural consequence of the ageing of a population, and could be a challenge for interventional cardiologists. Taking into account plaque fibrosis, percutaneous treatment of these kinds of patients is difficult. Massive coronary dissection, the inability to increase vessel lumen, stent delivery failure and its underexpansion are the most frequent obstacles to providing procedural success during coronary angioplasty.

To overcome the phenomenon of undilatable coronary lesion, several devices and techniques have been developed and are currently used in daily practice. Out of these, rotational atherectomy (ROTA) is recommended by the Guidelines on Myocardial Revascularisation of European Society of Cardiology, published in 2010.[2] The Society's experts have advised ROTA for highly calcified and fibrotic lesions that could not be passed with balloon or properly dilated before stent implantation. This strategy has received class I recommendation with level of evidence C.

Other devices for the preparation of calcific and fibrotic plaques cover high pressure balloons, cutting and scoring balloons and some techniques that facilitate coronary angioplasty.

The aim of this paper is to review the most popular devices that are used to treat patients with undilatable coronary lesions.

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Rotational Atherectomy in Drug Eluting Stent Era

The real development of interventional cardiology started in the 1980s with plain balloon angioplasty, which was followed by the introduction of coronary stents in the 1990s. In the meantime, different coronary devices were designed, in which high speed rotational atherectomy (ROTA) was one of the most tested in clinical practice.

The basic mechanism for ROTA is plaque ablation by diamond coated burr abrading calcific and fibrotic plaque. Due to the high speed rotation of the burr, microparticles (less then 10 μm) are produced. The size of the debris is so small that they are wash out from distal coronary microcirculation and caught by macrophages in the liver and spleen. The technical details of ROTA are described elsewhere.[3] Of note, current recommendations of ROTA performance are based on the results of a few clinical trials that were published more than 10 years ago. The initial idea for ROTA was plaque debulking as large as possible with aggressive burr selection protocol (means burr/artery ratio > 0.7), but the acute lumen gain was not satisfactory and raised a significant percentage of complications.[4, 5] Further studies have shown that a smaller burr/artery ratio is safer, and facilitates the next steps of coronary angioplasty (Figure 1). This approach is now called plaque modification.[6]

Clinical utilisation of rotational atherectomy has varied over the last 20 years. Stand alone techniques, treatment of in-stent restenosis, plaque debulking in complex lesion and supporting coronary stenting were all clinical and angiographic indications for ROTA. Unfortunately, combinations of calcific lesions and bare metal stents have resulted in a high incidence of in-stent restenosis,[7] and therefore the technique has been overshadowed for many years.

Drug eluting stents (DES) have changed the treatment of myocardial revascularisation in recent years.[2] Results of the ARTS II and SYNTAX trials[8, 9] have shown that multivessel coronary angioplasty may be considered for treatment. Secondly, a subgroup of elderly patients with many comorbilities are at high risk of cardiac surgery. The percentage of coronary calcification is high in this subgroup, and coronary angioplasty should be supported by ROTA if indicated. On the other hand, concerns

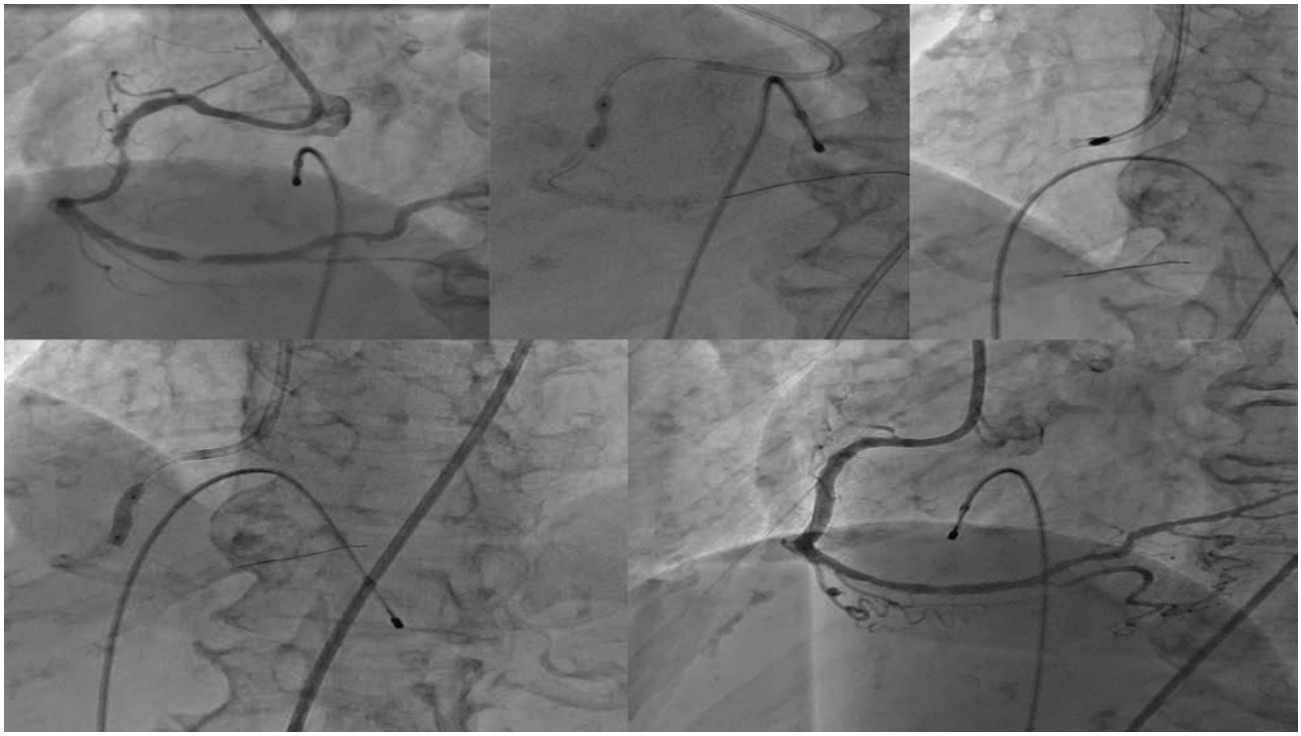

Figure 1. Case example of undilatable lesion in right coronary artery. The patient had unsuccessful coronary angioplasty for NSTEMI – mid segment lesion was resistant to non-complain balloon and stent delivery to distal lesion was observed. During the next attempt, rotational atherectomy with 1.75 mm burr was successful, followed by 3 drug eluting stents implantation.

regarding DES implantation in highly calcified lesions have been raised. One could speculate that manipulation and stent delivery through calcified lesion may destroy polymer coating, and stent struts apposition could be impaired.[10, 11] These facts may be responsible for stent thrombosis and the high incidence of in-stent restenosis. Therefore, the idea of DES & ROTA symbiosis were developed. Several papers have reported a low risk of complication and adverse cardiac event during follow-up after drug eluting stent implantation preceded by rotational atherectomy.[12-14] One of the first reports, a study by Clavijo *et al*.,[12] has shown that sirolimus eluting stent implantation in calcified lesions is feasible and safe. These conclusions were confirmed by Benezet J. *et al*. who found a target lesion revascularisation rate of 8.8 % and a total percentage of adverse cardiac events of 12.7 %.[13] Overall, the highest published rate of target lesion revascularisation was 9.5 % with rate of major cardiac events of 15.8 %.[14] The usefulness of rotational atherectomy was clearly demonstrated by Fujimoto *et al*., who compared the long-term outcome of haemodialysis patients treated with or without ROTA.[15] The authors found not only a significant reduction in target lesion revascularisation (11.5 vs 36%, respectively) but also showed a non-significant trend to lower stent thrombosis (0 vs 7.1%, respectively).

The main limitation of all published papers dealing with ROTA followed by DES implantation was the fact that they were prospective or retrospective (mostly) registries conducted within a single centre. Recently, data coming from multicentre trial ROTAXUS were published.[16] A total number of 240 patients were randomised to ROTA plus stenting or stenting alone. The primary end-point of this study was late-loss at 9 months follow-up and it was larger in ROTA+stenting group, although binary restenosis was similar in both groups. The major cardiac adverse events rate difference was non-significant between groups (secondary end-point). However, several angiographic and procedural factors that can influence late results should be raised. First, more than 50% of patients had only moderate calcification and probably needed only standard therapy in most cases. Moreover, patients assigned to ROTA+stenting had significantly longer lesions. Higher inflation pressure was used in stenting alone group and only the first generation of DES–TAXUS stent (Boston Scientific Co.) was allowed that might modify late results. There were 2 procedural advantages of ROTA+stenting strategy. First, crossover from one strategy to the second was higher in the stenting alone group and overall strategy success was significantly higher in ROTA+stenting group. One can summarise the results of the trial in one sentence: ROTA is not superior to the standard approach in terms of angiographic end-points like late loss, but facilitates coronary intervention in patients with severe calcification. My personal view is that it is a great pity that patients with severe calcification have not undergone separate sub-analysis.

The study that has proven the efficiency of debulking strategy before stenting is the DOCTORS trial. Patients with chronic total occlusion were randomised to debulking+stenting or to a stenting alone strategy. There was a trend to lower binary restenosis rate in the debulking group and significant difference in terms of major cardiac events favouring debulking strategy.[17]

High Pressure Balloons

The first, reasonable step for undilatable lesion is a non-compliant

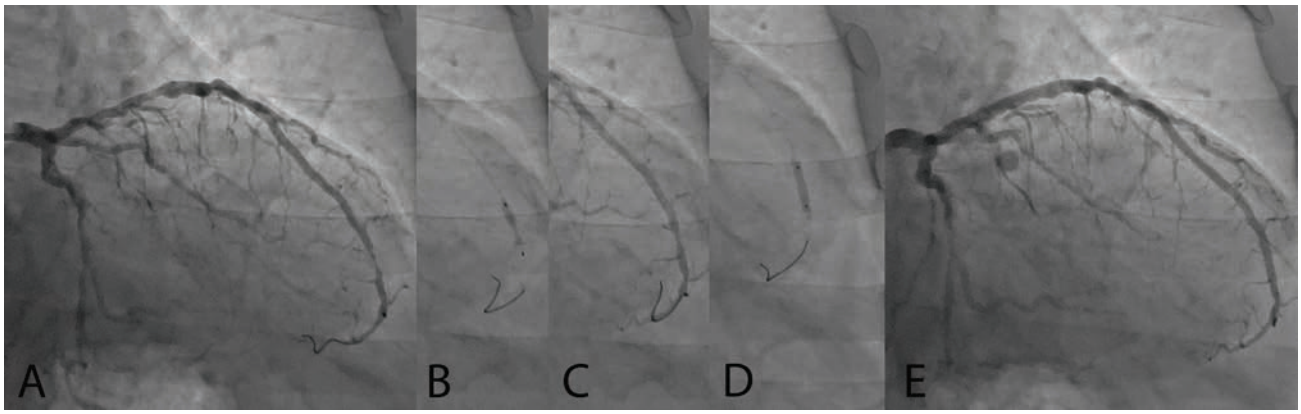

Figure 2. Severe stent underexpansion implanted in distal LAD (direct stenting technique) (A-C). High pressure balloon (OPN NC, Sis Medical Co.) was used to overcome the stenosis (D), with an excellent final result (E).

balloon. It is frequently used in every day practice although calcific and fibrotic lesions have a focal resistance point that might lead to balloons not fully expanding. This phenomenon is known as the "dog-bone effect" and the increase of inflation pressure is related to balloon rupture or vessel perforation. One of the mechanisms related to vessel injury is a "pin-hole" rupture, which means a small gap in balloon material. This rupture may result in a high pressure wave blow at the vessel wall with subsequent perforation. Recently, a new device was developed to counteract this phenomenon. Produced by SIS Medical, OPN NC balloon has a double layer construction. Due to the features of this balloon, the risk of balloon and vessel rupture is minimised because of very low compliance and lack of "dog-bone" effect. Additionally, the OPN NC balloon has a very low entry profile (0.016 inch) that improves balloon delivery at lesion. However, the most important attribute of OPN NC balloon is high inflation pressure with burst rate value of 35 atm. The SIS Medical company tests the balloon to 42 atm. High inflation pressure was also reported by Diaz *et al*.[18] and Raja *et al*.[19] In the series of patients (respectively 8 and 4 patients), they have demonstrated that inflation to 40 atm is safe, without cases of perforations and dissections. Of note, the OPN NC balloon was used to redilatate underexpanded stents in 5 patients and to treat in-stent restenosis in 2 patients. Unfortunately, the procedure with OPN NC to prepare the lesion, was unsuccessful. The second report included patients in whom OPN NC was used to prepare lesions, which was met with success.

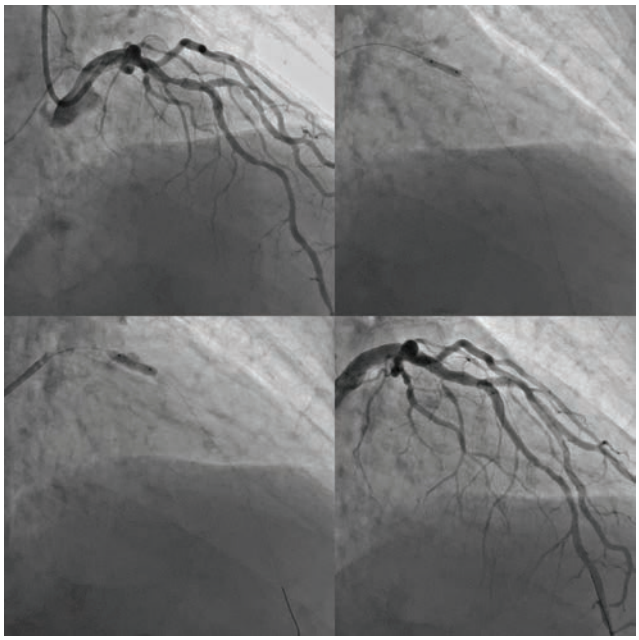

Figure 3. Cutting balloon case example. Predilatation with regular balloon (2.75x10 mm) showed incomplete dilatation. Subsequent cutting balloon angioplasty (3.0x10 mm) has improved vessel lumen, although stent residual stenosis was present finally.

However, the question of potential indications for OPN NC balloon could be raised. Of course, there are no clinical trials or large patient series published so far, and therefore our knowledge is limited. The reported cases have showed that the device is both safe and effective in the treatment of undilatable lesions. It seems that redilatation of underexpanded stent is one of the indications (Figure 2). The second is lesion preparation instead of rotational atherectomy, especially in the case of coronary dissection appears during coronary angioplasty. This is well-known contraindication to rotational atherectomy. Further studies are needed to establish the device's indications, but it seems that it worth have OPN NC balloon on the shelf to solve the issue of undilatable lesions.

Cutting and Scoring Balloons

The Cutting Balloon was introduced to clinical practice more than 2 decades ago.[20] It was believed that its non-compliant balloon and incision blades were able to score coronary plaque by severing fibrotic and calcific components. Unfortunately, the first device was quite bulky and it was often hard to deliver into the lesions. The current generation of the balloon is much improved by blade modification. The Flextome Balloon (Boston Scientific Co.) has 3 or 4 blades that have special points of minor resistance, providing flexibility and deliverability. The main indication for cutting balloon are complex, resistant lesions as well as in-stent restenosis treatment.[2] Although the evidence is limited, a small number of patients with calcified lesions were treated by Karvouni *et al*.[21] They found that balloon angioplasty followed by cutting balloon angioplasty before stent implantation provided a larger angiographic acute gain than plain balloon angioplasty alone (Figure 3). A more recently published paper by Vaquerizo B *et al*.[22] has shown that plaque

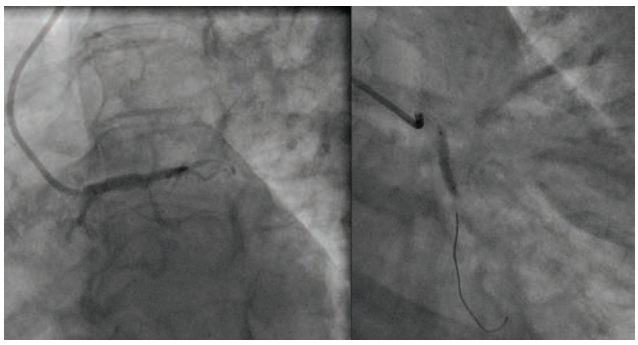

Figure 4. Buddy wire technique in circumflex artery originating at high grade. Occluded artery was reopened and drug eluting stent was placed using buddy wire technique.

modification in moderate calcified lesions is achieved in 57% of patients by cutting balloon angioplasty with acceptable long-term results after DES implantation. Out of the presented population, patients with severe calcified lesions were treated by ROTA, followed by cutting balloon angioplasty. The latter strategy is called ROTACUT by some authors.[23] Furuichi *et al*. have shown that both angiographic and intravascular ultrasound dimensions were significantly larger than in patients treated only by plain balloon angioplasty.[23] Of note, the authors have not reported long-term results of this strategy and our expertise of ROTACUT is limited. Despite ESC recommendations for in-stent restenosis, it seems that cutting balloon angioplasty is only a stand-by device for complex coronary lesions. Among other indications of cutting balloon, peripheral and carotid angioplasty should be mentioned.[24]

A novel coronary and peripheral device was recently developed and clinically tested. The AngioSculpt Balloon (Angioscore Inc.) is a semi-compliant balloon that has three nitinol rectangular spiral struts, which work in a similar way to cutting blades. The structure of the balloon provides precise plaque scoring. A paper by Fonseca A. *et al*. has shown that the device is feasible and safe in both complex and in-stent restenosis lesions.[25] These findings were confirmed by Costa *et al*. who have shown that AngioSculpt improved DES expansion.[26] The potential advantage of the device is stability within the lesion, and therefore it is recommended by European guidelines for treatment of in-stent restenosis (low risk of balloon slippage).

At the end of this section, it should be noted that there is one further device that could be used in undilatable lesions. Previously reported usage of ROTA in chronic total occlusion lesions could be replaced by a new penetrating catheter the Tornus (Asahi Intecc Co.). Based on its structure, the Tornus device is a microcatheter that can be advanced through the lesion using rotation (like a drill). Entry profile is quite low at the tip and increases as it progresses, producing larger lumen for regular balloons.[27]

Simple Techniques to Facilitate your Intervention

Undilatable coronary lesions are not only the ones that might lead to the failure of coronary intervention. Sometimes, mild coronary calcifications or fibrotic lesions are associated with stent delivery failure or stent dislodgement after normal balloon predilatation. One should remember that several angioplasty techniques were developed to enhance stent delivery if the guiding catheter fails to support the delivery. The most simple and popular is a "buddy wire" technique (Figure 4). The insertion of a second, often stiffer parallel wire provides stronger support with a specific rail that facilitates balloon and stent insertion.[28] Another option is wire placement in proximally located side branch (i.e. right ventricular branch from RCA) or additional wire placed in LAD when performing angioplasty of circumflex artery. These techniques stabilise guiding catheter in coronary ostium and could be also used for "anchor" balloon technique. There are 2 possibilities; inflating the small balloon in the proximal side branch or to inflate a larger balloon in the distal portion of the artery. The latter facilitates the insertion of a long, stiff stent in the proximal part of treated artery.[29]

An alternative technique, generally named the "telescopic technique" was developed to enhance guiding support. This class of approach covers several techniques. One of these is the usage of 2 guiding catheters, one large and a second which is smaller (i.e. 8 and 5 French). Briefly, the first is placed in coronary ostium and the smaller one is introduced into larger catheter and placed deeper than the ostium in coronary artery. Low-profile stents and balloons are deployed via 5 French catheter. It is obvious that the length of these 2 catheters has to be different, but it's possible to order shorter or longer ones or cut the larger catheter using a regular artery sheath as a valve instead Y-connector.

The aforementioned "home made" solution is quite bulky, and therefore the industry has developed a special device to support guiding catheters. The Guideliner Catheter (Vascular Solution Co.) provides mother-and-child guide extension, and is available in a few sizes (from 5.5 to 8 French) and 25 cm of extension section. The second item is based on guiding catheter body (Heartrail II , Terumo Co.) and is 120 cm straight, soft catheter that has inner diameter close to regular 5 French guiding catheters. Both devices are helpful during complex coronary interventions and allow a deep and safe intubation only to proximal and mid segments of the coronaries. This limitation is due to short usable length of majority of balloons' & stents' shafts, that are approximately 140 cm. Further limitations are related to Y-connector and the length of the deployed device.

One could argue that both the buddy wire technique and telescopic technique is not often needed. Single, stiff guidewire is sufficient for majority of coronary angioplasties, but sometimes manipulating and advancing the stiff wire is difficult. Lesion crossing with flexible and hydrophilic wire should be a first step, followed by microcatheter deployment and then wire replacement. Therefore, it is reasonable to have microcatheters in a catheterisation laboratory.[30]

The last, simple technique that can facility complex lesion angioplasty is the hugging balloon technique. It has been demonstrated that 2 small profile balloons inflated simultaneously in the coronary artery

can improve vessel lumen in case of refractory lesion.[31] Previously, this technique was also frequently used to dilate large coronary or sapheneous graft lesions, but this is no longer the case (low profile large balloons are available). A modification of this technique is now used during kissing balloon inflation (bifurcation treatment).

Summary

Undilatable coronary lesions are not frequently observed during every day practice. However, every interventional cardiologist could face the condition during both elective and emergency intervention. Knowledge and access to board instrumentation of devices are key-points to achieve procedural success. Rotational atherectomy is a ESC Guidelines supported strategy that is recommended in most cases of undilatable lesions. The disadvantage of this technique is a list of potential contraindications and the technique should mainly be used during elective cases by adequately trained physicians. For emergency interventions or angioplasties that are too late for ROTA, special balloons and techniques are available.

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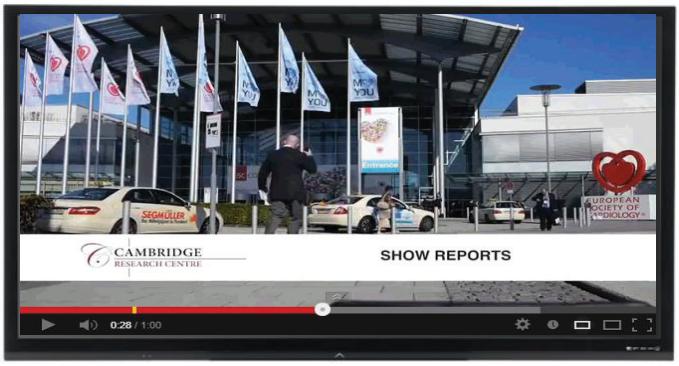

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Drug-coated Balloons for Coronary Interventional Procedures

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Introduction

Drug-coated balloons have changed the treatment strategy for coronary artery lesions. Presently available drug-coated balloons are loaded with the lipophilic paclitaxel, which inhibits cell division and cell migration, leading to a reduction in neointimal proliferation. With drug-eluting stents, the maximal concentration of the antiproliferative substance is highest around the stent struts.[1] With paclitaxel-coated balloons the antiproliferative drug is located at the balloon surface which is in contact with the vessel wall during the inflation period. In principle, this contact enables a homogenous dose delivery to the vessel wall, in contrast to drug eluting stents.[1] An inflation of 30 to 60 seconds allows the deposition of paclitaxel. Even a short contact of 10 seconds seems to be sufficient for administration of paclitaxel into the vessel wall,[2] allowing to treat critical lesions. The concentration of paclitaxel on paclitaxel-coated balloons is about 3 times higher (about 3µg/mm^2) compared with paclitaxel-eluting stents.[3-7] Up to 20% of the paclitaxel dosage is transferred from the balloon surface to the vessel wall.[7, 8] With this immediate drug release, there is no need for a polymer for drug administration, which was associated with chronic inflammation and late thrombosis with first generation drug eluting stents.[9] Without an additional stent implantation, dual antiplatelet therapy is shorter with use of paclitaxel coated balloons compared with drug eluting stents.

Most experience in coronary interventions with paclitaxel-coated balloons is from a coating including paclitaxel and hydrophilic nonionic X-ray contrast medium iopromide. This type of paclitaxel coating was used for the Paccocath balloons (Bavaria Medizin Technologie), SeQuent Please balloons (B.Braun, Melsungen, Germany), and with a similar technology for the Cotavance balloons (MEDRAD Inc, Warrendale, PA). Other coatings for paclitaxel coated balloon include urea (IN.PACT balloons, Medtronic, Minneapolis, MN), butyryl-tri-hexylcitrat (Pantera Lux, Biotronik, Bülach, Switzerland), or shellac (Dior, Eurocor, Bonn Germany). Randomised clinical trials demonstrated that there are relevant differences among different drug eluting stents in terms of angiographic and clinical outcome[10, 11] allowing sufficient treatment of complex coronary lesions with modern drug eluting stents.[12] Similar to drug eluting stents, there is no certain class effect for paclitaxel coated balloons. The type of paclitaxel coating has a relevant impact on angiographic and clinical results. Therefore efficacy and safety has to be shown in randomised clinical trials for every type of coating. This short review focuses on the clinical evidence for paclitaxel-coated balloon angioplasty for coronary interventional procedures.

Coronary Interventional Procedures

In-stent Restenosis

In randomised trials, paclitaxel coated balloon angioplasty (Paccocath, SeQuent Please) was superior to uncoated balloon angioplasty for the treatment of in-stent restenosis in bare metal stents[3] and in-stent restenosis in drug eluting stents.[5, 13] Superiority was demonstrated for both angiographic and clinical end points. Late lumen loss and angiographic restenosis rate were significantly reduced with use of the paclitaxel coated balloon paralleled by a significant reduction for the need of target lesion revascularisation and target vessel revascularisation compared with uncoated balloon angioplasty. This was demonstrated for both bare metal stents restenosis and drug eluting stents restenosis. Most important, this initial clinical benefit sustained during long-term follow-up. There was no sign for late catch-up with a significant reduction of target lesion revascularisation from 38.9% for uncoated balloon angioplasty to 9.3% with paclitaxel coated balloon angioplasty ($p=0.004$) during 5.4±1.2 years.[14] The SeQuent Please World Wide Registry (SeQuent Please) with 2095 patients is the largest experience with paclitaxel coated balloon. Treatment with paclitaxel coated balloon for in-stent restenosis was performed in 1561 patients. Target lesion revascularisation rate was significantly higher with paclitaxel coated balloon for drug eluting stents restenosis compared with paclitaxel coated balloon for bare metal stents restenosis (9.6% versus 3.8%, $p<0.001$) during 9 months clinical follow-up. This difference reflects the selection of drug eluting stents for lesions with a higher risk for restenosis. There was no difference for paclitaxel coated balloon angioplasty for treatment of in-stent restenosis in paclitaxel-eluting stents compared with treatment of in-stent restenosis in non-paclitaxel-eluting stents (8.3% versus 10.8%; $p=0.46$).[15]

Paclitaxel coated balloon angioplasty and paclitaxel-eluting stents were

similar for the treatment of in-stent restenosis in a randomised trial including 131 patients.[16] Target lesion revascularisation rate was 6% with paclitaxel coated balloon compared with 15% with paclitaxel eluting stents (p=0.15). The use of drug eluting stents for the treatment of in-stent restenosis resulted in a stent thrombosis rate of 1.6% within 1 year[17] and 2.7% within 2 years[18] despite dual antiplatelet therapy for at least 6 months. The need for dual antiplatelet therapy is shorter with paclitaxel coated balloon angioplasty compared with drug eluting stents treatment. With paclitaxel coated balloon angioplasty alone, dual antiplatelet therapy is administered for 4 weeks[19] in contrast to drug eluting stents with 6-12 months. Nevertheless, the rate of vessel thrombosis is low with paclitaxel coated balloon angioplasty and was only 0.1% in the SeQuent Please Word Wide Registry including 2095 patients with 2234 lesions.[15] Recently the ISAR-DESIRE III demonstrated that angioplasty with a paclitaxel-coated balloon was a preferable treatment strategy for in-stent restenosis of limus-eluting stents.[20] In this trial, 402 patients with an in-stent restenosis were consecutively enrolled and randomised to either a treatment with the paclitaxel coated balloon, implantation of a paclitaxel-eluting stent, or plain balloon angioplasty. In the six months angiographic follow up there was no difference between the paclitaxel coated balloon angioplasty and the paclitaxel eluting stent strategy in concern of binary restenosis rate (26.5% for paclitaxel coated balloon versus 24% the paclitaxel-eluting-stent, p=0.61) and target lesion revascularisation (22.1% for paclitaxel coated balloon, 13.5% for paclitaxel eluting stent, p=0.09). Both strategies were superior to the plain uncoated balloon angioplasty (56.7% binary restenosis, 43.5% target lesion revascularisation). The authors concluded that drug coated balloon treatment strategy for in-stent restenosis should be the preferred treatment.[20]

Based on registries, paclitaxel coating in combination with butyryl-tri-hexylcitrat [Tölg R, Transcatheter Cardiovascular Therapeutics 2011, San Francisco], urea-matrix,[21] or shellac[22] showed promising preliminary results. Randomised controlled trials are now important for the demonstration of safety and efficacy since there is no class effect of paclitaxel coated balloons.

De Novo Coronary Artery Disease

Paclitaxel coated balloon angioplasty of *de novo* lesions is an attractive idea. Without the need for stent implantation, the risk for vessel thrombosis is minimal including a shorter dual antiplatelet therapy treatment compared with drug eluting stents. However, flow limiting dissections and acute recoil may require the additional implantation of stents. Paclitaxel coated balloon angioplasty (SeQuent Please, B.Braun, Melsungen, Germany) has been studied in small vessels,[23] in combination with an endothelial progenitor cell capturing stent,[4] and in patients with *de novo* lesions and diabetes mellitus.[24] For small vessels, paclitaxel coated balloon angioplasty resulted in excellent angiographic and clinical results if there was no need for stent implantation due to recoil or dissection.[23] However, with the need for additional stent implantation angiographic late loss was clearly higher. It is well known from old intravascular ultrasound studies that the implantation of stents increases the amount of neointimal proliferation compared with plain old balloon angioplasty. Therefore, after additional stent implantation another paclitaxel coated balloon should be used, if the stent was implanted outside or at the edge of the initially treated segment with the paclitaxel coated balloon. This treatment strategy compensates for any geographic miss due to stenting of dissections of residual lesions. In the SeQuent Please World Wide Registry there was a large population with treatment of *de novo* coronary artery disease in vessels with mainly small diameter below 3.0mm.[15] In this registry another paclitaxel coated balloon was used in case of geographic miss after additional bare metal stent implantation. After clinical 9 months follow-up the need for target lesion revascularisation was low and did not differ between patients with or without additional bare metal stents implantation (1.0% versus 2.4%, p=0.31).

Treatment strategy with paclitaxel coated balloon angioplasty (SeQuent Please) plus bare metal stents compared with paclitaxel eluting stents for *de novo* lesions in patients with diabetes mellitus revealed similar results regarding in-stent (0.51±0.61 mm vs. 0.53±0.67 mm) and in-segment late loss. Furthermore, rates of target lesion revascularisation (8.9% vs. 10.3%) and major adverse cardiac events (13.3% vs. 15.4%) did not differ.[24] Dual antiplatelet therapy was given for 3 months after treatment with paclitaxel coated balloon plus bare metal stents, and for 6 months after drug eluting stents. Stent thrombosis rate was 0% for treatment of paclitaxel coated balloon as compared with 2.6% for drug eluting stent implantation at 9 months (p=0.94). In the PERfECT stent study, the impact of paclitaxel coated balloon angioplasty in combination with an endothelial progenitor cell capturing stent was studied. Endothelial progenitor cell capturing stents have CD34 antibodies attached to the surface of the struts leading to a faster and more complete endothelialisation.[25, 26] Since there is no antiproliferative drug included in the CD34 antibody surface the use of a paclitaxel coated balloon in order to reduce neointimal proliferation is an interesting concept. In the PERfECT stent study a treatment strategy of endothelial progenitor cell capturing stent plus paclitaxel coated balloon was compared with endothelial progenitor cell capturing stenting alone for treatment of *de novo* coronary artery disease.[4] The combined treatment strategy significantly reduced angiographic restenosis rate and subsequently reduced the need for target lesion revascularisation compared with endothelial progenitor cell capturing stenting alone. Furthermore, neointimal proliferation in the segment proximal and distal to the stent was reduced in the same amount as the neointimal proliferation within the stent. This is an interesting point for the combined treatment strategy, since with drug eluting stents about half of the restenosis are located within the stent and half of the restenosis are located in the segment proximal and distal to the stent.[27, 28] In the PERfECT stent study, the treatment strategy was to exceed the stented segment with the paclitaxel coated balloon angioplasty allowing administration of paclitaxel to the segment proximal and distal to the stent. In addition, dual antiplatelet therapy was limited to 3 months with no evidence of stent thrombosis up to 24 months follow-up. Whether paclitaxel coated balloon angioplasty plus provisional stent implantation is similarly

effective and as safe as drug eluting stents implantation for treatment of *de novo* lesions will be answered by the multicentre BASKET small trial (clinical trials.gov NCT01574534).

Coating other than the iopromide for SeQuent Please balloons have been studied in randomised controlled trials including *de novo* lesions. In small vessels paclitaxel in combination with shellac was clearly inferior to paclitaxel-eluting stents regarding angiographic and clinical end points.[29] Furthermore, paclitaxel coated balloon angioplasty with shellac coating in combination with bare metal stents was inferior to drug eluting stents for treatment of ST-elevation myocardial infarction lesions regarding angiographic (restenosis 28.6% versus 4.7%, p=0.01) and clinical (MACE 20.0% versus 4.1%, p=0.02) end points.[30] In small vessels (<2.8 mm) 182 patients were randomised to paclitaxel coated balloon with paclitaxel plus urea-matrix coating or paclitaxel-eluting stent including 6 months angiographic follow-up.[31] MACE rate was similar between the two groups (7.8% versus 13.2%, p=0.77). Although late loss was significantly lower with paclitaxel coated balloon compared with drug eluting stents (0.08±0.38 mm versus 0.29±0.44 mm, p<0.001), minimal lumen diameter and diameter stenosis within the stent were higher for paclitaxel coated balloon angioplasty compared with drug eluting stents resulting in a similar angiographic restenosis rate (8.9 % versus 14.1%, p=0.25). Need for bare metal stents in the paclitaxel coated balloon group was associated with a higher late loss compared with paclitaxel coated balloon alone (0.33±0.49 mm versus 0.03±0.32 mm). These results demonstrate that for treatment of *de novo* lesions the type of paclitaxel coated balloon coating had a relevant impact on clinical results.

Conclusion

Paclitaxel coated balloons have changed treatment strategies for coronary artery lesions. With paclitaxel coated balloons excellent results were obtained for treatment of bare-metal stent restenosis or drug-eluting stent restenosis while dual antiplatelet therapy is shorter compared to the use of drug-eluting stents and additional strut layers are avoided. For the interesting field of *de novo* lesions registries and randomised trials with limited patient numbers have shown encouraging results. Randomised clinical trials comparing paclitaxel coated balloon angioplasty with modern drug-eluting stents are ongoing. Most important, there is no class effect of paclitaxel coated balloons like with drug-eluting stents and every product has to be adjudicated by the amount of scientific data.

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Aortic Stenosis and Pulmonary Hypertension

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Introduction

Degenerative aortic valve stenosis (AS) is among the most prevalent valvular heart diseases.[1] In the near future, the disorder is expected to be even more common because of the increasing average age of the population. Symptomatic severe disease is universally fatal if left untreated. Still, one third of patients with severe AS are symptomatic but do not undergo aortic valve replacement (AVR) today.[2] When corrected with a prosthetic aortic valve in a timely fashion, degenerative AS is consistent with a typical age-adjusted lifespan.

Pulmonary hypertension (PH) associated with isolated AS is part of Group 2; PH due to left heart disease.[3] One of the general limitations of studies on PH and AS is the lack of invasive measurements, and the variability of PH definitions (Table 1). Systolic pulmonary artery pressure (sPAP) alone is insufficient for a precise definition of PH.[3] Multiple mechanisms underlying the increase in pulmonary artery pressure have been recognised such as the passive backward transmission of elevated left ventricular end-diastolic pressure, an elevated mean pulmonary artery wedge pressue (mPAWP, r=0.84),[4] as well as increased systemic arterial compliance.[5] Diastolic dysfunction has long been associated with PH in patients with AS.[6,7] However, PH has not been found to correlate with either left ventricular ejection fraction (LVEF)[4] or aortic valve area in patients with severe AS.[8] Increased left atrial pressure, particularly in the context of mitral valve disease, triggers pulmonary arterial stiffening and PH.[9] A recent study[10] confirms that pulmonary vascular changes due to left heart disease are relatively more common in mitral stenosis,[11] and less likely in AS. Pathophysiological mechanisms may include vasoconstrictive reflexes arising from stretch receptors localised in the left atrium and pulmonary veins, and endothelial dysfunction of pulmonary arteries that may favour vasoconstriction and proliferation of vessel wall cells. PH due to left heart disease is less frequently associated with intimal proliferation and plexiform lesions, and is predominantly associated with venous medial hypertrophy, as well as fibrosis[12] and arteriolar changes (Hunt *et al*. unpublished[13]).

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PH as a Risk Factor in Degenerative Aortic Valve Stenosis

Generally, PH in AS is common. In patients with severe AS increased sPAP is associated with increased mortality.[4,14-16] By contrast, Tracy *et al*.,[17] and Aragam *et al*.[6] reported no significant differences in operative mortality between patients with normal sPAP and those with PH, regardless of the severity of the PH. However, only 42 patients had severe PH in these series combined. In a study to develop a European System for Cardiac Operative Risk Evaluation (EuroSCORE), PH was a multivariable predictor of operative mortality (P = 0.001) in 19030 consecutive adult patients undergoing cardiac surgery under cardiopulmonary bypass.[18] More recently, a multivariate analysis of cases with haemodynamically confirmed severe PH and AS illustrated that the lack of postoperative reduction in mean pulmonary artery pressure (mPAP) was an independent predictor of mortality, whereas baseline mPAP was not.[19] Preoperative mPAWP was identified as a significant predictor of postoperative reduction in mPAP.[19] "Reactive" PH (or "out-of-proportion" PH)[3] defined by mPAP ≥25mmHg, mPAWP >15mmHg and transpulmonary gradient (TPG, i.e., the difference between mPAP and mPAWP) >12mmHg or pulmonary vascular resistance (PVR) >3WU has recently been found to be an independent predictor of 6-month mortality in a left heart failure population.[20]

Magnitude of the Problem

In a consecutive series of patients with AS who were undergoing

Reference	Number of Patients	Inclusion Criteria	Haemodynamic Definition of PH	Cases Affected (%)
Tracy GP *et al.*	52	AS prior to AVR	**All PH: sPAP ≥30mmHg**	**37 (71%)**
			mild PH: sPAP 30-39mmHg	10 (19%)
			moderate PH: sPAP 40-59mmHg	16 (31%)
			severe PH: sPAP >60mmHg	11 (21%)
Cam A *et al.*	317	severe AS	**All PH (unclear definition)**	**149 (47%)**
			mild-to-moderate PH: mPAP ≤35mmHg	114 (36%)
			severe PH: mPAP >35mmHg	35 (11%)
Silver K *et al.*	45	AS	**All PH: sPAP >50mmHg**	**13 (29%)**
			reactive PH: TPG ≥10mmHg	8 (18%)
Johnson LW *et al.*	92	severe AS	**All PH: sPAP >30mmHg**	**46 (50%)**
			mild-to-moderate PH: sPAP 31-50mmHg	31 (34%)
			severe PH: sPAP >50mmHg	15 (16%)
Roithinger FX *et al.*	76	Symptomatic AS	**All PH: sPAP >30mmHg**	**53 (70%)**
Gerges C *et al.*	358	≥ moderate AS	**All PH: mPAP ≥25mmHg**	**182 (50%)**
			"isolated" post-capillary PH: DPG <7mmHg	162 (45%)
			"combined" pre- and post-capillary PH: DPG ≥7mmHg	16 (9%)
* all measurements were performed by invasive right heart catheterisation				

Table 1. Prevalence of pulmonary hypertension in aortic stenosis, including the variable definitions of pulmonary hypertension.*

diagnostic cardiac catheterisation, 29% presented with sPAP >50mmHg. Congestive heart failure, a lower LVEF and cardiac index,[21] and more severe mitral regurgitation[21, 22] were observed in this group compared with patients without PH. Almost two-thirds of patients with sPAP >50mmHg had a TPG of ≥10 mmHg.[21] In Johnson's series, the prevalence of PH (defined as sPAP >30mmHg) was 50% (46/92 patients) and that of severe PH (invasively measured sPAP >50mmHg), was 16% (15/92 patients).[8] In another invasively measured series of 317 patients with severe AS (aortic valve area <1cm^2) severe PH (defined as mPAP >35mmHg) was present in 81 patients (25%).[19]

sPAP showed no significant difference according to age and sex, although it was significantly higher in patients in New York Heart Association functional classes III and IV and in patients with coexistent systemic hypertension.[4] In another study,[17] 71% of patients with isolated AS had preoperative PH defined by an echocardiographically estimated sPAP ≥30mmHg.

Recently, diastolic pulmonary vascular pressure gradient (DPG, i.e., the difference between invasive diastolic pulmonary artery pressure [dPAP] and mPAWP) has been shown to identify patients with "out-of-proportion" PH due to left heart disease, who have increased mortality and significant pulmonary vascular disease.[10]

Own Data on the Prevalence of PH in AS

We analysed a data set of 3107 all-comers undergoing first diagnostic right heart catheterisation (RHC) at the Medical University of Vienna. In 358 patients a diagnosis of at least moderate degenerative AS had been established (aortic valve mean gradient 48.7±18.2mmHg, valve area 0.7±0.2cm^2, 58.7% males, age 69±12 years). In 182 patients with AS, 51% PH (i.e., mPAP ≥25mmHg) was documented. In 178 patients mPAWP was ≥15mmHg and 162 patients were classified as "isolated" post-capillary PH (diastolic pulmonary vascular pressure gradient [DPG] <7mmHg). 16 were classified as "combined" pre- and post-capillary PH (DPG ≥7mmHg). There was a moderate correlation between invasively measured sPAP and sPAP estimated by echo (r=0.684) and in 41 patients (11%) PH was not detected by echocardiography. The data of this large unselected patient population with severe degenerative AS demonstrate that PH is prevalent in this condition (50% of patients affected), and that 9% of patients with PH classify as "combined" pre- and post-capillary PH.

Reversibility of PH After Aortic Valve Replacement

After AVR, pulmonary pressures decrease substantially in a majority of patients by 52%-34%.[17] Roithinger *et al.*[23] reported that in patients with AS and PH, sPAP decreased from 52.4±17mmHg to 38.9±6mmHg, dPAP from 24.7±9mmHg to 12.6±3mmHg, and mPAWP from 22.3±10mmHg to 12.1±3mmHg. There were excellent correlations between the percentage decrease in sPAP after AVR

and increase in aortic valve area and prosthesis diameter among 53 patients with various degrees of PH, much of which was confirmed by other groups.[15] Patients with postoperative persistent PH had decreased survival in Melby's series. Five-year survival was 78±6%, with echocardiographically estimated normal sPAP and 45±12% with severe PH (defined as echocardiographically estimated sPAP ≥60mmHg, P<0.001).[16]

In patients with AS and severe systolic dysfunction (LVEF ≤35%) with a transvalvular gradient <30mmHg who underwent AVR, a 21% perioperative mortality and 24% late mortality occurred. Unfortunately, the severity of PH was not reported.[24]

In contrast to the STS pre-aortic valve replacement operative risk score,[25] both the additive[18] and the logistic[26] EuroSCOREs, as well as the new EuroSCORE II[27] have taken preoperative PH into account. Most recently the definition of PH by sPAP in EuroSCORE II has been stratified in moderate PH with an sPAP of 31-55mmHg and in severe PH with an sPAP >55mmHg. Recent data confirm the utility of the logistic EuroSCORE in a population of octagenarians.[28] AVR in patients with severe PH secondary to the valve disease is associated with a significant survival benefit. Medical therapy alone carries a dismal prognosis, and AVR should be considered urgently in these patients.[16, 29]

Summary of Key Points

1. PH in aortic valve stenosis is classified as PH due to left heart disease defined by invasive right heart catheterisation.
2. PH due to aortic stenosis is:
a. "Isolated" postcapillary PH (mPAP ≥25mmHg, mPAWP >15mmHg, DPG <7mmHg), or
b. "Combined" pre -and postcapillary PH (mPAP ≥25mmHg, mPAWP >15mmHg, DPG ≥7mmHg).
3. Any PH (mPAP ≥25mmHg) occurs in approximately 50% of all patients with AS.
4. However, PH with significant pulmonary vascular disease (mPAP ≥25mmHg, mPAWP >15mmHg, DPG ≥7mmHg) is rare and is seen in approximately 9% of patients with PH and AS.
5. Although the two subsets of PH in AS have not been prospectively validated, available data suggest that all PH has a significant impact on outcomes in patients undergoing aortic valve replacement and should be considered in preoperative risk assessment. Future outcome analyses need to utilise invasively measured pressures, and adhere to guideline definitions for PH.

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Renal Denervation in the Treatment of Hypertension and Other Disease States with Elevated Sympathetic Activity

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Introduction

Denervation of the sympathetic nerves has been a subject of interest as a potential interventional therapeutic target for the treatment of hypertension as early as the 1930s. Based on observations of hypertension in renal disease, Page and Heuer[1] hypothesised that nervous influences from the kidney may be causally related to essential hypertension. For this reason, they performed the first (albeit unsuccessful) bilateral renal denervation in a patient with uncomplicated essential hypertension. Despite the negative outcome, their hypothesis was further investigated in subsequent studies, which indeed provided evidence for a beneficial effect of surgical sympathetic denervation on blood pressure.[2-4] However, clinical applicability has been unattainable so far, due to the severe side-effects and complications (including perioperative mortality) of this invasive procedure.[3]

Recently, the belief in sympathetic denervation as a treatment strategy has been fuelled with renewed enthusiasm by the development of a new intervention method which utilises a radiofrequency ablation catheter for endovascular denervation of the renal sympathetic nerves.[5] This invention provides a minimally-invasive approach, with promise of much lower complication rates. The first positive results of percutaneous renal denervation (pRDN) in patients with therapy-resistant hypertension combined with evidence for sympathetic hyperactivity in various other diseases have generated a universal excitement about the possible applications of this novel treatment modality.

This paper aims to outline the rationale of renal denervation and provide an overview of the applications that are currently under investigation.

Sympathetic Control of Blood Pressure

Central sympathicoactivation of the kidney is conducted through the efferent sympathetic nerves that originate from the thoracic and lumbar sympathetic trunk. They terminate in the renal tubules, the juxtaglomerular apparatus and the renal blood vessels, where they regulate sodium reabsorption, renin secretion and renal vascular resistance, respectively.[6-8] Enhanced sympathetic firing rates increase sodium reabsorption, leading to an expansion of blood volume and resulting in higher arterial blood pressure levels. The activation of the Renin-Angiotensine-Aldosterone-system (RAAS) further enhances the sodium reabsorption and causes direct vasoconstriction, elevating arterial blood pressures.[9]

The kidneys give feedback to the central nervous system through the afferent renal nerve pathway. These afferent nerves are activated through changes in the chemical environment of the renal interstitium (e.g. adenosine during renal ischemia, uremic toxins) from the renal chemoreceptors and renal hydrostatic changes from the renal baroreceptors.[7, 10, 11] This information is relayed to the central neuronal circuits, modulating central sympathetic tone by mediating baroreflex and vasomotor tone through circuits in the medulla and activating vasopressinergic neurons in the hypothalamus.[6, 7]

The afferent nerves also execute short feedback loops, known as the renorenal reflexes, that relay information from the afferent fibers via the neuraxis directly back to the renal efferent fibers.[12] For instance, in a high-sodium diet, activation of the afferent renal nerves contributes to suppression of the efferent nerve activity, leading to accelerated sodium excretion.[13] This mechanism allows the renal function to be self-regulated and execute rapid adjustment of urinary sodium and water excretion.[14]

Martine Beeftink received her medical degree at the University of Utrecht in 2011. After two years of clinical training, she is currently studying for a PhD at the University Medical Center Utrecht under the guidance of Prof. Dr. P.A.F. Doevendans and Dr. M. Voskuil. Her research will focus on renal denervation, with special interest in the effects on heart failure with preserved ejection fraction.

Michiel Voskuil received his medical degree in 1999 and completed his PhD under the guidance of Prof. Dr. JJ Piek at the cardiac catheterisation department of the Academic Medical Center (AMC) in Amsterdam, with his thesis finalised in 2003. His training in cardiology and his fellowship in interventional cardiology were also undertaken at the AMC. Since 2010 he has worked as an Interventional Cardiologist at the University Medical Center in Utrecht. Outside of the regular percutaneous coronary intervention program, Dr. Voskuil's areas of interest are the catheter treatment of hypertension and congenital heart disease in adults.

This dual function of the kidney as both effector and modulator of the sympathetic nervous system, allows them to finely regulate blood pressure homeostasis, but also holds the potential of developing a vicious circle that generates a maintained sympathetic hyperactivity. In fact, experimental studies have shown that activation of the sympathetic nervous system causes hypertension.[15] Moreover, in patients with hypertension, the level of sympathetic activation relates directly to the severity of the disease and the presence of end-organ damage.[16, 17] Therefore, modulating sympathetic tone is a logical therapeutic strategy, as illustrated by the longstanding and broad application of beta-adrenergic receptor blockers.

Percutaneous renal denervation (pRDN) now composes a new therapeutic technique for modulating sympathetic tone. It is a minimally invasive, catheter-based technique that delivers radiofrequent energy to the wall of the renal artery, taking advantage of the fact that both the afferent and efferent sympathetic nerves travel within and closely adjacent to the renal arterial wall.[18] The radiofrequent energy causes circumscribed transmural injury that affects the nerve fascicles without clinically important damage to the vessel wall, resulting in ablation of the sympathetic nerves.[19]

This results in an effective lowering of sympathetic nervous activity as has been demonstrated by lowered muscle sympathetic nerve activity (MSNA), which is a measurement for sympathetic outflow to the periphery.[20] Also, direct measurements of catecholamines in the inferior vena cava showed attenuation of the increase in catecholamine levels that follows after electrical stimulation of the renal sympathetic nerves when the denervated renal artery was stimulated.[21]

The clinical effect on therapy-resistant hypertension was tested in a proof-of-principal trial in 45 patients with a systolic blood pressure (SBP) >160mmHg despite being treated with at least three antihypertensive drugs.[5] After bilateral treatment of the main renal artery, office-based blood pressures were reduced by -14/-10 at 1 month and -27/-17 at 12 months. These results were confirmed in a randomised controlled trial that showed a blood pressure reduction of -32/-12mmHg at 6 months in the pRDN group, whereas blood pressure in the control group did not change.[22] The reduction of blood pressure was sustained at 12 month follow-up and control patients who crossed over to pRDN showed a similar blood pressure reduction to patients in the intervention group.[23] Similar results have been achieved in a few smaller cohorts,[24-27] including one in patients with milder hypertension (SBP 130-160mmHg).[28] None of the studies reported serious long-term adverse effects. Observed perioperative complications included renal artery dissection (treated by stenting, without further sequelae or prolonged hospitalisation), pseudoaneurysm of the femoral artery and hypotensive complaints.[5, 23] No significant deterioration of kidney function[5, 22-25, 28] or renal artery stenosis[5, 24, 28] was found.

These results give hope for patients with therapy-resistant hypertension who are otherwise at a continuous risk of developing cardiovascular complications. It also opens doors for other possible indications for pRDN. Sympathetic hyperactivity can not only be found in hypertension, but is present in other diseases that involve sympathetic target-organs, such as left ventricular hypertrophy, heart failure, cardiac arrhythmias, kidney disease, diabetes mellitus and metabolic syndrome.[29]

It may be that increased sympathetic activity in these diseases is merely a reflexion of disease progression. However, increasing evidence suggests that adrenergic stimulation in fact plays a major role in the pathophysiology of end-organ damage as described below.

Sympathetic Control in Other Diseases

Heart Disease

Insufficiently treated hypertension leads to cardiac remodelling, fibrosis, hypertrophy and eventually heart failure.[30] For a long time, pressure overload was considered to be the primary underlying pathophysiological cause. However, it is now recognised that direct adrenergic stimulation also largely contributes to myocardial remodelling in hypertension.

Experimental research has demonstrated that increased levels of the sympathetic neurotransmitter norepinephrine results in myocyte hypertrophy, increased apoptosis of cardiomyocytes and deficits in cardiomyocyte contractility.[30] The responsible mechanism appears to involve cardiotoxic increases in intracellular calcium and activation of local inflammatory pathways through direct effects of catecholamines[30, 31] and oxidative and inflammatory stress through activation of the RAAS.[30, 32] However, the exact mechanism remains to be elucidated.

Clinically, the level of sympathetic nervous activity (SNA) is correlated to the left ventricular mass in patients with essential hypertension[33] and increases further in the presence of diastolic dysfunction and heart failure.[17] It is unlikely that this is merely a reflection of disease progression, because in patients with similar blood pressure levels a higher level of SNA was found in those with diastolic dysfunction.[17] In addition, experimental adrenergic stimulation by infusion of norepinephrine causes concentric left ventricular hypertrophy in the absence of elevated blood pressure.[34, 35]

Conversely, influencing the sympathetic pathways in rats resulted in an improvement of left ventricular hypertrophy, left ventricular dilatation and heart failure.[36, 37] This may indicate that cardiac remodelling in hypertensive patients may respond to pRDN. Indeed, a small study in humans demonstrated a reduction in left ventricular mass in patients treated with pRDN for therapy-resistant hypertension.[38]

These results may indicate a beneficial effect of pRDN in patients with heart failure with preserved left ventricular ejection fraction (HFpEF). Initially, this condition was considered merely a transitional state from left ventricular hypertrophy to systolic heart failure.

However, it is now recognised as a separate entity, and recent observations indicate that it is becoming the dominant form of heart failure in the community, with increasing morbidity and mortality.[39, 40] The condition is characterised by impaired ventricular relaxation and reduced compliance of the ventricles, leading to diastolic dysfunction and eventually heart failure.[41] The underlying structural changes in the myocardium include the same spectrum of changes associated with sympathetic stimulation, indicating a possible role of the sympathetic nervous system in the pathophysiology.[17] Indeed, sympathetic nerve activity is elevated in these patients and increases proportionally to the severity of the disease.[17, 42] Unfortunately, there is currently no successfully proven therapy for HFpEF yet. Although favourable effects would be expected from treatment with β-adrenergic receptorblockers and RAAS- influencing drugs, the results from large clinical trials have been disappointing.[43, 44]

The positive effects of pRDN in hypertension provide optimism that similar results may be achieved in HFpEF. A randomised clinical trial is currently being undertaken to investigate whether pRDN can improve cardiac function and symptoms in these patients.[45]

In systolic heart failure, the role of the sympathetic nervous system has been acknowledged for quite some time, and drugs that interfere with the RAAS and β-adrenergic pathways have been the cornerstones of treatment for decades now. Nevertheless, heart failure continues to have high morbidity and mortality rates.[46] As the doses of the pharmacological drugs are usually insufficient for complete suppression of β-adrenergic and angiotensin II receptors, it has been hypothesised that pRDN may have additional benefits when added to the pharmacological treatment.[47] These effects may reach beyond improvement of ventricular function and also reduce heart failure complications such as cardiac arrhythmias and renal failure.

The risk of sudden cardiac death in congestive heart failure is correlated to the cardiac norepinephrine spillover rate and arterial plasma norepinephrine levels, indicating potential benefits from sympathetic nervous system supression.[46] Left cardiac sympathetic denervation (LCSD) has been shown to improve arrhythmia in patients with catecholaminergic polymorphic ventricular tachycardia, long QT syndrome and other life-threatening ventricular arrhythmia.[48-50] However, this intervention still requires surgical intervention under general anaesthesia. Moreover, LCSD results in localised suppression of sympathetic stimulation only. So far, there is little experience with pRDN for ventricular arrhythmia, but theoretically it can combine treatment of arrhythmia with the beneficial effect of systemic suppression of sympathetic activity and the possibility to perform the intervention under local anaesthesia. The first-in-man experience with pRDN in two patients with therapy resistant electrical storm significantly reduced ventriculartachyarrhythmia, but further research is needed to confirm these preliminary results.[51]

The effect of pRDN on supraventricular tachyarrhythmias that occur frequently is an association with hypertension and diastolic dysfunction, which shows some promising results. Renal denervation has been shown to reduce heart rate and atrioventricular node conduction time.[52, 53] When pulmonary vein isolation (PVI) is combined with pRDN, it leads to reduced inducibility of atrial fibrillation during rapid atrial pacing and reduces atrial fibrillation recurrences compared with PVI alone.[54] A double-blind randomised trial is currently being undertaken to confirm these results.[55]

There is a strong relation between heart failure and kidney failure. Not only is renal failure a frequent complication of heart failure and hypertension, renal failure is also associated with an increased risk of cardiovascular disease. When both diseases exist concomitantly, the risk for morbidity and mortality exponentially increases.[56] Moreover, lower glomerular filtration rate is an independent predictor of cardiac death in heart and the prognostic value is increased when combined with cardiac sympathetic nervous activity.[57, 58] Experimental research has demonstrated improved renal haemodynamics following pRDN in swine.[59] Moreover, it improved renal function and prevented hypertension in a chronic kidney model in rats.[10, 60] However, these results have not yet been confirmed in humans.

The Metabolic Syndrome

The metabolic syndrome is a common disorder that entails high blood pressure, impaired glucose tolerance, elevated cholesterol levels and obesity. The syndrome is associated with a high prevalence of subclinical organ damage that substantially increases cardiovascular risk. This includes microalbuminuria, impaired renal function, increased left ventricular mass, diastolic dysfunction, arterial stiffening and a higher incidence of large artery plaques.[61, 62]

There are several hypotheses about the exact mechanism that is involved in the development of the metabolic syndrome and its complications, with the sympathetic nervous system being a prime suspect. Elevated levels of SNA are present in patients with obesity, diabetes mellitus and hypertension. In diabetes, the magnitude of SNA is related to the severity along the diabetes spectrum ranging from impaired glucose tolerance to insulin-dependent diabetes mellitus type 2.[63] This is not surprising, as sympathetic stimuli alter glucose metabolism and insulin sensitivity through local haemodynamic effects, decreasing the local availability of insulin, and increasing adipose tissue lipolysis, increasing the release of free fatty acids into the circulation.[61] The hypothesis is further supported by the observation that the organ damage seen in diabetes and obesity highly resembles the spectrum of complications seen in high sympathetic states, as described above. Moreover, in obese patients sympathetic activity is closely related to subclinical organ damage, such as impaired endothelial function, increased left ventricular mass index and impaired cardiac function.[64] Therefore, it seems reasonable to investigate the effects of sympathetic denervation in patients with the metabolic syndrome or complicated

diabetes mellitus.

A retrospective study investigating these effects in patients with resistant hypertension showed significant reductions in fasting glucose and insulin levels, not correlated to the blood pressure reduction.[65] However, more research is needed to investigate whether renal denervation can indeed be used as a non-pharmaceutical approach in insulin resistance.

Interaction of Disease States

Although these possible indications for pRDN have been discussed separately here, the role of the sympathetic nervous system appears to be much more complex. Not only is there great overlap in the observed (micro-)vascular and cardiac complications, there is also great interaction between the different disease states.

Clearly, obese patients are more prone to developing diabetes. Additionally, in both obese patients and diabetics there is a higher prevalence of hypertension. There are indications that sympathetic hyperactivity is potentiated when both diseases are present in the same individual, but the evidence is not unambiguous. However, complication rates are indeed increased when patients suffer multiple disease with increased sympathetic tone.[61]

It gets even more complex when Obstructive Sleep Apnoea Syndrome (OSAS) is taken into the equation. OSAS has been considered the responsible mechanism for sympathetic hyperactivity in obesity by stimulation of the sympathetic chemoreceptors. However, sympathetic hyperactivity is also present in lean patients suffering from OSAS.[66] Furthermore, OSAS has been related to hypertension, heart failure, metabolic syndrome, chronic kidney disease and cardiac arrhythmias, and concomitant presence is related to higher complication rates and adverse outcome.[67]

Conclusion

Sympathetic hyperactivity appears to play an important role in the pathophysiology of hypertension. Modulation of the sympathetic nervous system using pRDN has shown beneficial effects in patients with (resistant) hypertension. This has fuelled the expectation that other disease states with sympathetic hyperactivity may benefit from pRDN as well. However, further research is needed to confirm these hypotheses and to unravel the intricate continuity of the sympathetic nervous system and the associated conditions.

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Optimising PCI Outcomes with Combined FFR and OCT Guidance

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Introduction

The fast evolution of percutaneous coronary interventions (PCI) techniques and devices has lead to a significant improvement of short and long-term outcomes. Due to its less invasive nature as compared to coronary artery by-pass graft surgery (CABG), PCI has become the most common revascularisation procedure worldwide, and looks set to continue as the prefered treatment in the future. However, PCI remains an invasive procedure, where post-procedural hazard events rates parallel the patient and lesion complexity, and therefore finding the right balance between the risk and benefit related to such intervention compared to optimal medical treatment on one side and CABG on the other or, in other words, defining clear-cut indications for PCI revascularisation continues to challenge the cardiologist community. Angiographic evaluation of coronary stenosis is often inaccurate in determining the disease severity.[1] Furthermore, the amount of anatomic information provided by angiographic evaluation alone might be insufficient to guide the PCI strategy and techniques. For this purpose, different haemodynamic assessments and intracoronary imaging techniques have been developed. The interplay between the benefit offered by the most widely used haemodynamic assessment technique fractional flow reserve (FFR), and a new intracoronary imaging technique the optical coherence tomography (OCT) in further shaping the indications and improving the outcomes after PCI will be discussed in detail in this review.

Technique Description

Fractional flow reserve (FFR),[2] defined as the ratio of maximum flow in the presence of a coronary narrowing as compared to normal maximum flow, is a lesion-specific index of stenosis severity that can be calculated by simultaneous measurement of mean arterial, distal coronary, and central venous pressure (P_a, P_d, and P_v, respectively), during pharmacological vasodilation. In practice the P_v value can be omitted from the equation and the FFR value can than be calculated as a simple ratio of P_d/P_a during maximal hyperemia. An FFR value of 0.75 has almost 100% accuracy in indicating ischemia, while a FFR of more than 0.80 excludes ischemia with an accuracy of 95%.[3] Values between 0.75 - 0.80 were considered as a "grey zone", however nowadays the actual consensus is that only values of > 0.80 are considered as non-significant, while any value below this cut-off is considered significant.[4]

FFR Guidance in the Treatment Strategy Choice

FFR represents that particular fraction of normal maximum myocardial blood flow being maintained despite the presence of the epicardial coronary stenosis, and therefore is a very reliable and extremely reproducible measurement in detecting coronary ischemia. The technique *in se* is simple, safe and not time consuming. Therefore FFR has emerged as a very useful tool in the hands of interventional cardiologists in providing accurate treatment strategy guidance within the catheterisation laboratory, in both limits of the PCI treatment spectrum: between PCI or optimal medical treatment and between CABG or PCI.

While the concept of FFR as a myocardial ischemia detecting modality has not changed since the introduction of this technique, its application in the clinical practice has undergone a conceptual transformation in the last two decades. Indeed DEFER trial, the first FFR trial,[5] showed that, independently from the angiographic evaluation at presentation, lesions with haemodynamic non-significant stenosis resulted in similar rates of primary endpoint when medically treated as compared to PCI arm, suggesting that such lesions might not require mechanical revascularisation. Such a concept was brought one step further by the FAME trial.[6] In this landmark trial, FFR guided PCI treatment of multivessel coronary disease resulted in better clinical outcomes than PCI based on angiographic visual evaluation. Seen in another perspective, the major finding of this trial is that in the setting of multivessel coronary disease, the revascularisation procedures should address only ischemic lesions. Indeed, the benefit offered by FFR is mainly due to the fact that it reduces the number of lesions needed to treat in order to alleviate ischemia. As a consequence, FFR guidance avoids unnecessary revascularisation procedures for non-ischemic lesions (FFR> 0.80), and therefore on a patient level such an approach is associated with a significant reduction on the overall PCI-related short- and long-term adverse events. Furthermore, by reducing the number of lesions that need to be treated, such an approach automatically reduces

the Syntax Score. Indeed, the combination of the angiography derived anatomical information with the haemodynamic lesion severity assessments by means of FFR, has led to the concept of the functional Syntax Score.[7] Theoretically, the functional Syntax Score might be a more elegant approach than an anatomical one and might further shift the balance in favour of PCI, as compared to the more invasive surgical revascularisation alternative.

Another pivotal trail, FAME II, provided a clear and uncontestable answer to the long debated issue: the choice between mechanical revascularisation and optimal medical treatment for lesions with haemodynamic significant stenosis (FRR ≤ 0.80).[8] The trial was stopped early as the adverse event rate in the optimal medical treatment arm was significantly higher compared to the mechanical revascularisation. The FAME II trial results, completed the spectrum of clinical applications for FFR in guiding decisions in both sides of the cut-off value, with FFR values ≤ 0.80 mandating revascularisation.

While FFR has been proven extremely useful in guiding the need for mechanical revascularisation, its role in providing additional information to further optimise the technical aspects of the PCI procedure is limited. Indeed, other intravascular imaging techniques are more appropriate for this purpose. One of these techniques, optical coherence tomography (OCT), will be discussed in detail in the next section.

Cardiovascular Optical Coherence Tomography

Cardiovascular Optical Coherence Tomography is a catheter-based invasive imaging technique. The OCT catheter contains an imaging core at the distal tip emitting a light source in the near infrared spectrum (ca.1300 nm wavelength). Similar to intravascular ultrasound (IVUS), the core is rotated during imaging and a motorised pullback is performed to scan the coronary artery segment of interest. As a result, OCT provides high-resolution cross-sectional images of the coronary arteries, formed by reflection and attenuation of the light beam from different components in the vessel wall. Compared to IVUS, OCT has a ten-fold higher axial resolution (≤ 20 µm), enabling a detailed evaluation of the vessel wall microstructure and of deployed stents. With the actual generation, frequency-domain or swept-source OCT systems, the pullback speed can reach up to 20 mm/s and allows imaging of 4-6 cm of coronary artery segments within seconds, which is tenfold higher compared to the previous systems. The advancements in the technique in combination with the enhanced image resolution as compared to IVUS have lead to a widespread use of OCT imaging in a broad range of patients and lesions in everyday clinical practice. The possible clinical applications of OCT are multiple. As with IVUS, reference lumen dimensions and lesion length are easy measurable, allowing for optimal device selection. Furthermore, the ability of OCT to differentiate the normal vessel wall from atherosclerotic plaques and to characterise the composition of atherosclerotic disease in detail allows for precise delimitation of the most appropriate target segment and landing area for the stent. Indeed, previous studies have demonstrated that angiographic guidance for stent positioning can lead to inadequate plaque coverage in up to 30% of the procedures with stent edges landing in lipid-rich plaques.[9] Such geographic longitudinal miss might give rise to edge dissections, often not detectable by angiography, and therefore create the mechanical substratum for stent thrombosis (early and late) or edge restenosis. Indeed, pathological studies have associated vessel injury with stent restenosis[10] and an association between vessel trauma and periprocedural myocardial infarction.[11]

It is well known that stent malaposition or underdeployment is associated with high rates of stent thrombosis or restenosis. OCT as well as IVUS studies have shown that stents underexpansion or strut malapposition, both easily corrigible by balloon post-dilation, still occurs despite good angiographic result. OCT has a higher sensitivity for the detection of malapposed struts than IVUS, and OCT studies in the post-deployment setting have demonstrated a relatively high proportion of stent struts not completely apposed to the vessel wall.[12] This phenomenon is particularly evident in regions of stent overlap and in complex lesions, as well as in certain stent designs (thick struts, closed-cell design).[13] This is of particular interest especially in the context of coronary interventions involving bifurcations and highly calcified lesions. The higher incidence of stent thrombosis and restenosis seen in this subset of lesions possibly relays on the greater number of malapposed struts and frequent impairment of adequate stent expansion. In the optic of what is described in the previous paragraphs, OCT does provide excellent longitudinal and axial geographical guidance and therefore may potentially reduce procedure related short and long-term adverse events if used routinely in conventional PCI.

Moreover, as OCT offers detailed information on vulnerable plaques, reveals plaque rupture and presence of intracoronary thrombi, it represents a valuable tool to identify the culprit lesion and guide revascularisation in setting of primary PCI.[14] Such approach has been proven to be beneficial especially in the identification of the culprit lesion in multi-vessel disease patients when the infarct-related vessel is patent and shows only minimal luminal stenosis on angiographic evaluation.

Finally, OCT has emerged as an excellent imaging modality in identifying the underlying mechanisms of stent failure, including stent thrombosis and restenosis, which cannot be detected by angiography in other ways. OCT is able to differentiate mechanical stent failure (such as incomplete stent expansion or stent fracture) from impaired healing (such as absence of homogeneous strut coverage or late malapposition) in patients suffering from stent thrombosis, and can therefore guide interventional treatment decisions as well as the antithrombotic regimens. Detailed characterisation of neo-intimal tissue by OCT in the setting of in-stent restenosis lesions reveals different image patterns over time, with early in-stent restenosis mostly associated with delayed arterial healing, and the intriguing finding of in-stent neoatherosclerosis accounting for the late restenotic lesions[15, 16] In this perspective, since

unsatisfactory results of repeated stenting for the treatment of DES restenosis have been reported,[17] alternative treatment strategies, such as simple balloon dilatation or the use of drug-eluting balloons could be considered based on OCT findings in these patients.

There is a broad expert agreement that the detailed information provided by OCT on the presence and extent of atherosclerosis, as well as on the outcomes of interventional treatment can be of value in specific clinical scenarios.[18]

Conclusion

In conclusion, as possibilities on improvements in stent devices are being saturated, further optimisation of PCI outcomes can be achieved by further refining our treatment strategies and techniques. In this perspective, ischemia directed revascularisation under FFR guidance in combination with the OCT-derived geographical guidance can lead to further reduction of hazard events after PCI, therefore the routine use of these technologies in daily clinical practice in the catheterisation lab should be embraced.

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Upcoming Congresses and Meetings

ESC Congress 2013

31 August - 04 September 2013

Amsterdam, The Netherlands

The ESC Congress is the world's premier conference on the science, management and prevention of cardiovascular disease. The chosen spotlight of the 2013 congress is 'The Heart Interacting with Systemic Organs', and through this theme the ESC will encourage the critical discussion of new research and techniques, and how they transfer into clinical medicine with other organ experts. More than ever, the ESC Congress is shown to be the best forum for researchers to showcase their work. With over 9,600 abstracts submitted in 2012, the ESC Congress is a true representation of scientific developments in the field, and this will be continued at ESC 2013.

PCR London Valves

15 – 17 September 2013

London, UK

This event is a practical Course built by and for 'heart teams' with an interest in valvular heart disease interventions. The primary focus of the Course will be live demonstrations of all of the TAVI devices currently available on the market, and the main arena will be exclusively dedicated to demonstrations and case discussions. Indeed, this interactive element remains one of the core elements of PCR London Valves and all PCR courses. A number of topics will be up for discussion, including paravalvular aortic regurgitation after TAVI and patient selection. There will also be dedicated education sessions, which will include learning sessions on TAVI, transseptal techniques and transcatheter interventions. Additionally, there will be abstract and forum based sessions built around attendee's submissions, and an interactive case corner, which encourages discussion and lively debate. Last year, over 1300 professionals visited PCR London Valves, and this year's event looks set to be even bigger.

Heart Rhythm Congress 2013

20 – 23 September 2013

Birmingham, UK

Heart Rhythm Congress is an annual event which brings together all those with an interest in arrhythmias. It offers an educational opportunity for members of the medical, allied professional and industry communities to increase both their own and others' knowledge of heart rhythm disorders, and does so in an open, interactive environment. The congress boasts a full programme of scientific sessions along with training courses, patient group conferences, recorded cases, industry sessions, a patients' day and DoH and PCT meetings, with a trade exhibition running throughout.

Eurothrombosis 2013

03 - 05 October 2013

Uppsala, Sweden

Eurothrombosis 2013 is the official scientific meeting of the European Society of Cardiology's Working Group of Thrombosis. This year's meeting will have a translational focus, with lectures and symposia ranging from pre-clinical thrombosis research to clinical trials. In addition to addressing the most common clinical situations related to thrombo-cardiology, the programme will also cover novel fields such as microRNAs in cardiovascular diseases. Attendees will enjoy an exciting programme in a lively university environment.

British Society of Echocardiology

11 - 12 October 2013

Liverpool, UK

The British Society of Echocardiography (BSE) was formed in 1990 to promote the study and advancement of cardiac ultrasound imaging and Doppler techniques through professional representation, education and quality benchmarking. Membership is made up of cardiac physiologists, clinicians and others involved in cardiac ultrasound.

Transcatheter Cardiovascular Therapeutics (TCT) 2013

28 October – 01 November 2013

San Francisco, USA

TCT is thrilled to be returning to San Francisco in 2013, and will once again be committed to evidence-based medicine, live case presentation learning, state-of-the-art didactic presentations, and late breaking clinical science. The event will offer the latest research in interventional vascular medicine, live clinical cases for using the latest investigational technologies, late breaking clinical trials and education and training in advanced cardiac CT imaging.

26th British Society of Interventional Radiology Annual Scientific Meeting

13 – 15 November 2013

Manchester, UK

The British Society of Interventional Radiology (BSIR)'s 26th Annual Meeting will be building upon feedback from last year's highly successful event, and will feature a focus on Interventional Oncology. This will include sessions on the WHO form and what constitutes informed consent. In addition to lectures chaired by internationally renowned speakers, there will be masterclasses on particulate embolisation and vascular access devices, as well as interactive workshops on subjects such as DVT management. Scientific sessions will be available over all

three days and a 'What Industry Can Do For You' session has been introduced to encourage small group interaction between clinicians and industry.

British Society for Heart Failure 16th Annual Autumn Meeting

28 – 29 November 2013

London, UK

The BSH was founded in 1998 in response to the issues that the management of heart failure presents, and aims to inform and educate both patients and healthcare professionals. The 2-day Meeting is comprised of symposia, plenary lectures, oral and poster sessions, and aims to both support and increase attendees' knowledge of heart conditions, as well as presenting the latest findings and research in the field. Last year's event received some very positive feedback, and the 2013 Meeting looks set to continue this good work.

Society for Cardiovascular Angiography and Interventions 2013 Fall Fellows Courses

08 - 11 December 2013

Las Vegas, USA

If you are serving in the 4th year of your interventional cardiology fellowship, or serving in the 3rd or 4th year of your paediatric cardiology fellowship and are interested in cardiac catheterisation, you qualify to register for SCAI's Fall Fellows Course. The course is comprised of two programmes, the Adult Interventional Cardiology Course and the Congenital/Structural Heart Disease Interventional Cardiology Course, which both include hands-on stimulation workshops, world class facilities and benefit from the largest medical-simulation training programme in the US.

EuroEcho-Imaging 2013

11 - 14 December 2013,

Istanbul, Turkey

EuroEcho-Imaging 2013 is the official Annual Meeting of the European Association of Cardiovascular Imaging. The aim of this event is to create an exciting forum in which both clinicians and scientists can present and discuss the most up-to-date research and clinical findings on the broader spectrum of echocardiography together with the other cardiovascular imaging modalities. This year, the Meeting's main themes are 'Heart Failure' and 'Imaging in Interventional Cardiology', and the event will also have a focus upon education, with several teaching courses and specifically designed sessions being arranged. Additionally, the participation of young cardiologists and researchers will be encouraged through the organisation of two young investigator award sessions. The conference represents a unique opportunity for the cardiologist interested in the clinical and interventional applications of cardiovascular imaging to meet and interact with leading imaging experts from all over the world.

10th Annual Scientific Congress of the European Cardiac Arrhythmia Society

23 – 25 March 2014

Munich, Germany

The European Cardiac Arrhythmia Society aims to promote excellence in the care of patients with cardiac arrhythmias by fostering continuing medical education and training, supporting applied and clinical research and organising annual scientific Congresses. At the 10th Annual Congress, plenary sessions and symposia will cover a plethora of hot topics within modern arrhythmology and attendees will be addressed by internationally renowned speakers. Two of the major topics to be highlighted at the event will be 'Arrhythmias from Mechanisms to Management' and 'Implantable Device Therapy: Current and Future Role'. The Congress will also feature a wide range of workshops focusing on the practical aspects of arrhythmology, including 'Techniques and Tools for AF Ablation' and 'Cardiac Resynchronisation Therapy (CRT)'.

EuroPRevent 2014

08 - 10 May 2014

Amsterdam, The Netherlands

The Congress, organised by the European Association for Cardiovascular Prevention and Rehabilitation (EACPR), will take place in Amsterdam from 8th to 10th May 2014. The theme of the 2014 Congress is Global Cardiovascular Health, where the lessons learned in the West about cardiovascular health will be blended with the specific cultural, social and etiological factors that have led to the steady rise of metabolic and cardiovascular disease around the world. The event will bring the finest international health experts together to present the latest research and translate these findings into usable knowledge which can be implemented by practitioners, healthcare workers, researchers and policy makers. It is also a valuable forum where industry partners can network with the most influential policy makers and prevention experts around the globe. EuroPRevent is also very supportive of young investigators, and aims to provide a place for the next generation of researchers to network and exchange ideas. Moreover, joint sessions with local, European and International Associations willl be organised, which will focus upon the various existing prevention and implementation methods and programmes.

2014 ASH Annual Scientific Meeting & Exposition

17 - 20 May 2014

New York, USA

ASH is the largest organisation of hypertension researchers and healthcare providers in the US, and is committed to preventing and treating hypertension and its consequences. ASH has a domestic and international membership of basic science & clinical investigators, physicians, physician assistants, nurse practitioners, and pharmacists, as well as individuals with a scientific interest in hypertension.

EuroPCR 2014

20 – 23 May 2014

Paris, France

EuroPCR provides you with the latest techniques, updates and breakthrough science, allowing you to turn this information into actions that will improve the patients' quality of life. Bringing together the entire cardiovascular community, EuroPCR 2014 will provide you with a richly educational experience and an international platform for expression.

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