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INTERVENTIONAL CARDIOLOGY

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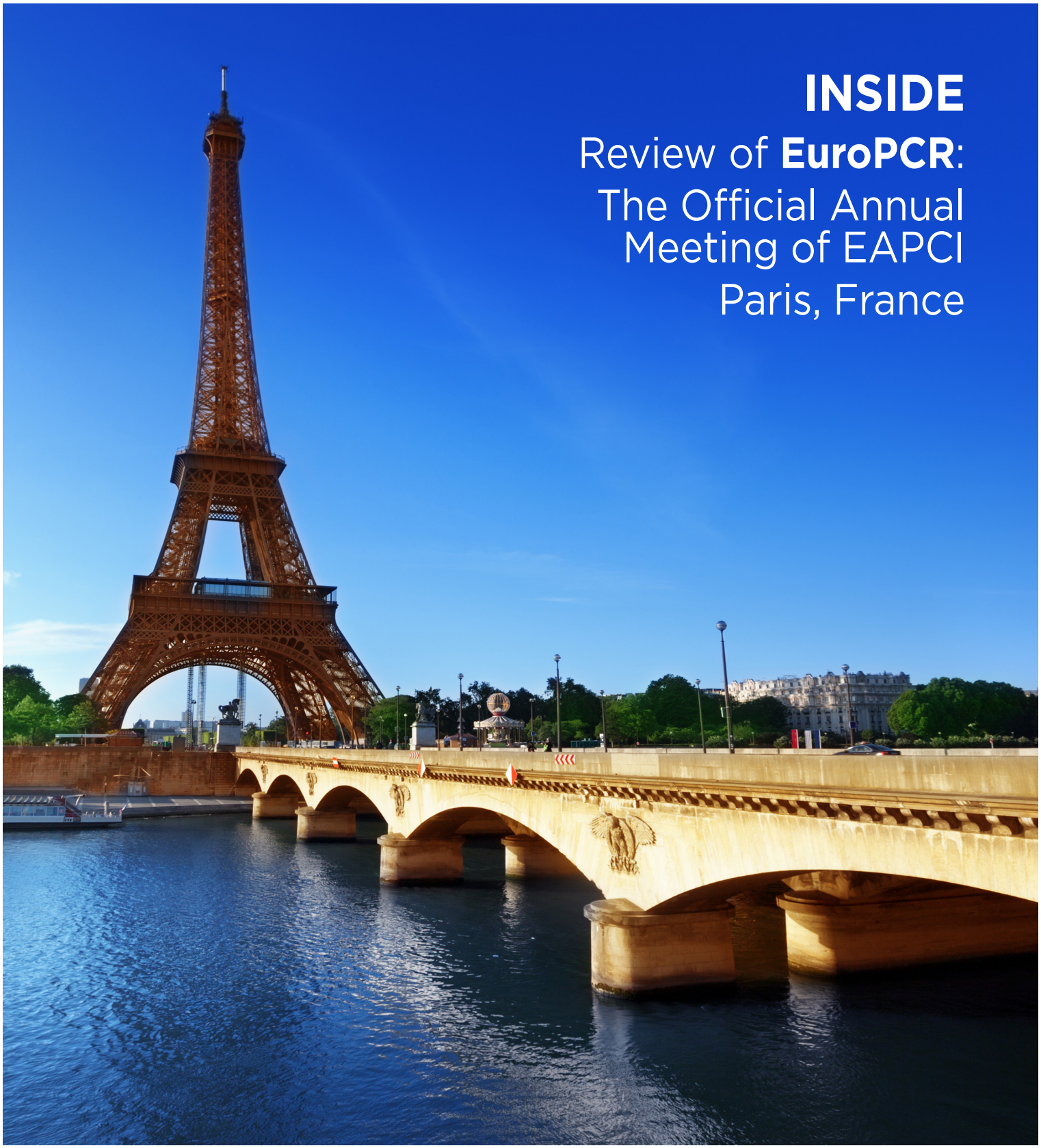

INSIDE

Review of **EuroPCR**: The Official Annual Meeting of EAPCI Paris, France

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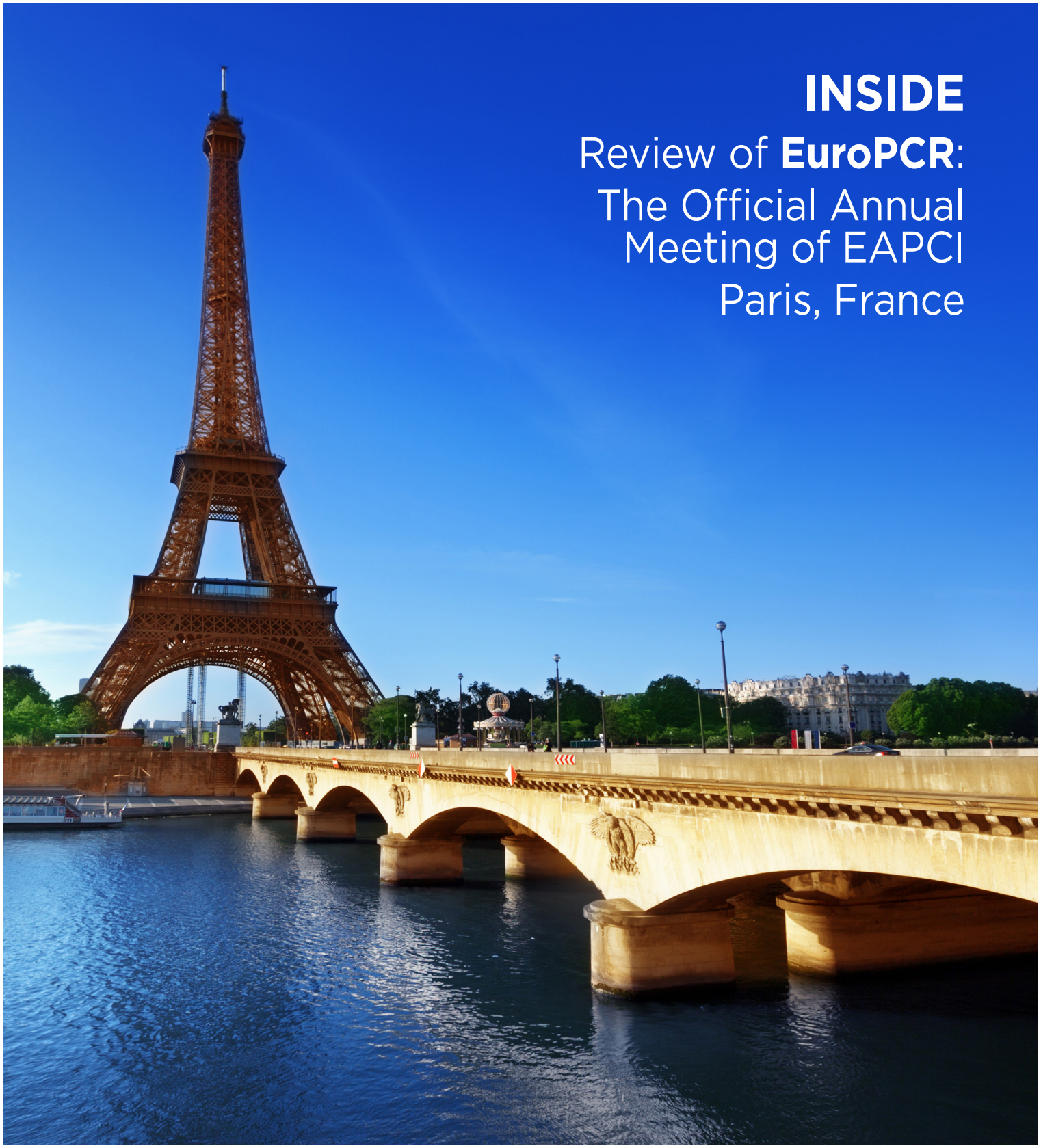

INSIDE

Review of **EuroPCR**: The Official Annual Meeting of EAPCI Paris, France

EMJ EUROPEAN MEDICAL JOURNAL

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Welcome

Kelly-Ann Lazarus, Editor

I am delighted to welcome you to the very first edition of *European Medical Journal – Interventional Cardiology*, which will be the start of an annual series aiming to provide professional healthcare specialists with informative and up-to-date news regarding breakthrough treatments and technologies.

This edition contains highly topical articles from well-respected interventional cardiologists. The articles cover a range of topics from drug-eluting balloons for percutaneous coronary interventions and pacemaker dependence after transcatheter aortic valve implantation, to plaque modification before coronary artery stenting and the effects of radiation exposure in the catheterisation laboratory.

Alongside these articles, there is also extensive coverage from EuroPCR 2013, the annual official meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). The highly successful congress, which took place in Paris from 21st to 24th May, drew together over 12,000 participants from the field of cardiology and showcased insightful and innovative material. Our independent review of EuroPCR can be found in our Congress Review section and covers these developments which include information on the world's longest coronary drug-eluting stent. I hope that you will find this section interesting and informative.

Great thanks are given to our highly esteemed editorial board for their continued support of *European Medical Journal – Interventional Cardiology*. Their assistance will aid us in our aim to continuously improve the quality of our journals and the information that we provide. I hope that this issue is a helpful tool for professional members of the interventional cardiology community to stay up-to-date with breakthroughs in research and will become the go-to place for annual cardiology updates.

Kelly-Ann Lazarus, **Editor**

Foreword

Dr. Ran Kornowski

Chairman, Department of Cardiology

Rabin Medical Center, Belinson and Hasharon Hospitals, Petach Tikva, Israel

Dear Colleagues,

I would like to take this opportunity to introduce you to a dynamic new entry into the field of cardiovascular medicine publishing; the *European Medical Journal-Interventional Cardiology*. Aiming to publish high quality peer-reviewed articles, this journal joins the growing trend of open access in medical publishing. All articles will be freely accessible, without any charge to readers. This measure ensures the widest possible dissemination of valuable cardiology knowledge to a global readership.

The journal encourages the submission of current therapeutic developments and techniques in all aspects of cardiovascular medicine. Clinical research, innovation topics, review articles, practice guides and case reports will also be featured. To safeguard the quality of the published articles, the European Medical Journal has assembled an editorial board of recognised European and American experts.

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

These are promising times for the field of interventional cardiology. The anticipation includes new cardiac imaging, bioabsorbable vascular scaffolds, catheter-based valve interventions and additional innovative diagnostic and therapeutic modalities. I hope that colleagues around the world will quickly appreciate the quality of the material published by the European Medical Journal, and will soon include it in their trusted sources of information. I look forward to the development of the *European Medical Journal-Interventional Cardiology* into an innovative forum for the propagation of cardiovascular knowledge to readers worldwide.

Best regards,

Dr. Ran Kornowski

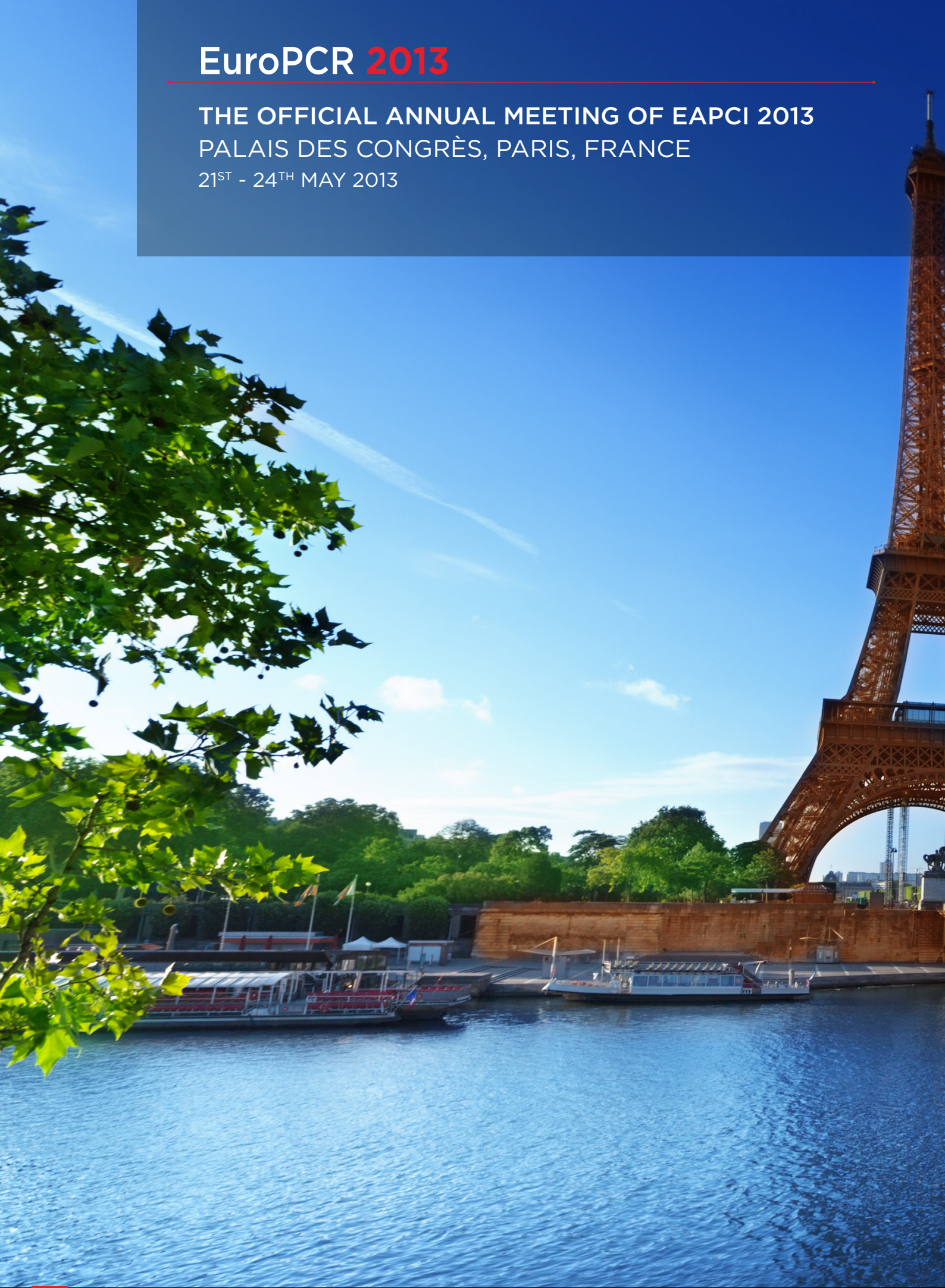
Chairman, Department of Cardiology, Rabin Medical Center, Petach Tikva; Professor of Cardiovascular Medicine, The 'Sackler' Faculty of Medicine, Tel Aviv University, Israel.

EuroPCR 2013

THE OFFICIAL ANNUAL MEETING OF EAPCI 2013

PALAIS DES CONGRÈS, PARIS, FRANCE

21ST - 24TH MAY 2013



EMJ EUROPEAN MEDICAL JOURNAL

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

WELCOME TO THE EUROPEAN MEDICA

The European Society of Cardiology's philosophy, "to serve the needs of each individual patient by helping the cardiovascular community share knowledge, experience, and practice", embodies the ideology behind such European conferences, and its branch, the European Association of Percutaneous Cardiovascular Interventions' (EAPCI) official congress, EuroPCR 2013 was no exception.

Held at the Palais des Congrès de Paris, the event saw an attendance of over 120,000, while boasting 120 exhibitors, 963 submitted abstracts, and 70 hours of live transmissions.

Attracting interventional cardiologists, cardiac and vascular surgeons, valve specialists, nurses, technicians, residents, industry researchers, and analysts, this year's EuroPCR saw an embracing of the latest technologies through instant messaging. By messaging React@PCR via smartphone during any lecture-based courses, delegates were able to post comments and ask questions to the sessions' chairs, directly contributing to the debate on stage.

This was particularly advocated during this year's Great Debate, which focused on two extremely topical issues in the world of interventional cardiology: the role of bioresorbable scaffolds, and the use of dual antiplatelet therapy. Chaired by Michael Haude and Martyn Thomas, several panellists argued that bioresorbable scaffolds will emerge as the "workhorse" intervention in a decade.

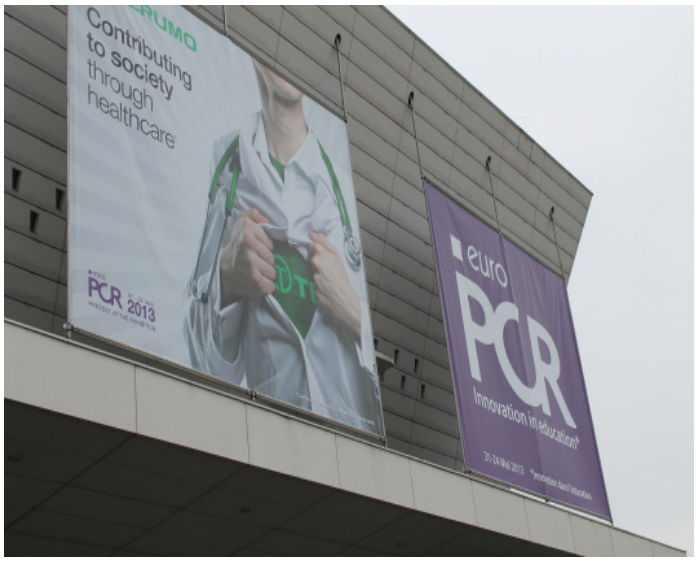
Upcoming talent, in the form of the Young Practitioners series, assisted in creating and developing such educational sessions as how to successfully perform PCI in an acute STEMI patient, as trainees and new independent operators expressed opinions to the community.

"Active Participants", programme sessions also saw the benefit of the Sharing Centre, an informal,

intimate lounge hosted by the founder of EuroPCR, Jean Marco. Involving world-renowned experts in the field as special guests, delegates were encouraged to wholeheartedly discuss any topic over coffee, on a personal basis.

A select few of the 1,740 abstract submitters also achieved greater success, in a highly competitive bequeathing of awards. Cases of note were Dr. Joanna

AL JOURNAL REVIEW OF EuroPCR 2013



Wykrzykowska and Dr. Maik Grundeken's "3D-OCT evaluation of bifurcation treatment with dedicated stent and bioresorbable scaffold", deemed Best Clinical Case, Dr. Alex Sirker's "Completely hooked on you" awarded Second Best Clinical Case, and Dr. Sudhakar George's "Long-term follow-up of 14,439 chronic total coronary occlusion angioplasty cases from the UK central cardiac audit database" awarded Best Abstract.

At a time when one in three adults worldwide suffers from high blood pressure, a medical condition implicated in a shocking 13% of all global deaths, the branch of interventional cardiology is proving to be more important than ever. But as EuroPCR continues to grow in size every year, their ethics of integrity, responsibility, and excellence proves the education of delegates is in safe hands.

EUROPE APPROVES 3D

A BRAND new technology designed to provide physicia three-dimensional (3D) disease assessment too disease (CAD) patients was displayed for the first time CE mark approval.

The Ilumien™ Optis™ PCI Optimization System™, created b company St. Jude Medical Inc., offers a real-time, 360-d the arteries, making it easier for physicians to visualise th

Using both fractional flow reserve (FFR) technology to the coronary arteries and intravascular optical cohere imaging technology, the Ilumien Optis' high-powered resolution to microscopically examine disease within an with stent placement.

"OCT technology has become increasingly important treat patients with coronary artery disease," said Dr. G Cardiovascular Department of Opsedale Papa Giovanni Optis system is a significant advancement in intravasc allowing physicians to comprehensively assess more ves easily plan their PCI procedure."

Dr. Guagliumi added: "The three-dimensional forma system provides a more true-to-life perspective of the

SECOND GENERATION, REPOSITIONABLE TA

The Lotus Valve, a second-generation transcatheter aortic valve implantation (TAVI) device, showed good device performance and low mortality after 30 days, after being successfully implanted in all 60 patients of the first REPRISE II trial.

"Results showed successful valve implantation in all 60 patients, meeting the primary device performance endpoint," lead author Professor Ian Meredith, Director of MonashHeart, Australia, said. "Importantly, the rate of moderate or greater aortic regurgitation decreased from 18% at the baseline study to 1.9% (one patient) at 30-day follow-up."

The Lotus Valve System has what first generation TAVI devices were lacking, with its valve pre-

> "It is exciting that the rate of moderate to severe aortic regurgitation is so low."
>
> *- Professor Stephan Windecker*

attached to the delivery system and a simple handle design, while also being fully retrievable, quick functioning in deployment, boasting an adaptive seal designed to minimalise paravalvular leakage and the ability to be fully repositioned.

Professor Stephan Windecker, Chief of Cardiology at Bern University Hospital in Switzerland, said: "An

D VESSEL RECONSTRUCTION TECHNOLOGY

ans with a comprehensive
ol for coronary artery
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by global medicine device
egree panoramic view of
e treated area.

measure pressure inside
ence tomography (OCT)
d laser offers twice the
artery in order to assist

t to help diagnose and
iulio Guagliumi, from the
XXIII, Italy. "The Ilumien
ular imaging technology,
sel in less time and more

t of the Ilumien Optis
arteries, which allows for

individual decision-making and precise guidance of stent placement to optimise coronary interventions."

Also known as coronary angioplasty, percutaneous coronary intervention (PCI) is a non-surgical procedure used to treat narrowed coronary heart arteries found in CAD. The FFR and OCT measurements, taken from the Ilumien Optis system by directing the FFR pressure guidewire as it is pulled back through the artery, helps physicians differentiate plaque build-up and determine if the arteries are causing ischaemia.

President of the St. Jude Medical Cardiovascular and Ablation Technologies Division, Frank Callaghan, said: "This next-generation system delivers critical information to physicians about the location and severity of disease within the coronary arteries, potentially resulting in better medical decision-making and overall cost-effective treatment."

> "The Ilumien Optis system is a significant advancement in intravascular imaging technology, allowing physicians to comprehensively assess more vessel in less time and more easily plan their PCI procedure."
>
> *- Dr. Giulio Guagliumi*

VI TECH BOASTS NEW POST-OP SUCCESS

important factor is that this is a truly repositionable device. And it is exciting that the rate of moderate to severe aortic regurgitation is so low."

Meanwhile, another small study has shown successful delivery and deployment of the investigational Helio System in high-risk aortic insufficiency patients.

The Helio dock system acts as an anchor to help stabilise the Sapien XT Transcatheter Heart Valve, with no in-hospital deaths occurring in any of the four patients involved. Although one patient had a stroke/TIA, one suffered a minor vascular complication, and one patient, who had a pre-existing renal impairment, had an acute kidney injury, lead author Dr. Sanjeevan Pasupati was keen to state that the key endpoint of freedom from all-cause mortality at 30 days was 100%, with all patients still living one year later. Within the study, the four patients had a mean age of 70+10 years, and were recruited between August 2011 and June 2012. Aortic insufficiency improved from moderate/severe before the procedure, to trivial after 30 days.

Dr. Pasupati, a specialist in coronary and structural heart disease intervention at Waikato Hospital, New Zealand, said: "What makes aortic insufficiency different from aortic stenosis, for which transcatheter aortic valve implantation is established, is the lack of calcium in the aortic leaflets and annulus, making it challenging to anchor the transcatheter heart valve. We need a system to anchor the valve."

WORLD'S LONGEST CORNARY DRUG-ELUTIN

The world's longest coronary drug-eluting stent (DES) for treating long lesions within the heart's blood vessels was announced on the first day of EuroPCR, following its CE mark approval.

Abbott's XIENCE Xpedition™ 48 Everolimus Eluting Coronary Stent System, at 48 mm long, holds the potential to lower overall costs by allowing physicians to use a single stent in long lesion treatment, enabling physicians to use fewer devices and reducing procedural time.

Previous studies have shown physicians choose to use multiple, shorter length stents in treating long blockages in up to 30% of interventional heart procedures, as conventional stent sizes may not always fully cover the lesion. This is despite research stating the use of a longer single stent may hold potential benefits, such as the use of fewer devices, less patient exposure to X-rays during the procedure, and lower costs.

"With global economic pressures impacting hospitals and healthcare systems around the world, products like XIENCE Xpedition 48 may provide important cost savings to the system," said Dr. Peter Smits of Maasstad Ziekenhuis, the Netherlands.

> "Products like XIENCE Xpedition 48 may provide important cost savings."
> *- Dr. Peter Smits*

"I believe that this new treatment option, backed by the robust clinical outcomes of the XIENCE family of drug-eluting stents, will help physicians in the treatment of long lesions."

Long lesions, increasingly common in diabetic patients due to changing lifestyle and dietary habits, are caused by fat and cholesterol build-up inside blood vessels, provoking such symptoms as shortness of breath, chest pains, or even heart attacks.

Being the first company to offer a DES longer than 38 mm, the XIENCE Xpedition 48 affirms Abbott's commitment to innovation. Abbott Vascular's Chief Medical Officer, Dr. Charles Simonton, added: "One of the hallmarks of Abbott's vascular product development is our ability to identify new ways to help physicians address the needs of their patients."

CARDIO IMPROVEMENT CONFIRMATION FOR

Data regarding a CE marked novel percutaneous device designed for the treatment of refractory angina was presented on the first day of EuroPCR.

The Neovasc Reducer™, following a 6-month follow-up of 15 patients listed in open label registries who were implanted with the device, showed a significant improvement in both their physical disability and angina, following examination through the Canadian Cardiovascular Society (CCS) grading scale.

> The Reducer can be fitted within a 20 minute procedure.

Professor Shmuel Banai, Neovasc Medical Director, said: "We consider these results very encouraging. In these initial Registry patients, quality of life improved as average angina scores were substantially signalling a significant im in their ability to engag activities without limiting c

Professor Banai added Neovasc Reducer appears no reports of serious safety

The Reducer itself is de provide relief from sympt as severe chest pain c even the slightest physica

G STENT CE MARKED

ANGINA PATIENTS

reduced, provement e in daily hest pain."

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esigned to toms, such caused by al exertion,

through altering the blood flow in the coronary sinus vein, and increasing the perfusion of oxygenated blood to specific areas of the heart muscle.

Neovasc CEO Alexei Marko added: "We expect definitive data from our COSIRA study in the coming months, which should enable us to plan for broader commercialisation in Europe and to further assess options for regulatory review and commercialisation in the U.S."

TAVI EFFICACY IN ASIANS CONFIRMED

Asian patients have nothing to fear after it was announced that transcatheter aortic valve implantation (TAVI) is both safe and effective, based on the first results from a multicentre Asian registry, reported at EuroPCR 2013.

"TAVI has become a treatment option for selected patients with symptomatic severe aortic stenosis. But currently data are virtually all from North American or European centres," Dr. Paul Chiam, Senior Consultant Cardiologist at the National Heart Center, Singapore explained.

"Early experience suggests that TAVI appears feasible and safe in a physically smaller Asian population, with low stroke and mortality rates and without an increase in vascular complications."

In order to discover whether the smaller average physique of Asian patients may affect outcomes after TAVI, Dr. Chiam started an investigator-driven registry, collecting data from 14 Asia centres concerning clinical outcomes from 253 patients having undergone TAVI. Patient demographics, clinical characteristics, and procedural and 30-day outcomes were recorded, from countries including China and Malaysia, between 2009 and 2012.

A procedural success rate of 97% accompanied with a low 30-day mortality and stroke rate at 3% and 1.6% respectively were reported at EuroPCR, while the mean New York Heart Association (NYHA) Functional Classification at 30 days was 1.4+0.6, and 9% of patients required a permanent pacemaker at that point in time.

This news coincided with a session debate on TAVI's effectiveness in intermediate-risk patients, reviewing what the specific challenges are and how outcomes compared to the data for surgery, following reports of TAVI being linked with atrioventricular conduction defects, strokes, and paravalvular leaks.

DIAGNOSTIC CORONARY ANGIOGRAPHY: CHANGES DECISIONS IN 25% OF CASES

Fractional flow reserve (FFR), when measured using pressure wire assessment during a coronary angiography for diagnosis of chest pain, leads to a significant change in the management of one in four patients, according to results from a EuroPCR-presented study.

Designed to analyse whether standard assessment of FFR in all the main coronary branches would change the management style from diagnostic angiography alone, the RIPCORD (Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain) study, entitled "Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?", recruited 200 patients being investigated for chest pain in 10 UK centres.

"Angiographic assessment of chest pain is flawed because it doesn't assess the functional significance of coronary artery disease," lead author Professor Nick Curzen, of the University Hospital Southampton NHS Foundation Trust, said. "Management of patients with stable angina alone is flawed and would be improved by routine use of FFR at the diagnostic stage."

All patients underwent diagnostic coronary angiography by a single cardiologist, who used the results to develop a treatment plan recommending methods of medical treatment, such as percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or to request more information.

A second cardiologist then measured each patient's FFR in all patient vessels of stentable (>2.25 mm) diameter. After showing the original cardiologist the results, a second treatment plan was formed, and then compared with the first, with a 26% change in suggested management noted.

> "Management of patients with stable angina alone is flawed and would be improved by routine use of FFR."
>
> *- Professor Nick Curzen*

Explaining that ischaemia is the most important determinant of clinical outcome in coronary artery disease, Professor Curzen added that while FFR provides an accurate and reproducible method for the detection of the blood supply restriction by measuring the drop in pressure across a lesion, "most patients with chest pains are assessed with angiogram alone."

BIOMATRIX™ DES SAFETY CONFIRMED BY REGISTRY DATA

The BioMatrix™ drug-eluting stent (DES) technology was deemed safe, following results based on a 12-month study period in a 'real-world' population of 5,559 patients.

Out of the number of patients studied, 5327 (96%) were followed-up at 12 months, with only 239 (4.3%) reported to experience major adverse cardiovascular events (MACE), a composite of cardiac death, myocardial infarction (MI), or clinically-indicated target vessel revascularisation (TVR). A very low rate of definite or probable stent thrombosis was also observed (0.6%), with most of these incidents only occurring in the first month.

The study involved patients who were treated with either BioMatrix or BioMatrix Flex™, both of which use Biolimus A9, a highly lipophilic anti-restenotic drug developed specifically for use with stents, together with an abluminal biodegradable polymer coating which fully degrades into carbon dioxide and water after 6 to 9 months. Designed to assess the reproducibility of the long-term, 'real world' results of LEADERS, e-BioMatrix is a prospective, multicentre, observational registry, with data pooled from two different sources: the e-BioMatrix PMS, involving 1106 patients, and e-BioMatrix PMR, with 4453 patients.

"The findings of this real-world registry are very important in helping us to learn more about the safety aspects of drug-eluting stents. The very low 12-month rate of definite and probable stent thrombosis confirm that stent thrombosis, while still associated with significant mortality, is no longer a frequent problem," said Principle Investigator Dr. Philip Urban, of Geneva's Hôpital de La Tour.

"Findings of this real-world registry are very important in helping us to learn more about the safety aspects."

- Dr. Philip Urban

ST. JUDE LOOKS TO ENLIGHTEN WORLD AS LARGEST RANDOMISED TRIAL PREPARED

A landmark clinical study is set to become the world's largest randomised, prospective trial to determine whether renal denervation and medication holds the ability to reduce risks of such major adverse cardiovascular events (MACE) as heart attacks and strokes.

In analysing whether the EnligHTN™ Multi-Electrode Renal Denervation System may offer additional health benefits, the study will follow approximately 4,000 patients who have a systolic blood pressure greater than 160 mmHg, enrolled in 150 sites spanning the globe, for 5 years under an event-driven trial design.

The trial goes against the trend of the majority of renal denervation studies, which normally only test the safety and efficacy of this technology in patients with drug-resistant hypertension, defined as systolic blood pressure above 160 mmHg, despite taking over three antihypertensive medications including a diuretic.

"The EnligHTNment trial will provide 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 Lüscher, Chairman of Zurich University Hospital's Cardiology and Cardiovascular Center, and a principal investigator for the trial.

> 100 million people worldwide are treatment-resistant where at least three high blood pressure drugs do not work.
>
> *- St. Jude Medical*

"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."

Primary endpoints include such examples of MACE as heart attack, stroke, heart failure with hospitalisation, and cardiovascular death, while secondary endpoints include changes in renal function. Prior studies of the EnligHTN Renal Denervation System itself have meanwhile demonstrated a safely sustained drop in blood pressure in patients with drug-resistant hypertension, reduced by 28 mmHg over 30 days. Comparatively, the risk of cardiovascular death itself is halved with every 20 mmHg decrease.

Saying he was pleased to see how St. Jude Medical can better assist physicians in treating at-risk patients, Frank Callaghan, President of the St. Jude Medical Cardiovascular and Ablation Technologies Division, continued: "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."

NEW CONCEPTS FOR SYMPATHETIC RENAL ARTERY DENERVATION: REVIEW OF EXISTING LITERATURE AND CASE REPORT

C.H. Heeger, L. Kaiser, S. Brooks, K.H. Kuck, Martin W. Bergmann

Department of Cardiology, Asklepios Klinic St. Georg, Hamburg, Germany

Disclosure: MWB has received speaker honoraria from Medtronic, Covidien and Cordis/J&J.

Citation: EMJ Int Cardiol. 2013:1,34-42.

ABSTRACT

Arterial hypertension (HTN) is one of the major risk factors for cardiovascular disease, and also leads to hypertensive heart disease, hypertensive nephropathy, cerebrovascular disease as well as cardiac arrhythmias. Despite receiving antihypertensive drugs, patients often do not reach their individual guideline blood pressure (BP) levels. Interventional sympathetic renal artery denervation (RDN) has been demonstrated to successfully lower blood pressure in patients with systolic blood pressure values ≥160 mmHg while on three or more antihypertensive drugs. The Symplicity™ device (Medtronic, Palo Alto, CA, USA) was shown to be safe, with side effects rarely occuring. Recent data from registries show that this procedure is efficient in about 70% of patients. New upcoming devices aim to significantly reduce procedure time and post-procedural complications through new concepts and strategies for RDN, and may possibly improve its effectiveness. Currently, radiofrequency (RF) is the dominant modality for RDN, but devices using energy delivery via ultrasound (US) have been developed. Intravascular optical coherence tomography (IVOCT) is a novel invasive diagnostic modality, which is able to analyse endothelial integrity at a resolution of approximately 10 μm. Recent IVOCT findings after RDN find evidence for endothelial damage and thrombus formation introduced through RDN, yet the clinical significance is uncertain since similar images are obtained when analysing coronary arteries after stenting. Nevertheless, irrigated RDN devices could reduce the observed issues and deliver more energy to deeper tissue levels similar to that observed in ablation of atrial fibrillation. This article provides an overview of currently available data and devices; furthermore we present a case report on the OneShot™ Renal Denervation System (Covidien, Campbell, CA, USA) and preliminary findings of IVOCT examinations after RDN.

Key Words: Renal denervation, refractory hypertension, intravascular optical coherence tomography.

INTRODUCTION

Today nearly one billion adults worldwide are suffering from arterial hypertension (HTN).[1] As one of the major risk factors for cardiovascular disease, HTN can lead to hypertensive heart disease, hypertensive nephropathy, cerebrovascular disease and cardiac arrhythmias.[2] Treatment strategies for HTN imply lifestyle changes such as smoking cessation, weight reduction, physical exercise and sodium restriction.[3] Combination treatment with drugs such as diuretics, angiotensin receptor antagonists, ACE inhibitors, direct renin inhibitors as well as beta-blockers and calcium antagonists is mandatory.[4]

Holman et al.[5] reported that patients assigned to 'tight controlled' HTN had a relative risk reduction of 32% for diabetes-related death, 44% for stroke, and 37% for microvascular disease compared to those in the 'less tight controlled' group. This relative risk reduction did not persist when blood pressure levels were no longer maintained.

Despite effective antihypertensive drugs, HTN often remains uncontrolled in terms of reaching guideline values, with only 25–35% of patients reaching their individual recommended blood pressure levels.[6] Moreover, around 30% of patients have systolic blood pressure ≥160 mmHg (>140 mmHg for patients

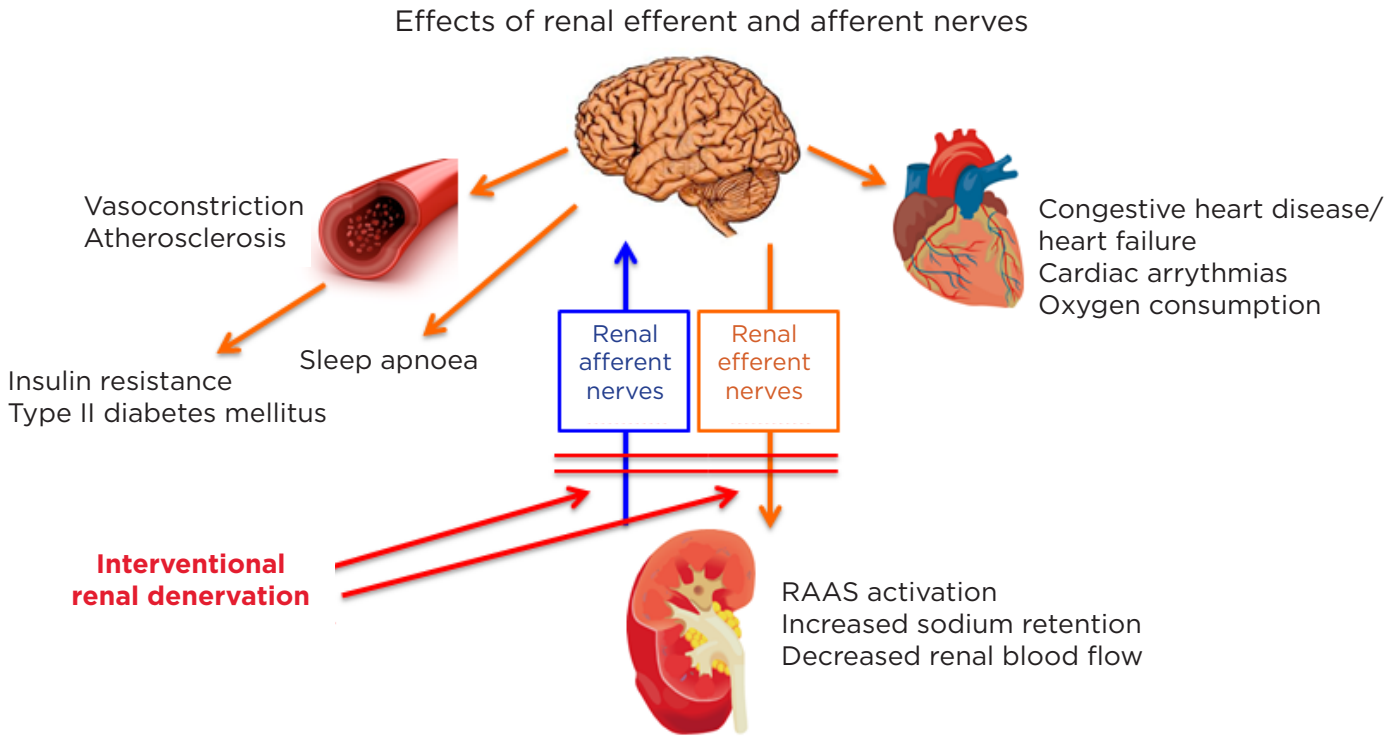

Figure 1: Effects of renal artery efferent and afferent nerves as a target for renal artery denervation (modified from Sobotka et al).[37]

with diabetes) at office-based measurements, despite taking three or more antihypertensive drugs ('refractory HTN').[7,2] Uncontrolled HTN leads to serious adverse cardiovascular events including stroke and cardiovascular mortality.[8] Therefore, there is an urgent need for additional methods to better control blood pressure levels.

High frequency ablation of the renal sympathetic afferent and efferent nerves is gaining momentum as a clinical choice to treat such patients (Figure 1). These nerves are part of a vicious circle where sympathetic drive leads to increased blood pressure, both by the renin angiotensin aldosterone system (RAAS) as well as central stimulation. To date, approximately 10,000 patients have been successfully treated by this method.[9]

Recently published studies have confirmed the safety and efficacy of interventional renal artery denervation (RDN) for the treatment of refractory HTN employing the Symplicity™ ablation catheter.[1,9,10] Several completed and on-going studies examine other potential clinical benefits of RDN using this device for the treatment of cardiac failure, sleep apnoea, diabetes mellitus and cardiac arrhythmia.[2,11] The Symplicity™ device is designed to deliver radiofrequency (RF) energy in a point-by-point application, each point ablation lasting two minutes, at four to six sites along the renal artery. During ablation, general sedation is necessary due to abdominal pain. Bilateral treatment of the arteries takes between 40 and 50 minutes with this system.[12] Our group reported a 30% non-responder (blood pressure reduction of systolic office based measurement ≤10 mmHg) rate after RDN with the Symplicity™ device, when analysed as part of a real-world registry.[13] Several devices have been developed that aim to decrease procedure time and possibly allow for better control with regards to the pattern of ablation (Table 1).

Rare long-term complications like renal artery stenosis have been used to justify further examinations of the consequences of RDN to the vessel wall.[14,15] IVOCT is a novel invasive diagnostic modality, which permits visualisation of the vessel wall with a resolution of about 10-15 µm. This technique allows for an accurate analysis of stent apposition and endothelialisation, endothelial integrity, plaque characterisation and thrombus formation.[16] IVOCT identified small endothelial lesions and thrombus formation following RDN employing the Symplicity™ device as well as the EnLigHTN™ Renal Denervation System (St. Jude Medical Inc., Westford, USA).[17] Preliminary data from our institution confirmed this observation. We were able to visualize small endothelial lesions in two subsequent patients after

Devices (producer)	Characteristics	Modality	CE mark	Major Trials (n) Status
Symplicity™ Renal Denervation System (Medtronic)	Non-occlusive flexible catheter with a single electrode tip	RF, 6Fr	+	Symplicity HTN I (152) completed Symplicity HTN II (106) completed Symplicity HTN III (530) follow-up
OneShot™ Renal Denervation System (Covidien)	Irrigated, helical over the wire balloon catheter	RF, 8Fr	+	RHAS (12) completed RAPID (50) follow-up
Paradise™ Renal Denervation System (ReCor Medical)	Balloon catheter combined with a US-emitting transducer and cooling system	US, 8Fr	+	REDUCE (11) completed REALISE (20) recruiting ACHIEVE (50) recruiting
EnligHTN™ Multi Electrode Renal Denervation System (St. Jude Medical)	Occlusive, over the wire balloon catheter with embedded multi-electrodes	RF, 8Fr	+	EnligHTN I (47) follow-up EnligHTN II (500) recruiting EnligHTN III (30) recruiting
V2 Renal Denervation System™ (Vessix Vascular, Boston Scientific)	Over the wire variable size balloon catheter with embedded bipolar electrodes	RF, 8Fr	+	REDUCE-HTN (150) follow-up
Symplicity Spyral™ Renal Denervation System (Medtronic)	Non-occlusive, multi-electrode helical catheter	RF, 6Fr	-	First Data presented on TCT 2012 by R. Whitbourne, St.Vincent´s Hospital, Melbourne, AUS (9). CE study finished but not yet presented
Celsius® ThermoCool® Renal Denervation Catheter (Cordis)	Irrigated, multi-electrode	RF	-	RENABLATE (30) recruiting

Table 1: Current and upcoming devices for RDN.

RDN with the Symplicity™ device (Figure 2, 3). The clinical significance as well as frequency of such events remains to be determined. IVOCT frequently detects similar lesions after percutaneous coronary intervention (PCI), where no clinical sequelae are observed.[18]

This article aims to give an overview of currently available data as well as upcoming devices and ablation strategies. Additionally, we present a case report of a patient treated with the OneShot™ Renal Denervation System (Covidien, Campbell, CA, USA) and provide preliminary IVOCT findings after RDN.

Current Data on the Symplicity™ RDN Device

RDN has a growing impact as alternate therapy for patients with therapy refractive HTN, defined as office systolic blood pressure ≥160 mmHg (> 140 mmHg for patients with diabetes) despite drug therapy with three or more antihypertensive drugs including at least one diuretic. The Symplicity HTN-2 randomised trial has shown a significant reduction in systolic blood pressure, with ≥10 mmHg shown in 84% of patients who underwent RDN 6 months after the procedure. [10]

Office blood pressure was reduced by -33/-11 mmHg and no adverse events were noted. The 1 year results of the Symplicity HTN-2 trial were recently published: 63% of the initial control group patients crossed over to the interventional therapy and showed a reduction in systolic blood pressure at ≥10 mmHg 6 months after the procedure. Office blood pressure was lowered by -24/-8 mmHg.[1] The first randomised group showed no additional reduction in office blood pressure between 6 and 12 months after the procedure, with the initial effect being maintained. Several studies have been published with similar

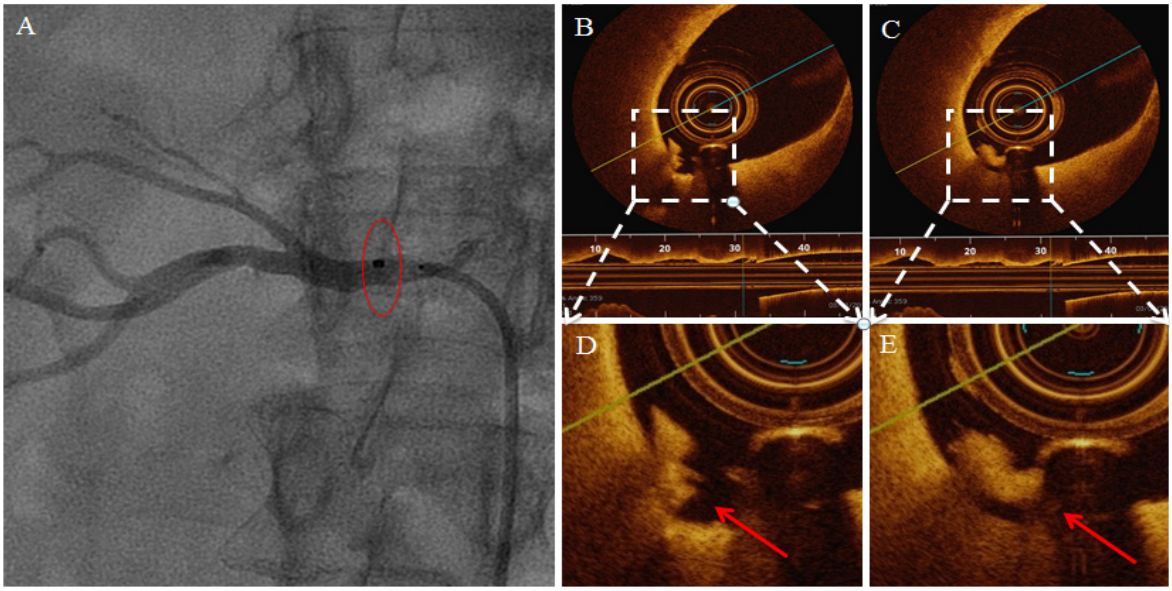

Figure 2. Intravascular optical coherence tomography (IVOCT) findings after RDN with the Symplicity™ RDN System. I

A: Angiography of the right renal artery with the Symplicity™ RDN catheter. Red circle marks the region analysed with IVOCT and presented in B,C,D,E. No endothelial lesions are visible via angiography.
B/C: IVOCT-analysis after RDN employing the Symplicity™ RDN system. D/E magnified region in white box. The red arrows mark local endothelial damage with thrombus formation. No other lesion was observed in this vessel after six ablation points.

results in the investigated patient cohort.[19-22] In our institution, we followed patients who underwent RDN in a registry called ALSTER BP to determine if the described findings can be reproduced in a real world setting.[13] The results underline the safety profile of interventional RDN procedures.

Since it is generally known that RDN influences sympathetic tone, several studies have been performed to investigate a possible influence, not only on the blood pressure, but also on other diseases modulated by sympathetic drive including heart failure, metabolic syndrome or atrial fibrillation, suggesting that there might be more targets for this therapy. RDN has been found to improve glucose tolerance in diabetic patients, reduce cardiac hypertrophy in the context of diastolic heart failure and improve control of sleep apnea.[19,22-26]

New Strategies for RDN

In order to improve actual RDN systems, several new devices have been developed (Table I). The goal of these systems is the reduction in procedural duration, by performing a single-shot energy application (RF or US) to the vessel wall while increasing effectiveness.[2] The shorter duration of RDN procedure will potentially lower the amount of contrast dye used. Furthermore, these devices aim

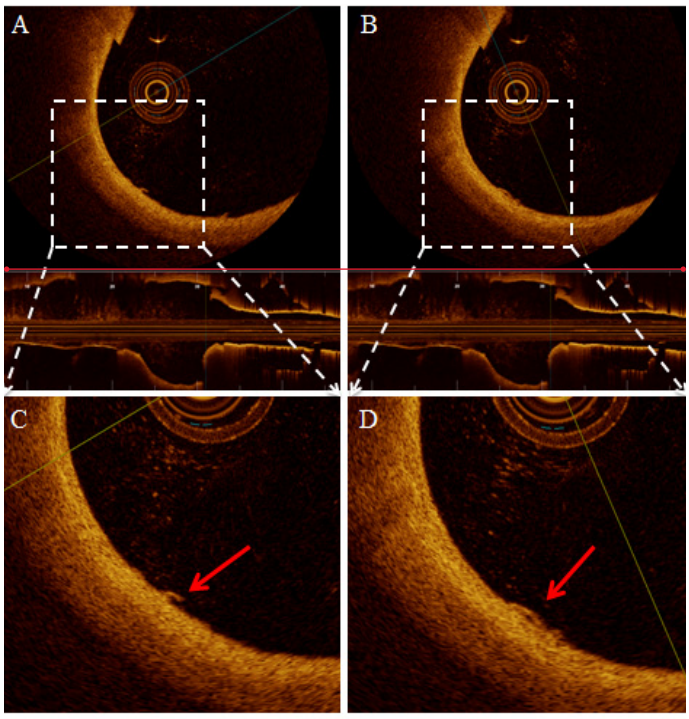

Figure 3: Intravascular optical coherence tomography (IVOCT) findings after RDN by Symplicity™ RDN System. II

A/B: IVOCT-analysis after RDN employing the Symplicity™ RDN system. C/D: Magnification region in white box. The red arrows mark local endothelial damage. This was the only lesion observed after six ablation points in this vessel.

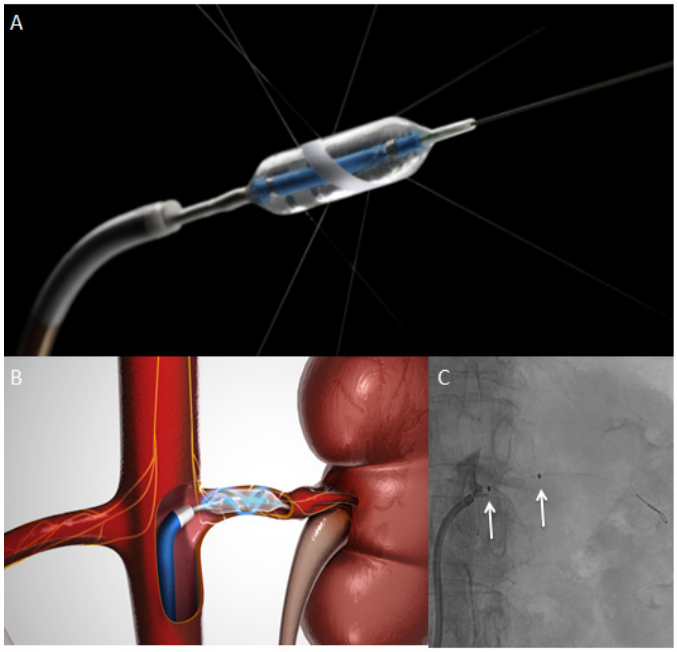

Figure 4: The Covidien OneShotTM RDN device.
A: The OneShot™ RF balloon catheter with a spiral RF electrode and irrigation holes. A low pressure irrigation runs continuously during balloon inflation, providing cooling of the non-treated region of the artery during ablation. B: Left renal artery cutaway showing inflated balloon with spiral electrode (silver with blue halo). C: Left renal artery selective angiogram showing inflated balloon with two radiopaque markers (white arrows) for visualisation.

to improve the responder rate by a more defined ablation pattern.

Symplicity Spyral™ Renal Denervation System

The Symplicity Spyral™ (Medtronic, Palo Alto, CA, USA) device is not yet commercially available. It will feature a radio-frequency-emitting, four-electrode, non-occlusive spiral catheter to significantly reduce procedure time. First data with the device were presented at the TCT 2012 congress but measurements are not yet published. The CE mark is expected shortly and studies are on-going.[27]

EnligHTN™ Multi Electrode Renal Denervation System

The EnligHTN™ multi-electrode Renal Denervation System offers a 'cage' with four embedded electrodes to deliver RF energy to the target vessel wall. Preliminary data of the first-in-human, multicentre, EnligHTN I study (ClinicalTrials.gov Identifier: NCT01438229) showed safety and efficacy in a small cohort of patients (n=47) with resistant HTN with a surprisingly early effect. The 6 month follow-up showed a rapid and sustained reduction of HTN, with 76 % of participants presenting with ≥10 mmHg reduction in systolic blood pressure and 33% reaching <140 mmHg measurements in office blood pressure.[28] Currently, further clinical trials are recruiting patients (EnligHTN II, ClinicalTrials.gov Identifier: NCT01705080 and EnligHTN III, ClinicalTrials.gov Identifier: NCT01836146). A recently published trial showed evidence for local tissue damage with oedema and thrombus formation after RDN measured by IVOCT. The comparison of the EnligHTN™ vs. the Symplicity™ devices showed no significant difference in the amount of oedema or vessel spasm. Nevertheless, one incidence of arterial dissection with the Symplicity™ catheter and two cases of endothelial and intimal disruptions were observed after RDN by the EnligHTN™ device. Furthermore, a trend towards a greater amount of thrombus formation and a significantly greater thrombus load per renal artery was observed after RDN with the EnligHTN™ system compared with the Simplicity system, in a small patient cohort.[17]

V2 Renal Denervation System™ (Vessix Vascular, Boston Scientific)

This RDN system uses a variable sized balloon catheter with embedded RF bipolar electrodes, the balloon allows RF applications in different vessel sizes. This system is able to totally occlude blood flow, minimising heat loss into the bloodstream, thereby increasing effectiveness of the procedure. First clinical data were presented at the TCT 2012 congress (REDUCE-HTN Pilot Study Cohort, ClinicalTrials.gov Identifier: NCT01541865).[29]

Paradise™ Renal Denervation System

The Paradise™ RDN system (ReCor Medical, Ronkonkoma, NY, USA) uses a balloon catheter with a cylindrical transducer that emits US energy circumferentially to the selected vessels. Since US passes through the surrounding fluids, no direct tissue contact is required to focus energy to a specified depth and induce high temperatures within the target vessel surrounding soft tissue. This allows for a liquid-cooling system around the transducer to cool down the arterial wall, reducing damage to non-target tissues. The first-in-man, single-arm, open-label REDUCE study (n=11 patients) showed an effective and sustained decrease in blood pressure. The 3 month follow-up measurements were comparable to RF RDN (which had reduction in office blood pressure of –36/–17 mmHg). The REALISE trial (ClinicalTrials.gov Identifier: NCT01529372) is a safety and efficacy,

single-arm, open-label, prospective study to be conducted on 20 eligible patients with a 12 month follow-up period. Completion will be approximately July 2014. The ACHIEVE study (ClinicalTrials.gov Identifier: NCT01789918) is a further single-arm, open-label, prospective, post-market, study (n=50 patients) with a twelve month follow-up period which is currently recruiting participants. In conclusion, the existing preliminary results indicate that US RDN is a safe and effective treatment for refractory HTN. Nevertheless, these results have to be proven in larger trials and registries.

Covidien OneShot™ Renal Denervation System

The first irrigated ablation system for RDN was presented initially by Maya Medical in 2012 with the release of the OneShot™ Renal Denervation System, now part of Covidien. This over the wire balloon-based irrigated catheter applies low-level RF energy with a single application per artery to perform rapid and effective RDN (Figure 4).

The irrigated RF balloon catheter features a helical configured mono-polar silver electrode on the non-compliant balloon. This ensures the desired spiral RF application with one single ablation. During the ablation procedure, saline continuously flows out of special irrigation holes in the balloon, which 'dilates' the balloon with a nominal pressure of one bar. These holes are designed to avoid injury of the non-target area and reduces overheating as well as clotting formation during RF delivery process.[12] The RF generator (RFG) provides the RF energy, while the intergraded pump system warrants saline irrigation during the whole procedure. A 7/8 Fr compatible system in combination with a conventional guidewire is used to deliver the balloon to the renal artery. Radiopaque markers at the distal and proximal balloon ends warrant exact positioning under fluoroscopy. Currently 5, 6 as well as 7 mm diameter and 20 mm length balloon sizes are available for renal arteries between 4 and 7mm diameters. For RDN, the balloon is inflated with normal saline automatically delivered by the RFG. The inflated balloon stabilises electrode contact within the renal artery and warrants wall contact during the ablation process. For RDN, a single, 2 minute, 25W RF energy delivery is performed in each artery, reducing the process duration to 4 minutes ablation time.[12]

Preclinical animal studies presented a good efficacy and safety profile at 6 months of follow-up, without any evidence of significant angiographic stenosis or intimal hyperplasia.[12] The RHAS (Renal Hypertension Ablation System) trial (n=8 patients) showed promising results for humans concerning feasibility and efficacy. A mean change of -31 mmHg on systolic blood pressure after 30 days and -34 mmHg at 6 months follow-up was presented.[30] Change in systolic blood pressure at 1 month was similar to the data of the Symplicity™ HTN trials.[12] The RAPID trial (ClinicalTrials.gov Identifier: NCT01520506) is a prospective multicentre safety and efficacy 50-patient study and has enrolled participants in Europe and New Zealand. The study is in follow-up and data presentation is pending.

Cordis Celsius® Thermocool® Renal Denervation System

Ablation for cardiac arrhythmias has developed into two directions, namely 3D mapping systems for precise analysis of arrhythmia patterns, as well

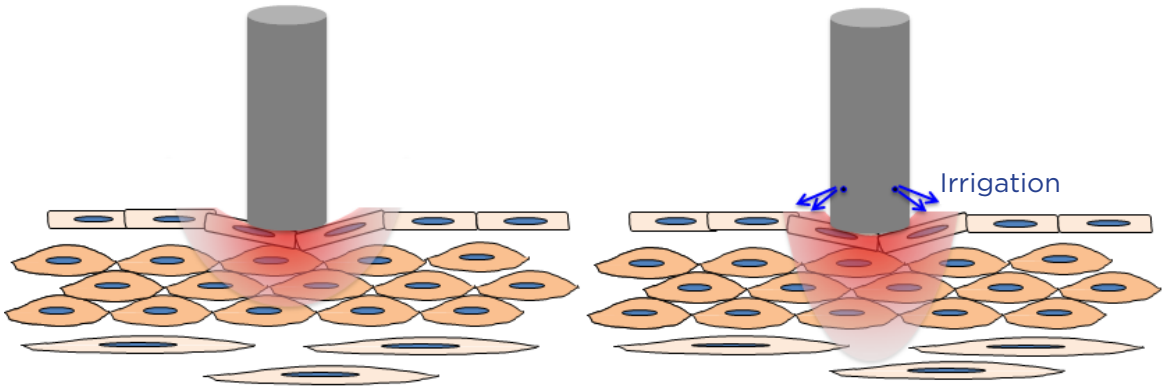

Figure 5: Irrigated RF ablation as investigated in pulmonary vein isolation: Irrigation limits the 'backheating' of the ablation electrode, enabling maximum energy to be delivered deeper into the tissue.

as irrigation technology to maximise lesions depths while reducing char formation. A similar approach is taken with the development of Cordis in conjunction with Biosense Webster, two subsidiaries of Johnson &Johnson. The first-in-man data are expected to be presented during 2013.

Irrigated RF Ablation

Irrigated RF ablation has the potential to limit endothelial damage while increasing lesion depth, possibly allowing for a more consistent sympathetic denervation. Figure 5 shows the potential benefits of this technique as irrigation next to the surface of the electrode limits the 'backheating' of the ablation electrode and results in maximum energy delivery to occur deeper in the tissue. As sympathetic innervation is anatomically located in the adventitia of the renal artery this technique may be particularly suitable for RDN. The design of the OneShot™ provides irrigation holes that deliver saline during the course of the procedure. In ablation for atrial fibrillation, irrigated cooling maintains a lower electrode-tissue temperature, thus reducing the occurrence of char and limiting damage to the endothelium.[31] Another device allowing for irrigated renal denervation is currently being investigated (Cordis RDN device).

CASE REPORT

Renal Denervation by the Covidien OneShot™ Renal Denervation System

The patient was a 49-year-old non-smoking, non-diabetes male with refractory HTN (>160 mmHg office systolic blood pressure) and repetitive hypertensive crisis (>200 mmHg) despite multiple drug therapy (candesartan 32 mg daily, metoprolol 95 mg twice daily, hydrochlorothiazide 25 mg daily, moxonidine 0.2 mg daily) and intolerance of calcium channel blockers. Secondary causes for HTN were excluded. Further diagnoses were coronary artery disease with status post-anterior myocardial infarction (08/2005) and PCI/Stenting of left anterior descending artery as well as hyperlipidaemia. The patient reported repetitive systolic blood pressure >180 mmHg systolic and suffered from headache and reduced capacity during these episodes. The patient gave written informed consent for RDN with the OneShot™ Renal Denervation System. RDN was performed under sedation with midazolam, propofol and fentanyl. Prior to ablation, 7500I.E. of heparin was administered to achieve an ACT of > 200 sec. An 8Fr guide catheter was used to introduce the device into the renal arteries. The diameter of both

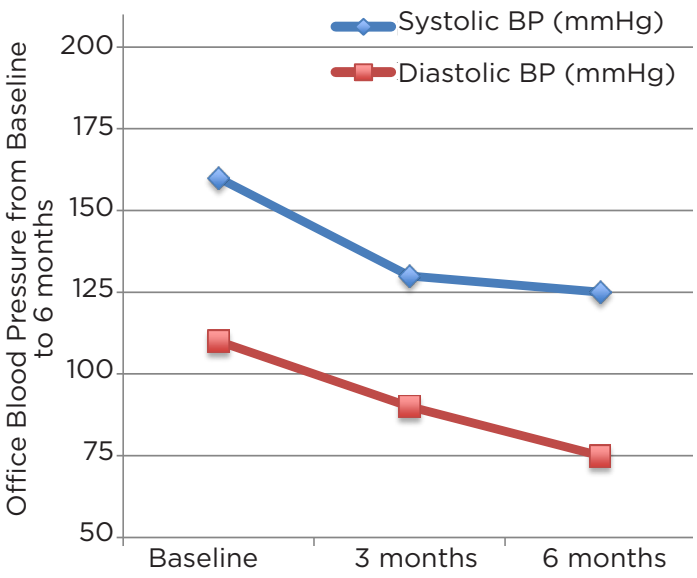

Figure 6: Follow-up after RDN via the OneShot™ RDN device. Office-based measurements of systolic and diastolic blood pressure at baseline, 3 and 6 months after RDN.

renal arteries was measured angiographically to 6.5-7.00 mm; therefore the 7 mm OneShot balloon was used to perform RDN with a single 2 minute ablation at each side. An angiography demonstrated no evidence of dissection or spasm of the renal arteries. Post-interventional creatinine levels remained stable. The patient was discharged from the hospital the next day in good condition. Dual antiplatelet therapy was administered with aspirin in combination with clopidogrel for 4 weeks according to our own protocol. The other medication remained unchanged. Mean office blood pressure 24 hours post-procedure was 149/105 mmHg. At 3 and 6 month follow-up visits, the patient was in good clinical condition, on the same medical regimen as at baseline and presented an effective reduction in blood pressure levels (Figure 6).

IVOCT Analysis After RDN

To date, no histological examinations of ablated human renal arteries have been published. Therefore, despite limited animal studies, nothing is known about the consequences of high energy application to the tender endothelial layer and the pathophysiological processes within the vessel wall after RDN.[32] Intravascular optical coherence tomography (IVOCT) is an invasive modality with the ability to provide detailed images at an axial resolution of 10-15 µm, enabling real-time visualisation of blood vessel wall microstructure in

vivo. This method enables accurate evaluation of tissue coverage after intracoronary stenting and has become an exploratory tool for different issues in the field of interventional cardiology.[16] For example, IVOCT is currently used for pre and post-procedural guidance in percutaneous coronary interventions, visualising stent apposition and endothelialisation as well as thrombus formation, characterisation of atherosclerotic plaques and artery wall dissection.[33-35] Recent findings of IVOCT analysis after RDN showed local endothelial damage with oedema and thrombus formation at the ablation spots.[36] IVOCT is able to visualise these vascular lesions.[17] We performed IVOCT analysis after RDN with the Symplicity™ system. Small endothelial damage sites (in one case with thrombus formation) were identified within the ablation area of the renal artery, suggesting that they were caused by RDN (Figure 4, 5). Based on published data from recent trials and registries, RDN is shown to be safe, with up to 3 year follow-up data available for patients participating in the Symplicity HTN-1 trial.[9] Nevertheless, the number of patients is still too low to evaluate the frequency of rare events.[14,15] Yet, no recommendation has been published regarding antiplatelet therapy following RDN with the Symplicity™ system. At our institution, we suggest the use of dual antiplatelet therapy for 4 weeks, to reduce the risk of thrombus formation after RDN.

Templin et al.[17] found evidence for an even higher formation of endothelial damage by the use of the EnligHTN™ Renal Denervation System compared to the Symplicity™ system. These findings suggest that the increase in electrodes may increase the risk for kidney infarction and renal artery stenosis through plaque formation induced by endothelial damage after RDN. The OneShot™ System aims to reduce these risks by the use of an irrigated balloon. We performed IVOCT analysis in two subsequent patients after RDN by this system and did not observe any endothelial damage within the examined renal arteries. We postulate that irrigated and fluid-cooled RDN devices may reduce the observed issues. Yet, these preliminary findings need to be proven in larger trials or registries to draw definitive conclusions.

CONCLUSION

Despite effective drug therapy, only 25–35% of HTN patients are reaching their individual recommended blood pressure levels, leading to end-organ damage and serious adverse cardiovascular events.[6] RDN is an effective technique for the treatment of refractory HTN; published data with the Symplicity™ device confirm efficacy, allowing for the introduction of this treatment into routine practice. This may limit HTN-associated end-organ damage. Several new devices are currently being studied in clinical trials, with the aim of reducing procedure time, while enhancing effectiveness and safety. These and any individual advantages and disadvantages have to be proven within the next years by executing larger clinical trials and registries. By performing IVOCT-analyses after RDN, it is now possible to understand the effects of the procedure concerning endothelial damage, thrombus and plaque formation as well as formation of renal artery stenosis.

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ICE-ASSISTED TRANSCATHETER CLOSURE OF INTERATRIAL SHUNTS: TEN-YEAR FOLLOW-UP

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ABSTRACT

Background. Intracardiac echocardiography (ICE) is rapidly becoming a necessary tool in the catheterisation laboratory. We sought to prospectively evaluate the effectiveness of ICE-aided transcatheter closure of interatrial shunts.
Methods. In a prospective 10-year registry, we enrolled 378 patients (mean age 48±13.7 years, 214 females) who had been referred to three different centres for catheter-based closure of interatrial shunts. All patients were screened with transoesophageal echocardiography (TOE) before the operation. Eligible patients underwent ICE study with mechanical Ultra-ICE probe (Boston Scientific Corp, USA) and closure attempt.
Results. After the ICE study and measurements, 23 patients did not proceed to transcatheter closure due to: unsuitable rims, atrial myxoma not diagnosed by pre-operative TOE, or inaccurate TOE measurement of defects more than 40 mm. The remaining 355 patients underwent transcatheter closure: TOE-planned device type and size were modified in 175 patients (49.3%). There were no cases of aortic or atrial erosion, device thrombosis, or atrioventricular valve inferences. Globally the rates of procedural success, pre-discharge occlusion, and major complications rate were: 99.1%, 93.3%, and 0%, respectively. On mean follow-up of 9.1±2.3 years, the follow-up occlusion rate was 98.7% with no long-term complications.
Conclusions. ICE-aided transcatheter closure of interatrial shunts appears to be safe and effective in adult patients thus, eventually minimising device size over and underestimation, and potential complications of balloon sizing and general anaesthesia.

Keywords: Atrial septal defect, percutaneous, catheter-based closure, intravascular, interventional, device, echocardiography, congenital, patent foramen ovale.

INTRODUCTION

Due to favourable results achieved by percutaneous closure as compared to medical therapy and surgical closure,[1-2] transcatheter closure has emerged as the first-line therapy for the management of secundum atrial septal defect (ASD), and thanks to the positive results of the last recent trials,[3-4] also for patent foramen ovale (PFO). It has been suggested that intracardiac echocardiography (ICE) improves safety and effectiveness of transcatheter device -based closure of interatrial shunts,[5-6] but the impact of this imaging tool on long-term follow-up has not yet been evaluated. We sought to prospectively evaluate 10-year outcomes of ICE-aided transcatheter closure of interatrial shunts in adults.

METHODS

In a prospective 10-year registry, we enrolled 378 patients (mean age 48±13.7 years, 214 females) who have been referred to three different centres for catheter-based closure of interatrial shunts. In line with our institutional protocol, all patients were screened with transoesophageal echocardiography (TOE) prior to the intervention. Inclusion criteria

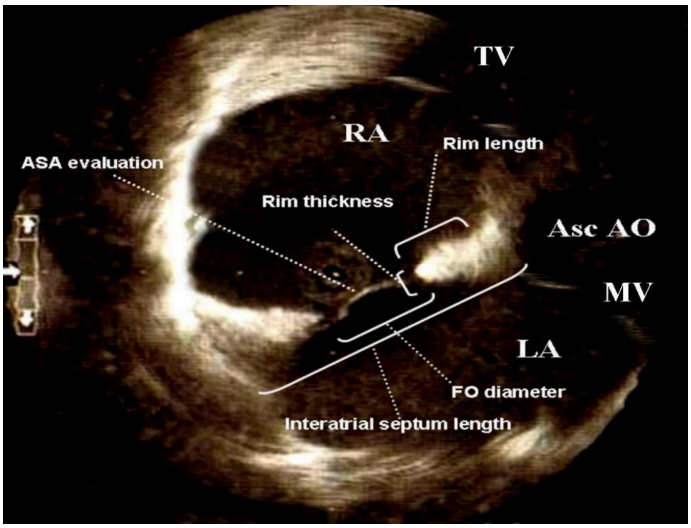

Figure 1: Typical measurements of right atrial components during ICE examination.
(Asc AO: ascending aorta; LA: left atrium; MV: mitral valve; RA: right atrium; TV: tricuspid valve).

for percutaneous closure of atrial septal defects included: Qp/Qs more than 1.5, enlargement of right atrium (more than 16.84 mm area) and ventricle (inflow tract of right ventricle more than 35 mm),[7] and atrial septal defect less than 40 mm. Indications for percutaneous closure of patent foramen ovale (PFO) defects included all of the following: a concurrent shower or curtain shunt pattern on transcranial Doppler [8] with or without Valsalva manoeuvre, positive (single or multiple ischemic foci) cerebral magnetic resonance imaging or previous clinical stroke or transient ischemic attack, and medium or large patent foramen ovale on TOE.[9] All patients with secundum atrial septal defect and/or patent foramen ovale were investigated by transthoracic echocardiography and transcranial Doppler, respectively, before TOE. The Hospital Ethical Board approved the study and written informed consent was obtained from all patients enrolled in the study.

Echocardiography Protocols

TOE was conducted using a GE Vivid 7 (General Electric Corp., Norfolk, VA, USA) with bubble test and Valsalva manoeuvre under local anaesthesia. Patients who met the criteria for secundum atrial septal defect or PFO closure were offered an ICE study using the mechanical 9F 9MHz Ultra-ICE catheter (EP Technologies, Boston Scientific Corporation, San Jose, CA, USA). The ICE study was conducted as previously described,[10] by performing a manual pull-back from the superior vena cava to the inferior vena cava through five sectional planes; measurement of diameters of the oval fossa, the entire atrial septum length and rims were obtained with electronic calliper edge-to-edge on the aortic valve plane and the four-chamber plane. PFO tunnel length was also measured. Intracardiac echocardiographic monitoring of the implantation procedure was conducted on the four-chamber plane. Normal diameter of fossa ovalis was defined as fossa ovalis <15 mm in the four-chamber view. Atrial septal aneurysms were classified according to Olivares et al.[11] Hypertrophic rims were defined as having a thickness ≥8 mm, whereas lipomatosis was defined as thickness of ≥15 mm, on ICE study. Long tunnel-type PFO was defined as length ≥10 mm by intracardiac echocardiogram.

Radiological Equipment

We used the GE Medical System Innova 2100 20-20 cm Flat Panel radiological equipment in all cases. Field size used was 20-20 cm. An estimation of the effective dose was obtained from the measurements of the total dose-area product that is automatically recorded by the radiological equipment during the procedures. Fluoroscopy and procedural times were also calculated.

Closure Protocol

Combined antibiotic therapy (Gentamicin 80 mg plus Ampicillin 1 gm, or Vancomicin 1 gm if there was a documented allergy to penicillin) was administered intravenously one hour before the procedure. The right femoral vein was catheterised through a six French sheath which was used for preoperative right cardiac catheterisation, and replaced with larger long sheath for device implantation, whereas the left femoral vein was catheterized through a eight French sheath which was replaced with a pre-curved nine French long sheath for the ICE study.

Intraoperative Closure Criteria and Device Selection

On the basis of ICE findings and measurements, the operators selected the Amplatzer Occluder family (PFO Occluder, Cribriform Occluder, ASD Occluder, AGA Medical Corporation, Golden Valley, MN) or the Premere™ PFO Closure System (St. Jude Medical Inc. GLMT), the Biostar Occluder (NMT) or the GORE GSO device (WL Gore & Associates, Inc, Flagstaff, Arizona, USA). The operators selected the Amplatzer PFO occluder when atrial septal aneurysm was unidirectional and mild (2RL or 2LR), and the Biostar or the Gore Septal Occluder when the aneurysm

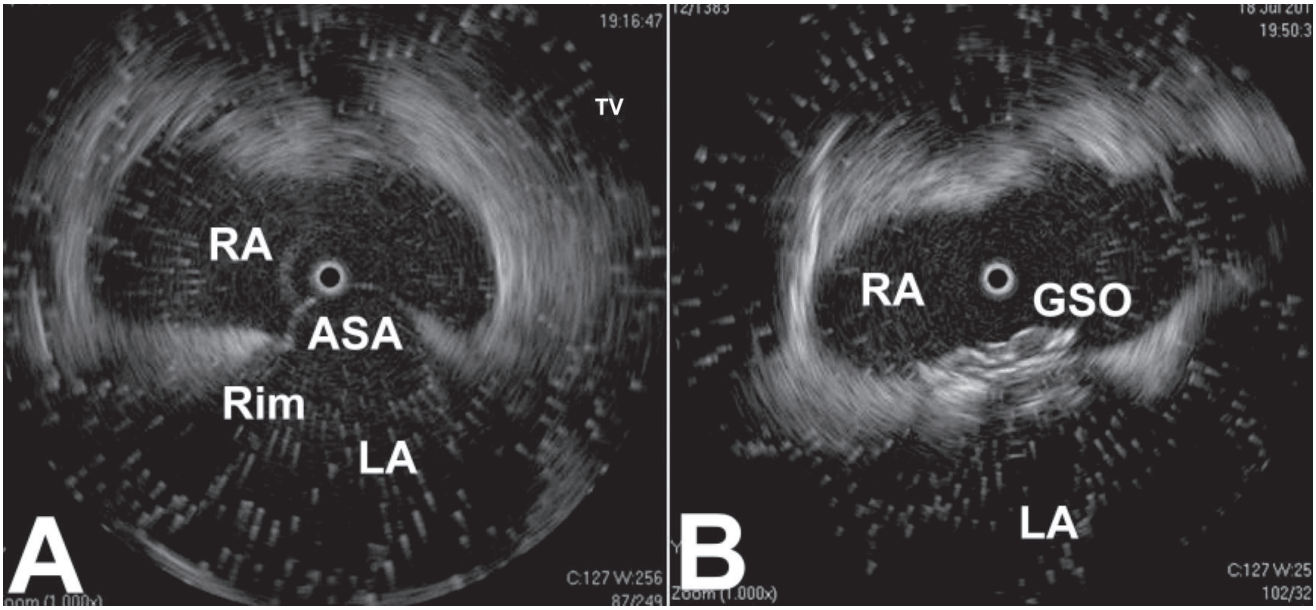

Figure 2: Patient with moderate atrial septal defect and hyperthrophic rims before (A) and after (B) closure with a Gore Septal Occluder (GSO).
(LA: left atrium; RA: right atrium; TV: tricuspid valve).

was unidirectional and moderate (3RL or 3LR atrial septal aneurysm). The Premere occlusion system was chosen when atrial septal aneurysm was absent or in the case of motionless or unidirectional atrial septal aneurysm (1R, 2L atrial septal aneurysm), when PFO tunnel length was more or equal to 10 mm, and in all case of hypertrophy of the interatrial septum rims (thickness more than 10 mm). The Amplatzer Cribriform Occluder was selected in the case of bidirectional moderate aneurysm (3 RL or 3LR), in all cases of large aneurysm (4 and 5RL or 4 and 5LR) and in all cases of multi-perforated atrial septal aneurysm, being careful to cross the most central hole in the oval fossa with the guide-wire during ICE guidance.

The Amplatzer ASD Occluder was selected in the case of secundum atrial septal defect, when anomalous venous return was angiographically excluded. Device sizing was obtained as described by Rigatelli et al.[12] by the measurement of the diameter on the aortic valve plane (short axis of an ideally elliptical defect) and the four-chamber plane (long axis of an ideally elliptical defect), which are perfectly orthogonal views. In all cases, care was taken to choose a device with an entire left disk diameter which did not exceed the ratio device size or entire atrial septum length of 0.8mm on ICE.

Medications

Aspirin 100 mg for 6 months has been prescribed to all patients with no coagulation abnormalities who received a Premere, Gore or Amplatzer devices. Aspirin 100 mg and Clopidogrel 75 mg for 6 months have been prescribed to patients who received the Biostar device. Warfarin for 6 months was prescribed to patients with coagulation abnormalities such as abnormal factor V of Leiden and anticardiolipin, antiphospholipid antibodies.

Follow-up Protocol

In patients who underwent closure, TOE was scheduled at 1 month and repeated at 6 months post-closure if there was more than a trivial shunt, to assess for potential erosions or thrombosis and residual shunts. Patients with PFO-related syndromes also underwent transcranial Doppler ultrasound and magnetic resonance imaging of the brain prior to and 1 month after the procedure. Transthoracic echocardiography was scheduled at 6 and 12 months after the transcatheter closure to assess mid-term residual shunt, and the effect of the device on atrial and heart valve function.

Any residual shunt was graded as trivial, small, moderate, or severe as previously described.[13] Clinical examination was scheduled at 1, 6, and 12 months.

Definition

Success was defined as the ability to release the device in a stable position under fluoroscopy and ICE guidance with no more than a trivial shunt on immediate angiography and on transthoracic echocardiography at 24 hours after closure. Immediate complications included various degrees of groin haematoma, atrial wall perforation, and pericardial effusion, entrapment of device, sheath or ICE equipment through venous valves or embryonic remnants, and air embolism. Pre-discharge occlusion rate was defined as a percentage of complete occlusion (presence of no more than a trivial shunt). Aortic erosion and device removal were included in the mid-term complication rate.

Statistical Analysis

Chi-square, corrected Chi-square, and T-student tests were used to compare frequencies and continuous variables, with a significance level $p<0.05$. Kaplan–Meier curve was employed to evaluate actuarial occlusion rates.

	Mean or No. (%)
Age	48±19.1
Male/Female	83/157
Secumdum atrial septal defect:	98/355 (27.6)
-Cribrosus atrial septal defect	38/355 (10.7)
-Mean right ventricle diameter (millimeters)	49±21.8
-Mean Qp/Qs	2.4±0.8
-Mean pulmonary artery pressure (mmHg)	39±11.3
-Residual shunt after surgery	1/355 (0.3)
Patent foramen ovale:	257/355 (72.3)
-Previous stroke	189/257 (73.5)
-Migraine with aura	41/257 (15.9)
-Migraine with no aura	54/257 (21.0)
-Positive cerebral magnetic resonance imaging	257/257 (100)
- Transcranial Doppler curtain pattern	98/257 (38.3)
- Transcranial Doppler shower pattern	159/257 (61.8)
-Platypnea orthodeoxya	3/257 (0.9)
-Contraindication to scheduled neurosurgery	3/257 (0.9)

Table 1. Demographic and clinical data of the 355 patients who underwent transcatheter closure.

RESULTS

After ICE study and measurements, 23 patients did not proceed to transcatheter closure due to: unsuitable rims in 13 patients after ICE recalculated rim length and thickness, atrial myxoma not diagnosed by preoperative TOE in 2 patients, and inaccurate TOE measurement of defects >40 mm (9 patients). The remaining 355 patients underwent attempted transcatheter closure (Table 1).

Device Selection and Measurement Results

After ICE study and measurements (Table 2), the TOE-planned device type and size was changed in 175 patients (49.3%): 97 patients with PFO (Amplatzer PFO Occluder rather than Premere for 10, Amplatzer Cribrosus rather than Amplatzer PFO for 35, Premere rather than Amplatzer PFO for 52 patients), and 78 patients with secundum atrial septal defect patients. Despite the fact that TOE may underestimate the size of the defect, it was used to obtain an estimate of the defect size range and interatrial anatomy so as to provide the proper range of device sizes and

Anatomical characteristics (mm)	TOE	ICE	p
Diameter of the interatrial septum	28±9.8	37±10.6	<0.01
Secundum atrial septal defect diameter	16.9±6.9	22±10.1	<0.01
Length of anterosuperior rim (aortic rim)	4.2±1.3	5.8±1.1	<0.03
Oval fossa diameter	20.1±4.5	23±7.9	<0.03
Patent oval foramen tunnel length	11±3.1	13±4.9	<0.04
Patent oval foramen size	5.4±0.6	6.3±0.5	<0.01
Rim thickness	9.2±9.6	12.2±7.6	<0.01

Table 2. Comparison between preoperative TOE and intraoperative ICE measurements of anatomical features of the interatrial septum.
(Measurements refer to the four-chamber view).

types in the cardiac catheterisation lab. In cases of floppy rims detected by TOE, ICE was able to precisely measure the thickness of the rims. Accurate measurement of rim thickness is essential since rim thickness less than 1.2 mm is unlikely to support the device disks: this resulted in larger ASD and fossa ovalis diameters as measured by ICE compared to TOE.

The Amplatzer ASD Occluder mean waist diameter was 27.7 mm in the 60 ASD patients, whereas the Amplatzer ASD Cribriform Occluder was 25/25 mm in 126 patients and 30/30 mm in 38 patients. The Amplatzer patent foramen ovale Occluder disk mean diameter was 25 mm in 32 patients, and 35 mm in 2 patients. The Premere device size was 25 mm in 30 cases, and 20 mm in 45 cases, The Biostar was 28 mm in 4 patients, whereas the Gore GSO size was 25mm in 6 patients and 30mm in 12 patients.

Procedural and Early Results

Transcatheter closure was successful in 352/355 (99.1%) of the patients. In one case of ASD the device was removed intraoperatively because of an incorrigible misalignment, in two cases of PFO, the implanted device was withdrawn as it was positioned too close to the aortic root on ICE.

In three cases of PFO, the release of the Amplatzer Occluder was difficult and complicated by thoracic pain because it became snared in a venous valve remnant during sheath advancement. Forced and prolonged sheath manipulation during the procedure was judged to be the cause of pericardial effusion in 3 patients, and groin haematoma not requiring blood transfusion occurred in 7 patients. 7 patients suffered either from arrhythmias: supraventricular tachycardia (2 patients) and atrial fibrillation (2 patients) within 24 hours of the procedure; sinus rhythm was restored in 5 patients with antiarrhythmic drugs, and in 2 patients with electrical cardioversion. In 2 patients (1 with a PFO and 1 with an secundum atrial septal defect), TOE at 1 month revealed moderate shunts, indicating that the initial successful closure had subsequently failed probably due to the worsening of device misalignment not fully evaluated on transthoracic echocardiography. It was therefore agreed, with the patients' consent, to surgically remove the devices.

10-Year Follow-Up

Over a 9.1±2.3 follow-up (range 2-10), only 1 patient (with a secundum atrial septal defect) had documented permanent atrial fibrillation. No aortic erosions or device thrombosis, or recurrent ischemic cerebral events were observed. Pre-discharge and follow-up occlusion rates are reported in Table 4.

	Pt (%)
Procedure success rate	352/355 (99.1)
Complications rate:	12 (3.3)
-sheath or device entrapment	2 (0.5)
-groin haematomas	7(1.9) †
-pericardial effusion°	2(0.5) ‡
-air embolism	1(0.2)
Fluoroscopy time (minutes)	7±4.2
Procedural time (minutes)	35.5±5.8
Total Dose Area Product (Gycm2)	26.7±1.88

Table 3. Procedure results.
°≤200 cc; † not requiring blood transfusion; ‡ conservatively managed.

DISCUSSION

Although our experience included patients with different clinical entities (ASD and PFO) our study suggests that ICE -guided device-based closure of interatrial shunts is safe, effective and allows for good long-term outcomes with a low complication rate and a low radiation exposure rate for the patients. In our experience, all were minor complications, such as groin haematomas and supraventricular arrhythmias, not ICE-related. These data compared very well with past literature of surgical repair and TOE-guided catheter-based repair. Previous studies on secundum atrial septal defect closure reported excellent immediate success and occlusion rates ranging 93 to 99%, with a complication rate ranging 6.9 to 14%.[14-16] In particular the most clinically dangerous long-term complications, such as erosion and device thrombosis have been reported to be 0.1 and 2.5%.[17-19] Transcatheter closure of ostium secundum atrial septal defect has been performed for years using deep sedation or orotracheal intubation, TOE, and the sizing balloon technique for size measuring the 'stop-flow' diameter of the defects. In most laboratories, ICE is replacing TOE, because it avoids general anaesthesia and related morbidity, as well as increasing patient comfort. A few cost assessment

	Rate	Notes
Pre-discharge occlusion: - Secundum atrial septal defect (98) - Patent foramen ovale (257) -Total	 94.9 % 82.5% 85.9%	 3 small shunts, 2 moderate shunts 25 trivial shunts, 10 small shunts, 10 moderate shunts
Follow up occlusion: - Secundum atrial septal defect - Patent foramen ovale -Total	 97.9 % 93.3% 94.6%	 1 moderate shunts: device removal (Amplatzer) 8 trivial shunts, 7 small shunts, 2 moderate shunts

Table 4. Pre-discharge and long-term occlusion rates.

studies, mainly conducted outside Italy, also suggest a beneficial economic impact of this technique on global costs.[20-21]

ICE has been demonstrated to provide a higher accuracy than TOE in anatomical measurements and implantation guidance,[22-23] shortening catheterisation and interventional procedure time with no difference in rate of closure. Moreover, ICE has been suggested as the optimal imaging technique for anatomical morphological measurements and sizing the defect, decreasing the radiation exposure dose[24-25] findings, which were all confirmed in our study.

As already demonstrated in our previous studies,[26-27] ICE is particularly accurate for measuring the length and thickness of the rims as it is possible to calculate the precise diameter of the secundum atrial septal defect, as suggested in data of patients who had floppy rims on TOE and were successfully closed with a larger device than the one predicted on the basis of TOE alone. Regarding PFO, we identified some 'sensible' characteristics that may affect the complications and closure rates including: the PFO tunnel length, thickness of the rims, oval fossa diameter, and atrial septal aneurysm severity. We believe that all these factors deserve careful attention because of their potential to result in device misalignment, improper device configuration, and uncovering of misdiagnosed fenestration, as previously demonstrated.[28] For both secundum atrial septal defect and PFO, selecting a device with a disk diameter that does not exceed the entire interatrial septum length on ICE can be a simple rule that prevents complications such as atrial and aortic erosion, or atrioventricular valve dysfunction.[29]

In conclusion, despite a number of limitations, including the different anatomic substrate between PFO and secundum atrial septal defect, and the different failure rates associated with different devices, our study confirmed our previous mid-term results suggesting that ICE evaluation may offer optimal guidance during catheter-based closure of interatrial shunts, thereby optimising long-term effectiveness and potentially lowering long-term complications.

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OCCUPATIONAL RISKS OF CHRONIC LOW DOSE RADIATION EXPOSURE IN CARDIAC CATHETERISATION LABORATORY: THE ITALIAN HEALTHY CATH LAB STUDY

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ABSTRACT

Contemporary interventional cardiologists have an exposure per person, per year, two to ten times higher than that of diagnostic radiologists. Cumulative doses after 30 years of working life are in the range of 50 to 200 mSv, with a projected professional lifetime attributable excess cancer risk in the order of magnitude of 1 in 100. Of special concern, the left side of the operator is more exposed (30% to 100%) than the right side, and less protected parts of the body (e.g. head and hands) can receive equivalent doses between 5 and 50 mSv per year.

Focused studies are clearly needed to define the occupational health risk of accumulated radiation exposure in catheterisation laboratories, particularly in respect of potential risk for circulatory diseases (i.e. heart disease and strokes) and effects on the cognitive function. This paper describes the rationale of the ongoing Healthy Cath Lab (HCL) Study, designed by interventional cardiologists, for interventional cardiologists. The Italian HCL project is a case-control study that will include a cohort of 500 highly exposed subjects (interventional cardiologists, nurses, and technicians working in the cath lab >3 years) and a 'best match' control group of 500 unexposed subjects. All aspects of in-room personnel radiation exposure (e.g. standard safety precautions, workload), as well the health status of each participant, will be investigated by using a web survey. In order to overcome the inherent limitations of the epidemiological approach, the relationship between radiation exposures and the risk of health effects will also be evaluated through 'early warning' signs, which are easy to measure and are capable to identify long-term risk for subsequent clinically overt disease. Examples of surrogate endpoints include chromosome aberrations analysis for cancer risk, carotid intima-media thickness and telomere shortening for atherosclerosis, and olfactory dysfunction for neurodegenerative disorders.

The HCL project will contribute in the defining of the potential occupational health effects of radiation exposure in cath lab, as well as strengthening 'the culture of safety' in the cath lab.

Keywords: Radiation exposure, personnel, health risk, biomarkers, Healthy Cath Lab Study.

INTRODUCTION

The use of radiation in medical diagnosis in Western societies is the largest man-made source of radiation exposure,[1-3] especially for the growing use of computed tomography and interventional cardiology. Over the last 20 years, the number of interventional cardiovascular procedures has increased rapidly. In Europe, arteriography and interventions were 350,000 in 1993 and >1 million in 2001.[4] On average, a left ventriculography and coronary angiography correspond to a patient radiation exposure of about 300 chest X-rays; and a percutaneous coronary intervention (PCI) or a cardiac radiofrequency ablation to 750 chest X-rays (range:350-2350).[5] In adult cardiology, interventional cardiology procedures account for 12% of examinations, and 48% of the total collective dose.[6] In children with congenital heart disease, invasive cardiology (with diagnostic and interventional catheterisation) accounts for 6% of all radiological examinations and 84% of the collective dose.[7] Typical effective doses for common cath lab procedures are reported in Table 1.[5,8-12] The high levels of patient exposure imply a significant professional exposure for the interventional cardiologist, who needs to operate near the patient and the radiation source. The single dose per procedure of the operator is on the order of magnitude of one thousandth microSV of the exposure of the patient.[13]

Effective occupational doses per procedure range from 0.02 to 38 microSv for diagnostic catheterisation and may reach even higher values per complex procedure, such as up to 200 microSv per single procedure of endovascular thoracoabdominal aneurysm repair.[13] Each operator performs hundreds or thousands of procedures each year, and therefore the cumulative dose in a professional lifetime is not negligible. The most active and experienced interventional cardiologists in high-volume cath labs have an annual exposure equivalent to around five mSv (below apron) per year, two to three times higher than that of diagnostic radiologists.[14]

Cumulative doses after 30 years of working life are in the range of 50 to 200 mSv, corresponding to a whole body dose equivalent of 2,500 to 10,000 chest X-rays with a projected professional lifetime attributable excess cancer risk of 1 in 100.[15] Of special concern, in interventional cardiologists the head organ dose is 10 to 20-fold higher than the whole-body dose recorded below apron.[16-18]

Although there is a general appreciation that radiation by itself is certainly not a good thing for the patient or the operator, the characterisation of health effects (cancer and non-cancer) of chronic low-dose radiation is still incomplete and difficult.[19-21] Recently, a joint effort of American professional societies led to the formation of the Multi-Specialty Occupational Health Group (MSOHG), dedicated to defining the occupational risks associated with working in a fluoroscopic laboratory in collaboration with experts in occupational health, epidemiology, and radiation effects from the United States Navy and the Radiation Epidemiology Branch of the National Cancer Institute.[20] The main initial goal of MSOHG is to perform epidemiological studies for assessing the incidence of cancer and other serious disease outcomes (including cardiovascular disease and cataracts) by comparing physicians performing fluoroscopically-guided procedures (including interventional cardiologists, radiologists, neuroradiologists and others), with non-interventional radiologists, and physicians who are unlikely to be exposed to occupational radiation (e.g. family physicians or psychiatrists).

Another study has now started in Italy, the Healthy Cath Lab (HCL) study, and is organised by the Italian National Research Council with endorsement from the Italian Society of Invasive Cardiologists.

This paper describes the rationale of the ongoing Italian project designed by interventional cardiologists for interventional cardiologists.

CURRENT STATUS OF KNOWLEDGE

Radiation Exposure of Interventional Cardiologists

Ionising radiation from the fluoroscopy tube is scattered by the patient while the cardiac intervention is underway (Figure 1). The operator's distance from the patient's skin entrance site is crucial because the level of scatter radiation is inversely proportional to the distance squared.[22] In addition, the operator's position and body height have a major impact on the amount of scatter radiation to different parts of the operator's body.[23-25]

Several investigations clearly showed that the left side of the operator is more exposed than the right side in most cases due to the usual layout of an interventional room, where the cardiologist operates from the right side of the patient so that the scatter radiation comes predominantly from

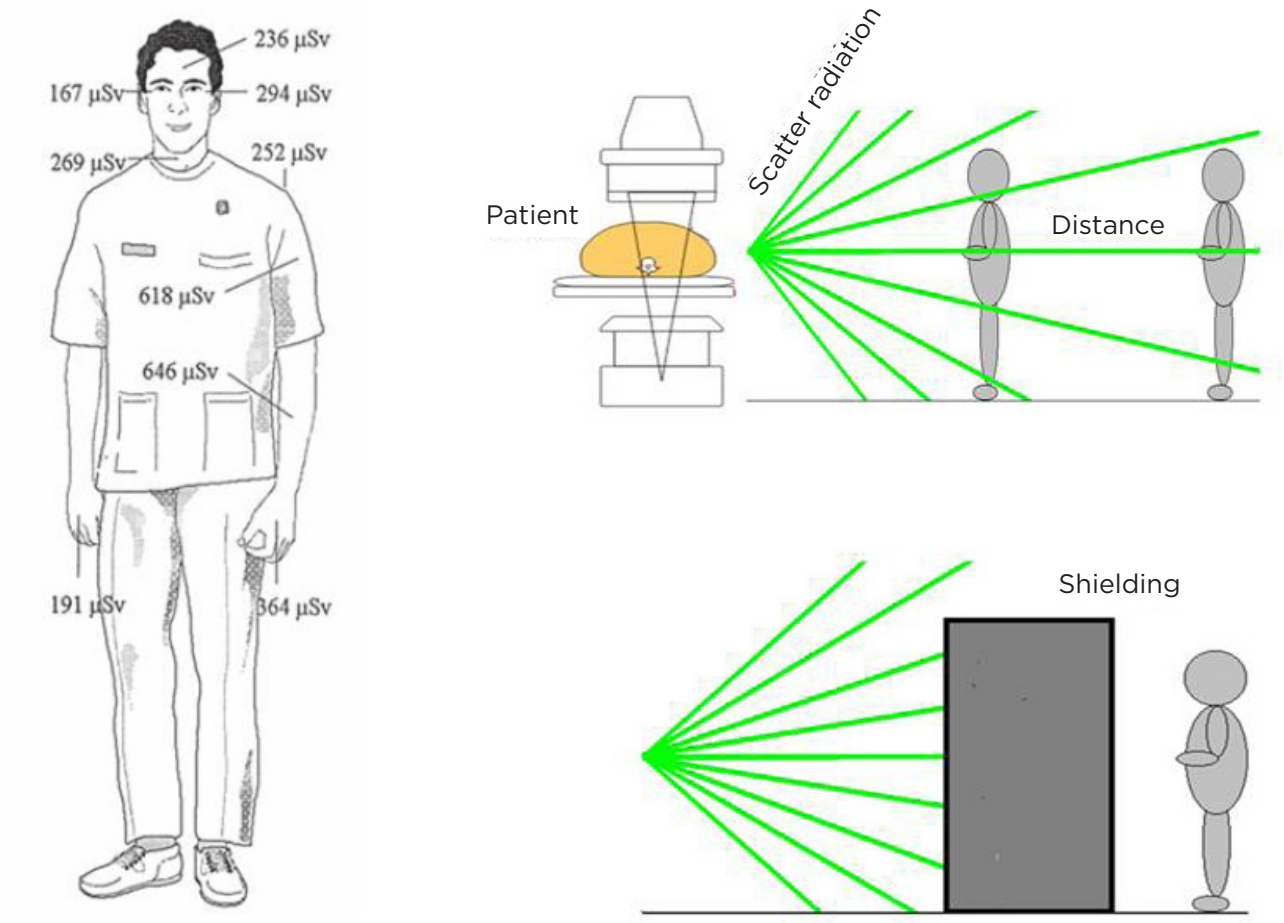

Figure 1. Radiation exposure distribution in the interventional cardiologist.
Radiation exposure on the left is almost double that on the right side.[14,22] Key factors in protection of cardiologists are distance and shielding. Increasing the distance from the radiation beam decreases the risk of exposure. Protective shielding includes structural shielding, mobile shielding and personal shielding. Eye, thyroid and brain that should be carefully protected by glasses, collars and cap.

the patient on his/her left.[23-25] Of special concern, in interventional cardiologists the head organ dose (if left unprotected) is 10 to 20-fold higher than the dose recorded beneath the apron.[26,27]

Annual exposure to the cardiologist's head is in the range of 20–30 mSv per year[27] or much higher if a ceiling-suspended screen is not used.[16,28] This implies that the lifetime estimated organ head dose for a busy interventional cardiologist after 25 years of work in the catheterisation laboratory is in the order of magnitude of 1 to 3 Sv (21). Unfortunately, the practice of interventional cardiology is sometimes accompanied a suboptimal perception of radiation risk and by negligent use of radiation protection tools.[29-31] Radioprotection awareness by operators is dramatically effective in reducing professional exposure by 90%.[16] Today, in most cardiology imaging laboratories and in interventional radiology fluoroscopy rooms, overhead radiation shields, thyroid shields, and leaded aprons are employed to reduce the radiation doses to the head and neck of operators. It is rare that unprotected radiologists or cardiologist would do an angiography procedure. Unfortunately, this was not the most common situation in the past, and even today it is not the rule in each and every laboratory.[29-31]

Cancer Risk

The radiation exposure in cath labs is associated with a small but definite stochastic risk of inducing a malignant disease, in the range of 1 in 100 for many operators who cumulate around 100 mSv professional exposure, corresponding to operators who carry out up to 400-800 PCI procedures per year for more than 20 years.[15] To date, however, clinical evidence of an increased cancer risk for interventional cardiologists is only suggestive,[21,32] with anecdotal reports of haematologic malignancies and other cancers being common conversation at societal meetings.[20]

Recently, two reports described the disproportionate number of tumours on the left side of the

brain, the region of the head known to be more exposed to radiation and least protected by traditional shielding.[33,34]

Clearly, the observational nature of these findings do not allow the establishment of a causal connection between occupational radiation exposure and the development of brain cancer, and substantially limits firm conclusions.[34]

On the other hand, there is a growing body of biological data showing cellular changes induced by professional low-dose X-ray radiation exposure in interventional cardiologists to low-dose radiation prompts cellular changes.[35-37]

Indeed, our recent biological data showed that occupational exposure to low-dose radiation is associated with an increased activity of antioxidant enzymes, as protection against the increased production of ROS as well as an increased susceptibility to apoptotic induction which might efficiently remove genetically damaged cells.[35]

Furthermore, interventional cardiologists have a two-fold increase in circulating lymphocytes of chromosome aberrations and/or micronuclei, which represent surrogate biomarkers of cancer risk and intermediate end points of carcinogenesis.[36,37] Importantly, the increase in chromosomal DNA damage is further enhanced in the presence of genetic polymorphisms of genes involved in DNA repair, suggesting that an individual predisposition may play an important role in the cellular response to radiation exposure and health risk.[38]

Radiation-Induced Cataracts in Interventional Cardiologists

Among eye tissues, the lens is the most radiosensitive and thus cataract formation may be the primary ocular complication associated with ionising radiation exposure.[19]

Until recently, the dose threshold for radiation-induced lens opacities was considered two Gy for a single dose or five Gy for fractionated dose. Currently, radiation-induced cataract, previously thought to be deterministic (tissue reactions), is recognised as possibly stochastic in nature, and occurring at much lower radiation exposure level than previously thought.[39]

Indeed, several epidemiological studies showed that an increased incidence of lens opacities at doses below 0.5 Gy.[40] Accordingly, on April 21, 2011 the International Commission on Radiological Protection (ICRP) slashed the earlier dose limit of 150 mSv in a year for the lens of the eye, to the present 20 mSv in a year, averaged over a defined period of 5 years, with no single year exceeding 50 mSv.[39] Eye cataracts, which can be observed in one-third of staff after 30 years of work[22] and the Occupational Cataracts and Lens Opacities in Interventional Cardiology: the O'CLOC study performed in France indicated a high risk of posterior subcapsular opacities in the population of interventional cardiologists.[41]

Reproductive Health

Ionising radiation exposure can affect the reproductive health of exposed fathers and exposed mothers.[42,43] For interventional cardiologists, the gonad dose (below lead apron) is in the same order of magnitude of the shielded thyroid dose, with a median of 10-100 microSv per cine-angiography procedure. The dose can be ten-fold higher for a complex interventional procedure. This leads to a cumulative exposure in the 0.5-1 Sv range over a professional lifetime of 30 years.[44]

A borderline increase with respect to chromosomic abnormalities (excluding Down's Syndrome) in children of female radiographers has been reported in the literature.[45] Furthermore, a small study on 90 exposed male radiographers (and 90 unexposed controls) reported a worrisome increase in the risk (with relative risks ranging from 2 to 10) of reproductive health problems, including miscarriages, still births, and major congenital abnormalities at birth.[46] Furthermore, exposed fathers might be mostly fathers of daughters, as suggested by preliminary data obtained in male radiographers.[47]

However, the human data on adverse hereditary effects that could be attributed to radiation remain contradictory, and exact quantification remains a scientific and social challenge.[44,48]

Non-Malignant Thyroid Diseases

Thyroid disease is another important target for deleterious effects of ionising radiation. Several studies have reported that the risk for malignant and benign thyroid nodules increased with external irradiation and internal radiation exposure as well as an association between autoimmune thyroid diseases and radiation exposure.[49] However, the effects of low dose radiation on functional thyroid diseases remains largely unknown.[49]

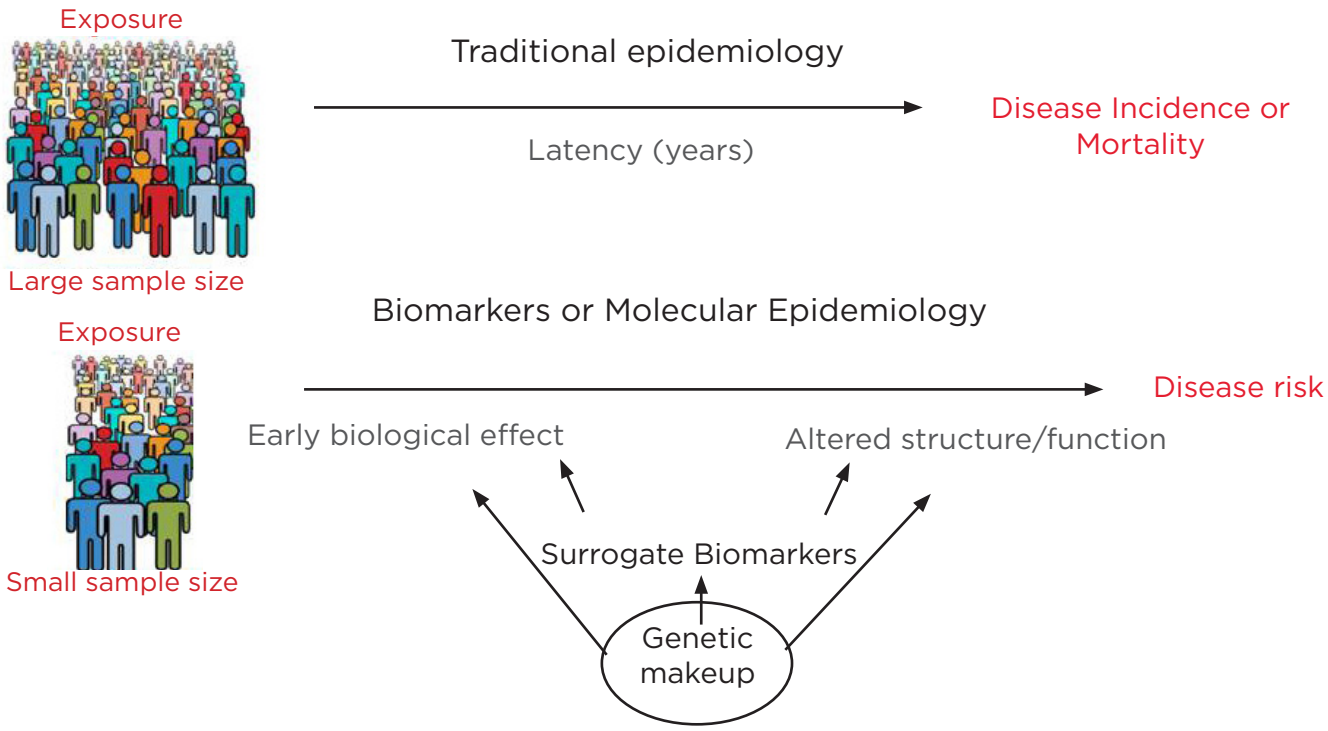

Figure 2. Conceptual model for using biomarkers and surrogate endpoints to assess exposure risk. Traditional epidemiology aims at identifying the relationship between the exposure and disease incidence or mortality. Along the continuum between exposure and disease development, selected biomarker sets may provide information on the extent of biological effects and early changes in the disease process as well as identify individuals with a particularly high risk of disease development, allowing to implement disease prevention programs.

Cardiovascular Disease

At the present time, there is good evidence that at moderate doses (>500 mSv) ionising radiation is a risk factor for cardiovascular disease, but it is unclear whether risks still persist in low doses.[21]

According to International Commission on Radiological Protection (ICRP) 2012, a dose of 500 mSv may lead to approximately 1% of exposed individuals developing cardiovascular or cerebrovascular disease, more than 10 years after the exposure, in addition to the 30-50% suffering of disease independently of the exposure.[50]

It is unclear whether or not the threshold is the same for acute, fractionated, and chronic exposures, and in the absence of evidence, it is assumed that the threshold dose is the same in all cases (50). A recent meta-analysis showed excess population risks for all circulatory disease from low-dose (cumulative mean <500 mSv) whole-body exposure or exposures at a low dose rate (i.e.<10 mSv/day) ranging from 2.5% to 8.5%/mSv, indicating that population-based excess mortality risks for circulatory disease are similar to those for radiation-induced cancer.[51] However, most of the epidemiologic evidence on low dose radiation and risk of cardiovascular death have important limitations, mainly due to the heterogeneity among studies (particularly for non-cardiac endpoints), the statistical power and small sample size and the lack of information on potential confounders.[51]

Brain Function Effects

The brain is a paradigm of a highly differentiated organ with low mitotic activity and is thus considered radio-resistant according to a fundamental law of radiobiology ('law of Bergonié and Tribondeau', 1906). However, cognitive dysfunction has been linked to white matter damage in the brain following radiotherapy.[52]

Furthermore, there is clinical evidence (Chernobyl fall-out) of cognitive impairment and schizophrenia.[53] Experimental studies showed a reduction in adult neuritogenesis by prenatal irradiation that may be associated with schizophrenia-like behaviour in rodents[54] and Alzheimer's disease.[55] Additional studies have provided evidence for apoptosis, neuro-inflammation, loss of oligodendrocyte precursors and myelin sheaths with apparent preservation of axons,[56] and irreversible damage to the neural stem cell compartment with long-term impairment

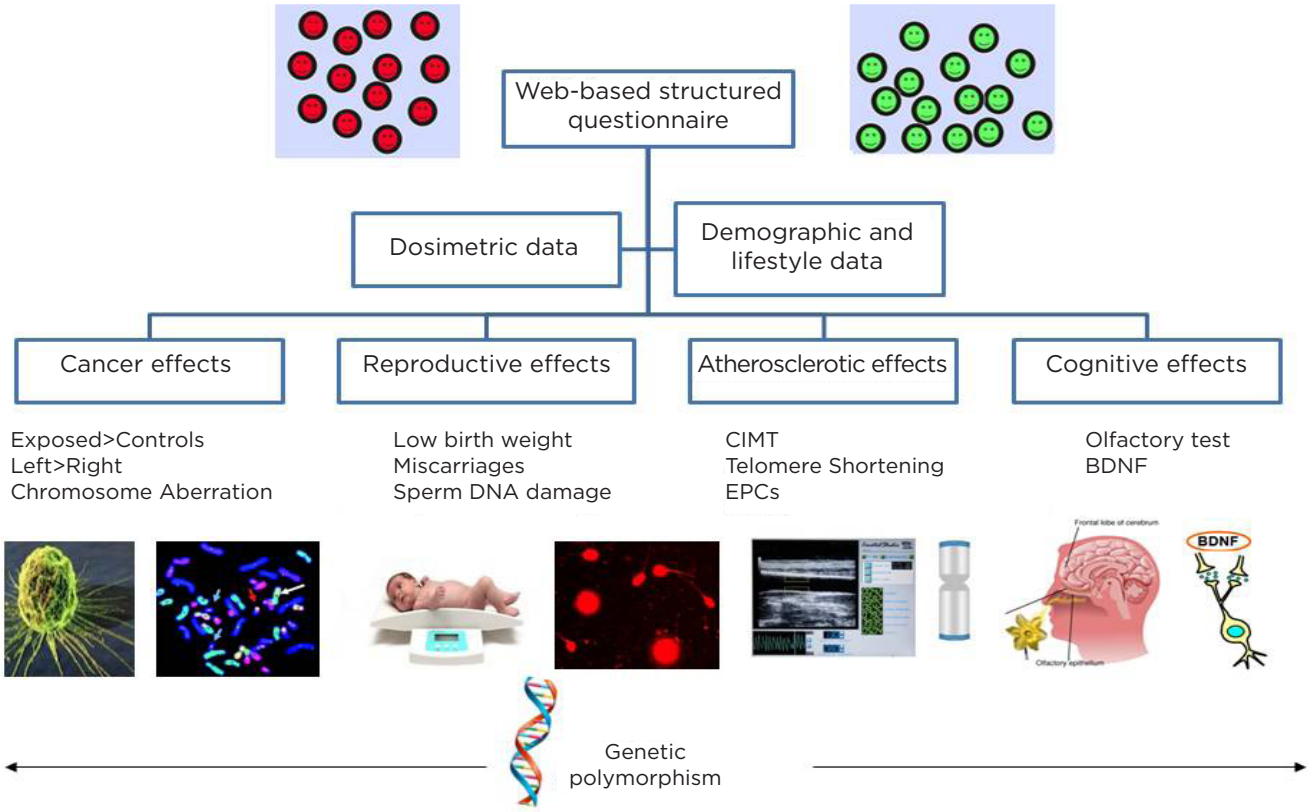

Figure 3. Overall view of the Health Cath Lab project.
Within a case-control study design, the project will employ molecular markers and clinical surrogate endpoints to investigate if occupational radiation exposure correlates with the risk of cancer and non-cancer disease.

of adult neurogenesis.[57] For any given cumulative dose, repetitive exposures are more detrimental for neurogenesis than single acute exposures.[58]

RATIONALE FOR THE ITALIAN HEALTHY CATH LAB STUDY

The overall picture is not completely reassuring and underlines the need to define the occupational cancer and non-cancer risks of accumulated radiation exposure in the cath lab.

The detection of the potentially increased health risks remains difficult through the epidemiological approach. This approach requires one million people followed-up for several decades to detect an extra-incidence of fatal cancer of moderate entity.[59] An alternative strategy to the epidemiological approach, is to detect the potentially increased radiation health risks through 'early warning' signs, which evaluate initial damage through surrogate endpoints which are easy to measure, non-invasive, and are capable of identifying long-term health risks (Figure 2).

The HCL study is focused on the use of surrogate but robust biomarkers for cancer and other disease, according to a recent recommendation of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2008) , asking that 'more attention should be given to other (radiation-induced) non cancer disease entities, and future epidemiological studies should be designed to assess clinical and sub-clinical endpoints as well as biomarkers'.[60]

The HCL research is a case-control study that will include a cohort of 500 highly exposed subjects (interventional cardiologists and nurses and technicians working in the catheterisation lab >3 years) and a 'best match' control group of 500 unexposed subjects (matched for age and gender).

A national survey has been launched by the Italian Society of Interventional Cardiology SICI-GISE in order to investigate all aspects of in-room personnel radiation exposure, including the presence of equipment, the standard safety precautions, the dosimetry methodologies adopted in all national cath laboratories, and all practice performed in working life (e.g. type and number of procedures, use of protective devices). Information on the health status of each participant will be collected through

a structured questionnaire, including questions on all study endpoints as well as on items concerning smoking habits, alcohol intake, drug consumption, medical history including diagnostic radiation exposures, and all other lifestyle and socioeconomic confounding factors.

Furthermore, the project will directly evaluate potential radiation-health risk damage through the systematic use of surrogate markers for subsequent clinically overt disease.

Examples of surrogate endpoints adopted in the present study include chromosome aberrations analysis in circulating peripheral lymphocytes for cancer risk, increased carotid intima-media thickness and telomere shortening for atherosclerosis, low birth weight in offspring and DNA damage in the male germ cell line for reproductive damage, olfactory dysfunction and circulating plasma brain-derived neurotrophin (BDNF) for neurodegenerative conditions (Figure 3). Finally, the evaluation of genetic polymorphism associated with radiation-response will help to identify subjects more vulnerable to radiation-induced health effects.[38]

CONCLUSION

Chronic radiation exposure represents major occupational health concern among interventional physicians. Further data will soon be available from both North American and Italian studies.

The Multispecialty Occupational Health Group (MOHG) is undertaking a cohort mortality study comparing cancer and other serious disease outcomes, including cardiovascular disease and cataracts.

However, epidemiological studies on occupational exposures require hundreds of thousands of workers followed-up for decades to detect a small increase in risk. Individual variability and poorly understood adaptive mechanisms may further weaken the link between physical dose and observed damage. HCL study will use surrogate but robust biomarkers for health risk in order to better define the fundamental biochemical, cellular and molecular mechanisms involved at chronic low-dose exposure.

The expected project output will be the development of potential biomarkers for a more effective radioprotection program. Such biomarkers may be useful to identify a subset of individuals more vulnerable to radiation damage, which might represent the target of preventive measurements (by radiation sparing policy or attempts to pharmacologic or dietary radioprotection). Finally, the project is expected to have a more profound impact on the growth of the suboptimal culture of safety among invasive cardiologists, contributing to eradicate the 'radiological machismo' which profoundly contributes to disseminating useless doses (and risks) in the catheterisation lab.[30]

	Diagnostic procedure	Average effective, mSv dose (range)	Equivalent number of chest x-rays
ADULT	Diagnostic invasive coronary angiogram	7 (2-16)	350 (100-800)
	Percutaneous coronary intervention	15 (7-57)	750 (350-2850)
	Dilation chronic coronary occlusion	81 (17-194)	4050 (850-9600)
	Aortic valvuloplasty	39	1950
	Head and/or neck angiography	5 (1-20)	250 (50-1000)
	Thoracic angiography of pulmonary artery or aorta	5 (4-9)	250 (200-450)
	Abdominal angiography or aortography	12 (4-48)	600 (200-2400)
	Endovascular thoraco-abdominal aneurysm repair procedure	76-119	3880-5950
	Pelvic vein embolisation	60 (44-78)	3000 (2200-3900)
PEDIATRIC*	Diagnostic cardiac cath	6.0 (0.6-23.2)	Age-dependent
	ASD	2.8 (1.8-7.4)	Age-dependent
	Patent ductus arterovenous occlusion	7.6 (2.1-37)	Age-dependent
	Balloon dilation	8.1 (2.9-2.0)	Age-dependent

Table 1. Typical effective doses from cath procedure exposure.
mSv = DAP x 0.183 *In pediatric catheterisation, the conversion factor is higher and very dependent on the patient's age: mSv = DAP x 3.7 for newborns; 1.9 for 1 year; 1.0 for 5 years; 0.6 for 10 years; 0.4 for 15 years.

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THE WOEST STUDY: IS NOW THE TIME TO UPDATE THE RECOMMENDATIONS REGARDING THE ANTITHROMBOTIC THERAPY IN PATIENTS WITH INDICATION FOR ORAL ANTICOAGULATION UNDERGOING CORONARY STENT IMPLANTATION?

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ABSTRACT

Triple therapy (TT) of warfarin, aspirin, and clopidogrel is currently recommended as the antithrombotic therapy for patients with an indication for oral anticoagulation (OAC) undergoing percutaneous coronary intervention (PCI) with stent implantation (PCI). While appearing to be the most effective regimen in preventing the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis, TT is however associated with an increased incidence of bleeding. In the recent 'What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing' (WOEST) study, dual therapy (DT) with warfarin and clopidogrel has been shown to be significantly safer than TT on the occurrence of total bleeding, with no decrease in efficacy, as the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis was also significantly lower. Owing to the limited effect of DT on the occurrence of clinically major bleeding, as well as to the large undersizing of the WOEST study for a reliable evaluation of the effect on adverse cardiac events, and especially stent thrombosis, the results of the WOEST study should not yet prompt the substitution of TT for DT as the antithrombotic regimen for patients with an indication for OAC who are submitted to PCI.

Keywords: Percutaneous coronary intervention, stent, warfarin, oral anticoagulation.

INTRODUCTION

Triple therapy (TT) of warfarin, aspirin, and clopidogrel is currently recommended in patients with an indication for oral anticoagulation (OAC), because of atrial fibrillation, venous thromboembolism, and mechanical heart valve, who undergo percutaneous coronary intervention (PCI) with stent implantation.[1-3] While acknowledging that it is generally derived from studies of suboptimal quality (i.e. single-centre, retrospective, and small size), such recommendation is based upon the observation of a general superior efficacy of TT on the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis.[1-3] Such superior efficacy however, is accompanied by lower safety, that is increased incidence of bleeding.[1-3]

Because of the established negative prognostic impact of bleeding in patients with acute coronary syndrome and/or submitted to PCI,[4] the identification of an antithrombotic regimen with a better risk/benefit ratio has long been advocated. The 'What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing' (WOEST) study,[5] where 573 patients with an indication for OAC and submitted to PCI where (open-label) randomised to TT or dual antithrombotic therapy of warfarin and clopidogrel (DT), appears to have achieved such result. At

12-month follow-up in fact, the safety of DT has been significantly higher than TT (64% relative reduction of the incidence of total bleeding), in the absence of any decrease in efficacy, which in contrast was also significantly superior in the DT compared to the TT group (40% relative reduction of the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis).[5]

From the results of the WOEST study[5] an important and urgent question arises: is it possible and indicated today, to recommend DT instead of TT as antithrombotic regimen in patients with indication for OAC undergoing PCI?

CONSIDERATIONS ON SAFETY

Primary End-Point

While, on the one hand, the higher safety of DT compared to TT cannot be ignored, on the other hand it should not be overlooked that the difference between the two groups is mostly driven by a decrease in the incidence of the bleeding events of less clinical importance (that is, either Thrombolysis in Myocardial Infarction (TIMI) minimal and minor, Global Utilisation of Streptokinase and Tissue Plaminogen Activator for Occluded Coronary Arteries (GUSTO) mild and moderate, and BARC 1, 2 and 3a), in the absence of significant differences in the incidence of bleeding of higher clinical relevance (that is, TIMI major, GUSTO severe, and BARC 3b and 3c) (Table 1). And even if the former may have a negative prognostic impact (though generally indirect, and due to an increase in ischemic events related to the withdrawal of antithrombotic therapies in response to bleeding), it is the latter to impact more and directly on the patient prognosis, owing to the location (e.g. intracranial, intra-ocular, intra-pericardial) and/or the associated hemodynamic impairment (e.g. shock, hypotension with associated ischemia).[4] The lower incidence of GUSTO moderate (statistically significant) and BARC 3a (of borderline statistical significance) bleeding observed in the DT group in turn, may be largely dependent on the significantly lower rate of blood transfusions (61% reduction),[5] as they represent a classification criterion for those types of bleeding (Table 1). Despite the existence of recommendations aiming to standardise the use of blood transfusions,[6] the wide variability and complexity of the individual clinical contexts (e.g. comorbidities, haemodynamic impairment) may make the use of blood transfusions extremely inhomogeneous,[7] at the point to question the actual validity of blood transfusions rate as an end-point in clinical trials.

With regards to the course of the Kaplan-Meier curves relative to the incidence of total bleeding, it is of note that they diverge immediately, continue to diverge during the first 30 days, and then proceed almost parallel up to the end of follow-up.[5] Such behaviour suggests that the lower safety of TT is less

Not significant:	TIMI major	Intracranial; decrease of haemoglobin ≥5 g/dl or haematocrit ≥15%
	GUSTO severe	Intracranial; leading to haemodynamic compromise
	BARC 3c	Intracranial; intra-ocular with vision impairment
	BARC 3b	Decrease of haemoglobin ≥5 g/dl; cardiac tamponade; requiring surgical intervention or inotropic support
	BARC 3a*	Decrease of haemoglobin 3-5 g/dl; causing blood transfusion
Significant:	TIMI minimal	Decrease of haemoglobin <3 g/dl or haematocrit <9%
	TIMI minor	Decrease of haemoglobin ≥3 g/dl or haematocrit ≥10%; decrease of haemoglobin ≥4 g/dl or haematocrit ≥12% with no overt bleeding
	GUSTO moderate	Causing blood transfusion without haemodynamic compromise
	GUSTO mild	Not satisfying moderate or severe criteria
	BARC 2	Requiring non-surgical medical intervention; leading to hospitalisation or increased level of care; prompting evaluation
	BARC 1	Not actionable and not requiring unscheduled studies, hospitalisation or treatment

* p=0.054 DT = double therapy; TT = triple therapy; TIMI = Thrombolysis In Myocardial Infarction; GUSTO = Global Utilisation of Streptokinase and Tissue Plaminogen Activator for Occluded Coronary Arteries; BARC = Bleeding Academic Research Consortium.

Table 1. Differences in the incidence of bleeding in DT and TT groups (primary end-point).

attributable to a prolonged exposure to such regimen, and more dependent on early variables (e.g. peri-PCI). Indeed, the limited use of the radial approach (about 25%), as well as of the continuation of OAC throughout PCI (about 40%), albeit not different in the two groups,[5] may have contributed to the higher incidence of bleeding in the group receiving a more aggressive antithrombotic treatment, TT. In OAC patients undergoing PCI, the femoral approach and the periprocedural interruption of OAC have been associated with an increased incidence of major bleeding and access site complications.[8] In the TT group of the WOEST study,[5] a relevant proportion (i.e. 7%) of higher clinically relevant bleeding occurred at the vascular access site.[5]

It is finally of note that the incidence of total bleeding (primary safety end-point) was three to four-fold higher than both reported in the literature[9,10] and planned at the time of sizing the study (44.4% vs. 12% in the TT group, and 19.4% vs. 5% in the DT group).[5] While, on the one hand, being in contrast with the exclusion from the enrolment of those patients at highest bleeding risk, such as those with previous intracranial bleeding and TIMI major bleeding during the previous 12 months,[5] on the other hand the explanation given by the authors, that is the tracking of all bleeding events (and not only major), and the prolonged use of clopidogrel associated with the preponderant use of drug-eluting stent (in about two-thirds of cases), appears hardly acceptable. In a prospective, observational study enrolling 622 atrial fibrillation patients undergoing PCI with drug-eluting stents in all cases, the 12-month incidence of total bleeding in the TT and DT (comprising however the combination of warfarin with either aspirin or clopidogrel) was approximately 12% and 7%, respectively.[9] Even though it is not possible to determine whether the excessive incidence of bleeding in the WOEST study, and especially in the TT[5] may have impacted on the results, it remains uncertain whether the same outcomes are to be expected also in the real-world populations of daily clinical practice.

CONSIDERATIONS ON EFFICACY

Secondary End-Point

The significant higher efficacy of DT compared to TT on the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis is difficult to interpret. While a reduction, albeit not statistically significant, of the majority of individual components of the combined efficacy end-point is apparent, the global effect appears mostly driven by the reduction (by 61%) in total mortality.[5] In turn, the decrease in total mortality is largely driven by the reduction, however of borderline statistical significance (p=0.069), of non-cardiac mortality, with no significant difference on cardiac mortality.[5] In the absence of a plausible pathophysiological mechanism to explain an effect on non-cardiac mortality of antithrombotic drugs, which acts by preventing adverse vascular events, it cannot be excluded that the results on mortality observed in the WOEST study[5] may only be a play of chance. It should not be overlooked however that the study was not sized to identify differences in the efficacy of DT compared to TT. If it is right, and proper, consider this when trying to interpret the results regarding the secondary efficacy end-point and mortality, even more so when trying to examine the incidence of stent thrombosis. Despite the fact the omission of aspirin in the DT group was not associated with an increase in stent thrombosis (for the prevention of which the pharmacological standard is currently represented by the combination of aspirin and clopidogrel, or another $P2Y_{12}$ receptor inhibitor), the WOEST study[5] does not actually allow any solid conclusion in this regard. The commonly reported yearly incidence of stent thrombosis (about 1-2%)[11] would have requested a much larger population size. This is even more true when considering that the WOEST population was at quite low risk of stent thrombosis, due to the low prevalence (25-30%) as indication for PCI of acute coronary syndrome, which is an established predictor of stent thrombosis.[11]

CONCLUSIONS

Based on the considerations above, it can be concluded that the WOEST study,[5] which must be regarded as the only prospective, randomised study carried out so far on this topic, essentially confirms previous observations of a general higher safety of DT compared to TT.[12] Again in accordance with previous observations,[9,10] the higher safety is largely attributable to a reduced incidence of minor rather than major bleeding. The WOEST study[5] does not provide usable information regarding the efficacy of DT on the incidence of adverse cardiac events, including death, myocardial infarction, re-revascularisation, and especially stent thrombosis. In this regard, it should also not be overlooked that because of the phenomenon of clopidogrel 'resistance' (which may involve up to 30% of patients, and is associated with an increased risk of adverse cardiac events),[13] a relevant proportion

of patients receiving DT may actually be exposed to the action of warfarin only. And the insufficient efficacy of warfarin monotherapy in preventing the adverse cardiac events after PCI has long been demonstrated.[14]

Therefore, as a whole, the results of the WOEST study[5] do not support the general use of DT in place of TT as an antithrombotic treatment for patients with an indication for OAC undergoing PCI. The uncertainty regarding the real efficacy of DT for the prevention of adverse cardiac events, and especially stent thrombosis, also precludes its use in selected patients, such as those at increased haemorrhagic risk.

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IMPORTANCE OF PLAQUE MODIFICATION BEFORE CORONARY ARTERY STENTING

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ABSTRACT

Lately, the importance of plaque modification prior to stent implantation, particularly the use of cutting and scoring balloons, has been a subject of debate. Pre-treatment or plaque modification before stent implantation is an important step to achieve the best possible result and ensure long term safety and efficacy of percutaneous coronary intervention (PCI). The rationale behind plaque modification is that it may minimise arterial injury and subsequent neointimal proliferation and/or restenosis. Artery scoring before stent implantation gives almost perfect stent apposition with reduced inflation pressure and minimised plaque shifting, it also prevents balloon slippage, alters calcification, increases artery compliance and enhances stent deliverability. Appropriate use of scoring balloons for plaque modification with subsequent stent implantation significantly increases acute and post-procedural results of angioplasty. With bioabsorbable stents and bioresorbable vascular scaffolds, plaque modification will be an essential tool to perform complete 'vessel repair procedures'.

Keywords: Angioplasty, cutting balloon, stent.

INTRODUCTION

Understanding the pathophysiology of atherosclerosis and emerging technological innovations in past decades has greatly advanced the treatment possibilities for coronary artery disease patients. Number of coronary angioplasties with stent implantation has grown substantially. Advances in this technique have expanded the indications for the procedure, dramatically improved safety, and reduced the rate of restenosis.[1-4] Nevertheless, stent-related failure leading to repeated revascularisation and life threatening adverse events is the major limitation of long term success of percutaneous coronary interventions (PCI).[5]

The main pitfall of plain old balloon angioplasty (POBA) was acute vessel occlusion due to recoil or dissection following balloon inflation and high rates of restenosis.[6,7] Introduction of bare metal coronary stents (BMS) dramatically reduced POBA-related issues and prevented negative remodeling of arteries.[8,9] However, BMS efficacy was sabotaged by significant proliferative artery response leading to neointimal hyperplasia-driven restenosis.[10] The era of drug-eluting stents (DES) designed to deliver antiproliferative agents preventing neointimal growth began with promising results regarding reduction of in-stent restenosis.[11] Enthusiasm with growing rate of DES implanted over years worldwide was casted away by concerns of DES-related risk of late and very late stent thrombosis owing to delayed endothelialisation and need for long-term dual antiplatelet therapy.[12,13]

Pretreatment of Plaque

To achieve the best possible result and ensure long-term safety and effectiveness of PCI there are three important steps to consider (Figure 1):

- pre-treatment or plaque modification before stent implantation;
- stent implantation;

- post-treatment to achieve full stent expansion and complete stent apposition.

Lately, the importance of pre-treatment and plaque modification prior to stent implantation, particularly the use of cutting and scoring balloons, has been a subject of debate. The rationale behind plaque modification is that it may minimise arterial injury and subsequent neointimal proliferation and/or restenosis. With regular balloon inflation the entire balloon surface contacts the vessel wall disrupting endothelium, non-uniformly compressing plaque and causing arterial wall damage. Scoring balloon produced injury is strictly localised to the scoring sites sparing most of endothelium, compressing plaque, and reducing trauma to the media layer.[14] Artery scoring before stent implantation gives almost perfect stent apposition with reduced inflation pressure even if very long stents are deployed. In bifurcation treatment it minimises plaque shifting between main branch and side branch, thus helping to avoid side branch stenting. Complex coronary lesion interventions in case of aorto-ostial, small vessel and calcified lesions, can benefit from pre-treatment with scoring devices to minimise balloon slippage, alter calcification, increase artery compliance and enhance stent deliverability. With bioabsorbable stents and bioresorbable vascular scaffolds it will be an essential tool to perform complete 'vessel repair procedures'.

CUTTING BALLOON

Cutting balloon (CB) features several atherotomes (microsurgical blades) depending on balloon diameter. The atherotomes are mounted longitudinally on the outer surface of a balloon and, during expansion, deliver longitudinal incisions in the plaque. The atherotomes deliver a controlled fault line during dilatation to ensure that the crack propagation ensues in an orderly fashion.[15] Cutting balloon (CB) increases vessel lumen diameter in a more controlled fashion and lower balloon inflation pressure is needed thus decreasing the risk of a neoproliferative response and restenosis (Figure 2).

The Cutting Balloon Global Randomised Trial was one of the first large multicentre studies to evaluate the effectiveness of cutting balloon angioplasty in the setting of simple coronary lesions.[16] Only de novo type A or B1 lesions in native coronary arteries, up to 20 mm in length and 2.0 – 4.0 mm in diameter, were eligible. A total of 1,238 patients were enrolled in the study and randomly assigned to treatment with a single cutting balloon inflation (n=617), with

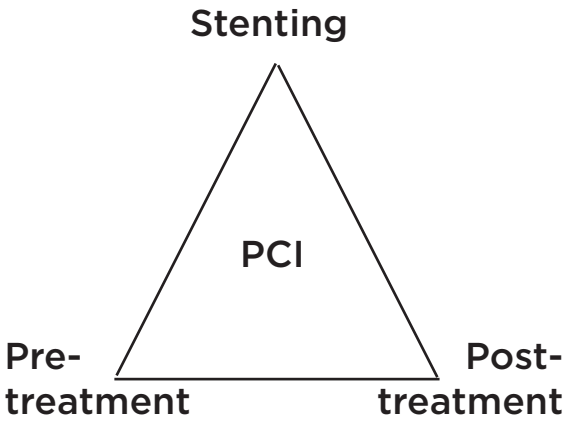

Figure 1. 'Trinity of PCI.

a balloon–artery ratio of 1.1:1 or POBA (n=621). The surgical dilatation using cutting balloon showed no reduction of binary angiographic restenosis rate at 6 months (31.4% for CB and 30.4% for percutaneous transluminal coronary angioplasty (PTCA); p = 0.75). The secondary endpoints of target lesion revascularisation (TLR) and major adverse cardiac events (MACE) after 9 months were also not statistically significantly, although freedom from target vessel revascularisation (TVR) was slightly higher in the CB arm (88.5% vs 84.6%, log-rank p=0.04). The trial showed that CB angioplasty alone was equivalent in safety and efficacy endpoints to POBA, but did not prove superiority. From perspective of plaque modification prior to stent implantation the results of this trial have no considerable value since no stenting was done after treatment with balloon.

Small vessel disease is of particular interest since the advantage of stenting with BMS over balloon angioplasty is moderate and only provisional stenting may be recommended to avoid repeated revascularisations and MACE.[17] The treatment with DES, compared to the BMS, is associated with a significant reduction of angiographic and clinical events.[18,19] However, the small coronary vessel remains an independent predictor of angiographic restenosis even in the DES era and possibly technically challenging due to stent deliverability issues. In a retrospective study of Iijima et al.[20] a total of 327 lesions of small coronaries (less than 2.5 mm in diameter) were treated either by CB (n=87), POBA (n=130) or BMS implantation (n=110). At angiographic follow-up, CB angioplasty resulted in less restenosis comparing to the plain balloon or stenting subgroups (31%, 46.5% and 43.9% respectively; p=0.048). MACE (death, myocardial

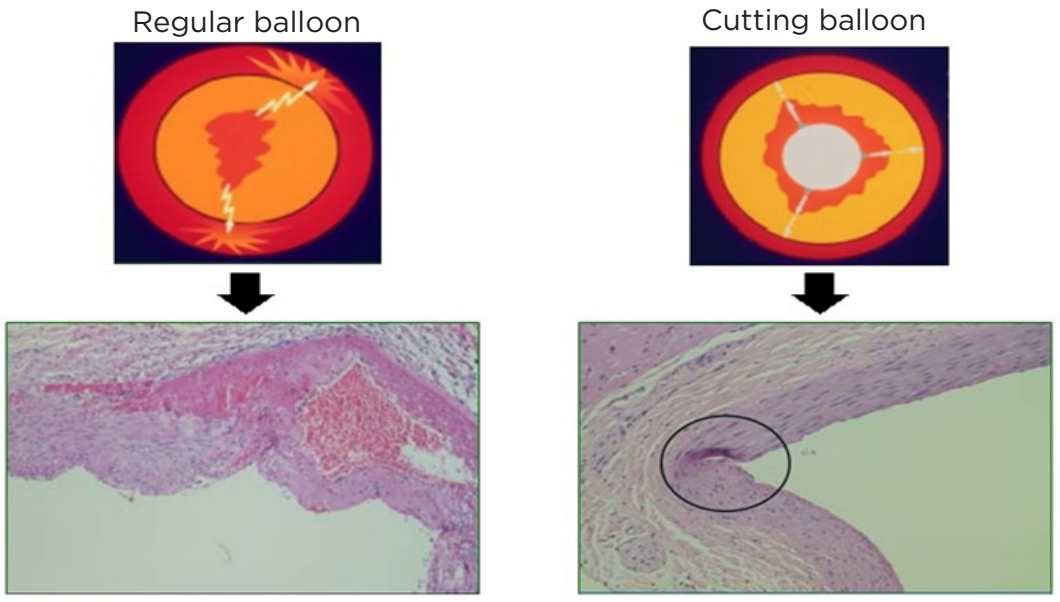

Figure 2. Regular balloon and cutting balloon: mechanisms of action.

infarction, and target lesion revascularisation) rates at follow-up were significantly lower in the CB angioplasty compared to other groups (CB, 20.3%; POBA, 37.3%; stent, 33.3%; p=0.036).

Efficacy of plaque modification prior to bare stent implantation was shown in Restenosis Reduction by Cutting Balloon Evaluation III (REDUCE III) Japanese prospective, randomised multicentre trial.[21] The hypothesis was that cutting balloon angioplasty (CBA) prior to bare-metal stent (BMS) implantation would assist in achieving full stent expansion with safety and improve accommodation of reactive intimal hyperplasia, thereby producing a favourable long-term outcome. The study enrolled 521 patients who were randomised to CBA before BMS (CBA-BMS; n=260) and to balloon-angioplasty (BA) before BMS (BA-BMS; n=261). The primary endpoint was angiographic restenosis (≥50% diameter stenosis at follow-up by quantitative coronary angiography (QCA)) and subsequent target lesion revascularisation (TLR) at 7 month follow-up. Intravascular ultrasound (IVUS) guided procedures were performed in 279 (54%) patients. Although balloon size prior to stenting was similar between the two groups, the inflated pressure was significantly lower with CBA than BA. Post procedural % diameter stenosis (%DS) was less in CBA-BMS than BA-BMS (14.0±5.9% vs 16.3±6.8%, p<0.01). %DS-follow-up was subsequently less in CBA-BMS than BA-BMS (32.4±15.1% vs 35.4±15.3%, p<0.05) associated with lower rates of restenosis in CBA-BMS than BA-BMS (11.8% vs 19.6%, p<0.05) and less TLR in CBA-BMS than BA-BMS (9.6% vs 15.3%, p<0.05). Patients were divided into four groups based on the device used before stenting and IVUS use (IVUS-CBA-BMS: 137 patients; Angio-CBA-BMS: 123; IVUS-BA-BMS: 142; and Angio-BA-BMS: 119). At follow-up, IVUS-CBA-BMS had a significantly lower restenosis rate (6.6%) than Angio-CBA-BMS (17.9%), IVUS-BA-BMS (19.8%) and Angio-BA-BMS (18.2%, p<0.05). In addition, multivariate analyses indicated that the use of BA (but not of CBA) was an independent predictor for stent restenosis at follow-up. The results of this study strongly suggested that use of appropriate plaque modification and IVUS guidance during intervention significantly increases acute and post-procedural result of angioplasty.

The restenosis rates obtained with IVUS guidance and use of CBA in REDUCE III study were comparable to those achieved with DES.[21] To examine whether IVUS-guided CBA with BMS could convey similar restenosis rates to DES, a quantitative coronary angiography-matched comparison was done between an IVUS-guided CBA-BMS strategy of

REDUCE III study and DES strategy of the Rapamycin-Eluting Stent Evaluation At Rotterdam Cardiology Hospital (RESEARCH) study patient populations. QCA-matched comparison resulted in 120-paired lesions. While acute gain was significantly greater in IVUS-CBA-BMS than DES (1.65±0.41 mm vs. 1.28±0.57 mm, p=0.001), late loss, not surprisingly, was significantly less with DES than with IVUS-CBA-BMS (0.03±0.42 mm vs. 0.80±0.47 mm, p=0.001). However, no difference was found in restenosis rates (IVUS-CBA-BMS: 6.6% vs. DES: 5.0%, p=0.582) and TVR (6.6% and 6.6%, respectively).[22]

Percutaneous coronary interventions (PCI) with DES implantation are used to treat high risk lesions and clinical conditions including bifurcation lesions, long lesions, calcified lesions, left main disease, diabetes, and multivessel disease. The risk of suboptimal stent deployment: stent underexpansion, incomplete stent apposition and incomplete lesion coverage increases are strong IVUS predictors of stent restenosis and stent thrombosis.[23,24] For such interventions, IVUS guidance is required and plaque modification prior to DES implantation has a pivotal role. Different pre dilatation strategies have yet to be established in the DES population.

ANGIOSCULPT

AngioSculpt scoring balloon featuring new flexible nitinol helical scoring elements, was evaluated in IVUS guided study conducted by de Ribamar Costa et al.[25] 224 consecutive patients with 299 *de novo* lesions treated with one DES in a non-randomised fashion were assigned to direct stenting without pre-dilatation (n=145); conventional semi-compliant balloon (n=117) or pre-dilatation with AngioSculpt scoring balloon (n=37). The primary goal was to assess stent expansion defined as the ratio of IVUS-measured minimum stent diameter (MSD) and area (MSA) to the predicted stent diameter (PSD) and area (PSA). Patients pre-treated with AngioSculpt had significantly better stent expansion, reaching 88%±18% of the predicted final stent area (p<0.001). No significant difference was found between patients pre-treated with the conventional semi-compliant balloon and those with direct stent deployment (76%±13% vs 76%±10%, p=0.8). Only 0.6% of direct-stent patients and 5% stents placed after conventional pre-dilatation achieved PSD as opposed to 18.9% of stents pre-treated with ASC (p<0.001). The MSA/PSA and MSD/PSD ratios were larger with ASC pre-dilatation; and a greater percentage of stents had a final MSA >5.0 mm^2. The main conclusion of this study is that DES are commonly underexpanded and fail to achieve even minimum standards of stent expansion that may lead to DES related adverse events. Notably, conventional balloon pre-dilatation does not improve the final stent expansion compared to direct stenting.[25]

PLAQUE MODIFICATION FOR TREATMENT OF BIFURCATION LESIONS

The issue of restenosis in complex anatomies such as bifurcated coronary lesions remains unclear. In our opinion, plaque debulking with directional coronary atherectomy or modification with a scoring device before stent deployment could minimise arterial injury and subsequent neointimal proliferation, and could prevent restenosis formation. We believe that plaque modification with a scoring device or directional coronary atherectomy before stenting minimises plaque shifting between the main branch and side branch and thus could help to avoid sidebranch stenting as well as giving better stent apposition with reduced inflation pressure, even if very long stents are deployed.

Tsuchikane et al.[26] reported registry data of 99 patients with bifurcation lesions, who received directional coronary atherectomy before stenting. Simple stenting was achieved in 97 patients. The 9 month binary restenosis rates in the main branch and side branch were 1.1 and 3.4%, respectively. TLR was performed only in two patients.

We performed a single-centre substudy (Nordic I, II + Riga bifurcation registry) with the purpose of demonstrating the safety and efficacy of plaque modification with a scoring device prior to main-vessel stenting and/or side-branch treatment in

MACE	CB (n=209)	Non-CB (n=347)	p value
Death, n (%)	7 (3.3)	10 (2.9)	0.802
MI, n (%)	7 (3.3)	9 (2.6)	0.609
Non-Q-wave MI, n (%)	6 (12.0)	4 (8.0)	0.518
ST, n (%)	5 (2.4)	10 (2.6)	0.999
TLR, n (%)	11 (5.3)	38 (11.0)	0.021
TVR, n (%)	17 (8.1)	48 (13.8)	0.056

Table 1. Nordic I, II + Riga bifurcation registry cutting balloon substudy: 8 months outcomes.

bifurcation lesions.[27] We compared CB (n=209) versus non-cutting balloon (n=347) interventions in bifurcation lesions. Primary end points were cardiac death, myocardial infarction, stent thrombosis, TLR and TVR after 8 months. Our results showed (Table 1) that TLR was lower in the CB group (5.3%; n=11) compared with the non-cutting balloon group (11.0%; n=38; p=0.021).

These results are very promising and we believe that plaque debulking before stenting, especially in complex bifurcated lesions, can avoid the need for complex stenting and may provide a good long-term outcome in patients within the first year.[26,27]

CONCLUSION

Plaque modification prior to stent implantation using cutting and scoring balloons is an essential tool to achieve the best possible result and ensure long-term safety and efficacy of PCI.

Appropriate of use-scoring balloons for plaque modification with subsequent stent implantation significantly increases acute and post-procedural results of angioplasty. IVUS guidance for intervention with lesion pre-treatment and BMS implantation can significantly lower rates of restenosis and TLV achieving results comparable to those with DES. Lesion modification with scoring balloon prior to DES implantation facilitates stent expansion that may provide better long term vessel patency and eliminate late DES related adverse events. In bifurcation lesion intervention, prior plaque debulking can avoid the need for complex stenting and may provide a good long-term outcome. With bioabsorbable stents and bioresorbable vascular scaffolds plaque modification will be an essential tool to perform complete 'vessel repair procedures'.

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RETROGRADE APPROACH FOR CHRONIC TOTAL OCCLUSIONS: THE IMPORTANCE OF EXPERIENCE AND PROCTORSHIP

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ABSTRACT

Recanalisation of chronic total occlusions has remained suboptimal in the field of percutaneous coronary intervention (PCI). Hopes for a better outcome have been raised since its introduction and evolvement of new techniques, including retrograde approach. Along with conventional antegrade approaches this technique led to a success rate of more than 90% in experienced and chronic total occlusion-dedicated centres. This article focuses on contemporary retrograde approach strategy and the importance of experience and proctorship in PCI of coronary chronic total occlusions (CTO).

Keywords: Chronic total occlusion, retrograde approach, coronary angioplasty.

INTRODUCTION

Chronic total occlusions (CTO) are common in contemporary interventional cardiology practice with an incidence of up to 30% of patients with angiographically significant coronary artery disease.1 Antegrade approach success rate in dedicated CTO centres is usually between 65-70%.[2,3] A major improvement in CTO percutaneous coronary interventions (PCI) was the introduction of the retrograde technique, which allows the advancement of a guidewire in a coronary segment distal to occlusion through collateral vessels. The retrograde CTO PCI technique was initially published in 1990 by Kahn and Harzler,[4] who performed balloon angioplasty of a left anterior descending coronary artery (LAD) CTO through a saphenous vein graft (SVG). In 1996, Silvestri et al.[5] described retrograde stenting of the left main stem through a SVG, whereas the first attempt of retrograde PCI through septal and epicardial collateral was described in 2006.[6] Widespread use of retrograde approach for CTO recanalisation in the last few years reached a high success rate of approximately 80% to nearly 100%, in experienced centres.[7]

It has been shown that CTO recanalisation improves angina status, left ventricular function, survival, and reduces the risk of ventricular arrhythmias.[8,9] In particular, meta-analysis reported by Joyal et al.[8] demonstrates that during a 6-year follow-up, patients in whom CTO PCI was successful had significant reduction in recurrent angina compared to patients with an unsuccessful procedure.

Although several studies have shown an improved survival rate in patients with PCI of CTO,[8] the overall benefit of recanalisation of CTO is still limited by the deficiency of randomised controlled trials comparing CTO PCI with medical therapy, or with coronary artery bypass graft surgery. However, two randomised trials are currently ongoing. The first is the Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion

(DECISION-CTO), evaluating whether, compared to optimal medical therapy, CTO PCI will reduce the composite endpoint of all-cause death, myocardial infarction, stroke, and any revascularisation 3 years after randomisation. The second is the European Study on the Utilization of Revascularization versus Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions (EURO-CTO) trial, which has a primary endpoint of death or non-fatal myocardial infarction during a follow-up of to 36 months.[10]

ACCESS ROUTE AND TECHNICAL SET-UP

Bilateral arterial access is mandatory for CTO recanalisation attempt. Both femoral and radial access have been shown to be effective.[11,12] A combination of radial and femoral access is very attractive and is most frequently performed in order to reduce bleeding complications. Adequate heparinisation is necessary, particularly to prevent the potentially lethal complication of thrombosis of donor vessels. For this reason, it is recommended to check the activated clotting time (ACT) every 30 minutes during the procedure and maintain ACT in range of more than 300 seconds.[12] An advantage of heparin is the reversibility of its effect in case of complications (i.e. perforation), in contrast to bivaluridin and GP IIb/IIIa inhibitors where usage is not advisable in CTO PCI, and may lead to delayed pericardial effusion and tamponade even in minor perforations.

With regard to the technical set-up of the procedure, passive support with coaxial alignment or ability to actively introduce the guiding catheter (over the guidewire and the balloon) into the coronary artery for active support is essential. All retrograde techniques require excellent guiding support, and for the retrograde limb, the use of short guide catheters (90 cm guide catheters) is highly recommended to facilitate wire externalisation.

CROSSING COLLATERALS AND RETROGRADE TECHNIQUES

Before starting the procedure, angiographic analysis of collateral channels (CC) is crucial. Assessment of CC is based on the Werner's classification: CC0=no continuous connection between donor and recipient artery; CC1=continuous, thread-like connection; and CC2=continuous, small side branch-like size of the collateral throughout its course.[13] There are two types of CC: septal and epicardial. Retrograde wiring of a septal collateral is preferred over wiring of an epicardial collateral, because septal collaterals are usually not very tortuous and have multiple branches.[14] The major limitation to septal wire advancement is a severe tortuosity, not the size of the collaterals. With increasing experience and performance, we have learned that a straight, faintly visible or even invisible septal CC can often be crossed.[15] It is easier to advance a wire through septal collaterals from the LAD to RCA in comparison to the opposite situation, because of the frequent tortuosity at the RCA end of the septal collaterals.[16] In contrast to septal CC, the leading prerequisite for epicardial CC crossing is the adequate size, but not the extent of tortuosity. With Corsair Microcatheter, tortuosity of epicardial CC, usually longer than septal, is not a limitation.[15] Epicardial CC should be used only if no septal CC are suitable. This approach comes from the fact that epicardial rupture is a more serious complication than septal rupture, and that the epicardial use is more often associated with procedural ischemia.15 Two techniques of septal collaterals crossing are commonly used: the first, 'septal surfing' technique where septals are crossed in a blind fashion without contrast guidance, and the second, in which the collateral continuity assessment was performed with tip contrast injection via a microcatheter.[17] Dedicated hydrophilic-coated polymer jacket floppy wires with small distal tip loads as Sion (Asahi Intec) and Fielder FC/XT (Asahi Intecc), and <1 mm, 30–45 degree bend at its distal tip, are workhorse wires for collateral crossing. For epicardial collaterals, the Sion guidewire (Asahi Intecc) allowed high success and low perforation rates.14 Collateral crossing is facilitated with microcatheter support. Currently, the microcatheter of choice is the Corsair catheter (Asahi Intecc) – an over-the-wire hydrophilic catheter composed of eight thin wires – which provides exceptional CC tracking and crossing as well as retrograde guidewire control.[14]

After successful collateral wiring there are three options for crossing the occlusion: 1) retrograde true lumen puncture, 2) antegrade crossing using the 'just marker' or ''kissing wire'' technique; and 3) various dissection techniques.[14]

Retrograde True Lumen Puncture

The same hydrophilic wire used to cross the collateral is advanced to the lesion, supported with a microcatheter or over-the-wire (OTW) balloon and CTO is crossed retrogradely. In some cases, this wire must be replaced with a tapered tip or stiffer CTO-dedicated guidewire, such as Miracle series, UltimateBross or Confianaza Pro series

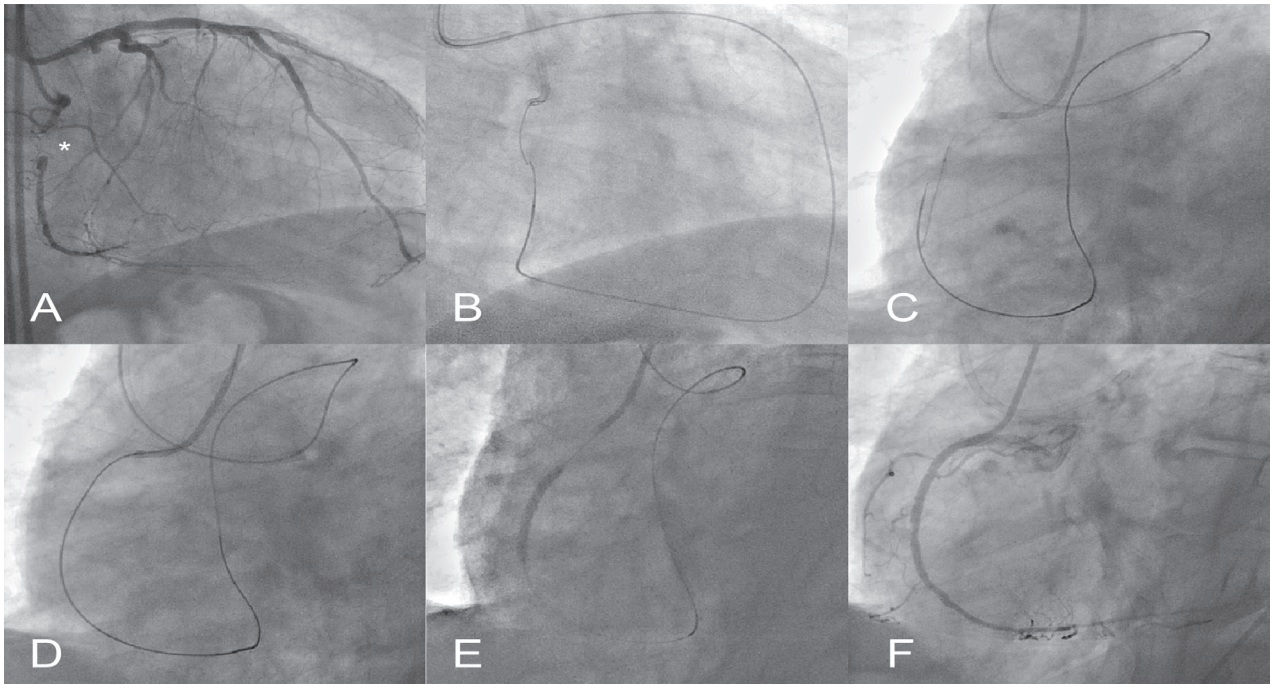

Figure 1. An example of the reverse-CART technique, in patients with two failed previous attempts of antegrade recanalisation with parallel wire technique.
Panel A: Simultaneous dye injection reveals occlusion of the right coronary artery well collateralised via septal collaterals from left anterior descending artery;
Panel B: Retrograde wire (Fielder FC) easily reached the distal cup supported by Corsair microcatheter. Different retrograde wires (including Cofianza Pro 12) could not negotiate proximal true lumen. Tips of the antegrade and retrograde wires meet at the proximal cap of the occlusion;
Panel C: Inflation of the balloon (Mini Track 2.0 x 20 mm) introduced over the antegrade wire in order to 'break' proximal cap of the occlusion;
Panel D: Retrograde wire (Confianza 12 Pro) enters the true lumen and antegrade guiding catheter, followed by Corsair. Retrograde wire is removed and replaced with 300 cm long wire which is externalised;
Panel E: Corsair is withdrawn at the level of septal collaterals, which allowed lesion predilatation and stent implantation using externalised guide wire;
Panel F: Final result.

(Asahi Intec). Retrograde wire crossing to proximal true lumen can be facilitated with antegrade intravascular ultrasonography (IVUS).[18] This is a fundamental retrograde technique with success rate of approximately 40%,[19] based on the fact that the distal cap of occlusion may be softer, with less calcification than the proximal cap. After crossing with a retrograde guidewire occlusion site into the proximal true lumen, a microcatheter is advanced over the retrograde guidewire into the antegrade-guiding catheter. This enables externalisation of the retrograde-dedicated wire (RG3, Asahi Intecc) through the antegrade-guiding catheter, followed by routine antegrade angioplasty over the externalised wire. This manoeuvre could be facilitated by the various trapping techniques (trapping wire or trapping retrograde microcatheter). One modification of wire externalisation is the recently published Rendezvous method[20] which allows retrograde and antegrade microcatheter connection within the mild curvature of the antegrade catheter. In the next step, antegrade guidewire is inserted through the bridging connection of the two aligned microcatheters, from antegrade to the retrograde microcatheter, and proceeded beyond the occluded site. When the antegrade guidewire is positioned into the distal portion of the donor vessel, the retrograde guidewire with microcatheter is gently retracted.

Antegrade Crossing

In this technique, the purpose of the retrograde wire is to mark distal true lumen and to assist anterograde wire crossings without contrast injection.[21] On the other hand, the kissing wire implies antegrade and retrograde wire management to the meeting point followed with antegrade wire progression to distal true lumen.[21]

Dissection Techniques

A crucial step forward in CTO procedures and retrograde approach was the development of dissection techniques. In 2005, Katoh presented the Controlled Antegrade and Retrograde Subintimal Tracking (CART)[22] technique establishing the new era of retrograde CTO recanalisation.

The CART technique involves passing the balloon along with the guidewire in the false lumen at the distal CTO site, and the balloon is inflated to create sufficient space in the false lumen. Then the antegrade wire can be introduced into this space, aiming to reach the distal true lumen through the space created by the retrograde balloon.[22] The dedicated microcatheters for collateral crossing decreased the necessity for septal dilatation, allowing the reverse CART technique to become the most utilised in the modern era[23] (Figure 1). The principle is similar to the CART technique, with the difference being that subintimal space is created by the antegrade balloon dilatation, which facilitates crossing the occlusion with the retrograde wire. Intravascular ultrasound guidance in reverse-CART techniques introduced by Japanese authors Ge et al.[24] can also be used with significant reduction in the amount of contrast, procedure time and radiation dosage.

COMPLICATIONS

Thrombosis or dissection of the donor artery, collateral perforation or occlusion, and PCI equipment entrapment are unique and potentially life-threatening complications, related to retrograde CTO PCI. Donor artery injury can be caused during repeated attempts to wire the collateral vessel, especially if the retrograde guidewire is not supported by a microcatheter or OTW balloon during manipulations.[25] Removal and exchange of the microcatheter or wire externalisation could result in a suction of the guide catheter with dissection of the donor artery, followed by global ischemia and haemodynamic deterioration. For this reason, careful manipulation of the guide catheter with constant pressure monitoring is required, as well as avoiding the engagement of extensively diseased donor coronary artery. The second retrograde CTO PCI-specific complication is collateral perforation or occlusion. Although tamponade has been reported after septal perforation,[25] this complication is without serious consequences in most cases. On the contrary, epicardial collateral perforation could lead to rapid tamponade, requiring urgent pericardiocentesis. Entrapment of the PCI equipment has usually been described in septal collaterals when septal dilatation was not performed and in attempt for retrograde stent delivery.[26]

IMPORTANCE OF EXPERIENCE AND PROCTORSHIP

According to 2012 EuroCTO club consensus document,[12] all interventional operators should have adequate theoretical knowledge for appropriate patient selection, and the practical experience in order to avoid common CTO PCI mistakes. It is also suggested that more than 300 antegrade procedures and minimal number of 50 CTOs per year, should be done prior to beginning retrograde attempts. Before starting retrograde CTO procedure, operators should gain experience and be proficient in anterograde CTO PCI. Understanding of material, familiar use of specific CTO wires and microcatheters, as well as the knowledge of antegrade techniques is necessary.

Learning curve for the retrograde technique should be a deliberate, stepwise process including operator dedication and persistence, proctoring and continuing medical education.[27] Its steep learning curve and initially low success rates will improve with time, practice and increasing experience.[27] Proctorship and discussion with highly experienced retrograde operators, of each specific case, especially unsuccessful, should be particularly emphasised in this process. Adoption of the retrograde approach in CTO PCI is indisputable, and dependent on enthusiasm, dedication, persistence, and support from local environment and management. On a practical level, careful patient selection and analysis, operator experience, material and specific technique utilised, as well as the management of complications, are true predictors of the success of the procedure.[27-29] Recently we have demonstrated that adequate training and international proctorship for this complex and demanding technique are a necessity and a prerequisite in achieving high overall success rates, with acceptable complication rates and excellent long-term survival.[17] On-site training, close dialogue with skilled retrograde operators are also associated with improved procedure outcome.[27]

CONCLUSION

The outcome of this approach and strategy is that retrograde approach, with widespread use of novel devices and techniques, has reached success rate of 90-95% in complex CTOs, very close to the success rates of non-occlusive CTO PCI.

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MULTIVARIATE ANALYSIS AND OUTCOMES IN PERCUTANEOUS CORONARY INTERVENTION; FROM STATISTICS TO CATH LAB.

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ABSTRACT

High quality randomised clinical trials (RCTs) and meta-analysis represent the highest levels of evidence, but in everyday clinical practice, observational studies are often exploited as a quick and easy way to understand the performance of clinical and interventional strategies. In this setting, multivariate analyses are exploited to drive useful and independent information, but due to potentially confounding messages, should be critically appraised and used in everyday clinical practice.

Keywords: Multivariate analysis, PCI, stent.

NETWORK META-ANALYSIS, HEAD-TO-HEAD META-ANALYSIS AND RANDOMISED CLINICAL TRIALS; SHOULD OBSERVATIONAL STUDIES BE DISREGARDED?

In recent years patients, physicians and governments have been looking for the most accurate and economically sustainable combination of new drugs, diagnostics and interventional technologies in a rapidly changing economic scenario, pursuing several options in this quest, including comparative effectiveness research.[1]

Actually, from a scientific point of view, a growing bulk of new pharmacological and technological choices have been offered, especially in the cardiovascular field.[2-9] According to widespread opinion, well-conducted randomised controlled trials provide the most valid estimates of the relative efficacy of competing healthcare interventions.[10] A meta-analysis of randomized clinical trials (RCTs) that directly (head-to-head) compares two different interventions or drugs is thus considered the highest quality evidence. However, many interventions and drugs have not been directly compared in RCTs. This may relate to a large number of factors, ranging from the need for important resources,[1] fear of negative results for direct comparisons, and the underreporting of non-significant or negative data.[11] For example, placebo-controlled trials are often enough to obtain the regulatory approval of a new drug, once again limiting any ensuing direct comparisons.

On the other hand, especially in interventional cardiology, a high number of non-randomised studies are still performed in order to save

economical resources,[1] to create hypotheses, especially for non-randomisable patients, or to shed light on the generalisability of results from existing randomised experiments.[11]

In an attempt to exploit the broad potential resources of observational databases, various statistical models are currently employed. Several different multivariable approaches are available to control for systematic baseline differences naturally occurring between groups in the non-randomised setting.[10,12] Even more, their striking importance lies on defining the impact of several independent variables on a single dependent variable, thus avoiding confounding effects coming from observed variables in non-randomised studies.

Nevertheless, multivariable analysis should be performed according to precise statistical issues,[13-18] in order to offer understandable results and to offer a more prevalent impact on everyday practice.

TIPS AND TRICKS TO PERFORMING AND INTERPRETING MULTIVARIATE ANALYSIS

In Theory

The first important step for any researcher performing multivariate analysis, and for those reading articles, is to choose the most accurate model.

This choice should be performed according to a simple selection of parameters,[10] that firstly, have differences or similarities in follow-up and secondly, a number of events for covariates.

One of the most historically exploited models is represented by binary logistic regression, which evaluates the independent predictive role of one or more independent variables of interest. Actually, to appraise the logit of the probability of an event (dependent variable) given one or more dependent variables, event probabilities are appraised as a function in order to appraise. This model performs accurately, especially for studies with a similar follow-up, not adjusting for time-variation, and independently from number of events for covariate.

On the contrary, Cox proportional hazard analysis[20] also adjusts for differences in follow-up duration and censored data, by assessing the relationship of explanatory variables to survival time controlling for covariates and known confounders.

Last but not least, propensity score[21] which is defined as the conditional probability of receiving an exposure or treatment given a vector of measured covariates. Propensity could be exploited to perform a matching analysis (by obtaining two sample sizes of patients with a similar risk baseline profile) or may be incorporated into Cox multivariate models, and should be exploited for studies with a low ratio of events per covariate. For both of these models, some similar points should be accurately assessed.

The first choice of variables should be based on prior epidemiological evidence (i.e. an established association from prior well-conducted experimental or clinical studies) and strong associations (e.g. pb0.10 or pb0.05 at bivariate analysis) stemming from the specific dataset of interest.[22,23]

Specifically, for propensity scores both the calibration and possible discrimination of the model should be evaluated. With calibration, the distance between the observed (treatment, yes or no) and the predicted outcome from the model (propensity score) are assessed through the Hosmer–Lemeshow goodness of fit test. On the contrary, with discrimination (through area under-the-curve), authors understand how the predicted probabilities, derived from the model, classify patients into their actual treatment group.

In Practice

In a recent clinical review of our group,[24] we analysed all observational studies comparing bare metal and drug-eluting stents (DES), which demonstrated that independently from any impact factor, a better exploitation and methodological appraisal of multivariable analysis is needed in order to improve the clinical and research impact and reliability of non-randomised studies.

In all studies, a low number of events per variable was a common feature, potentially suggesting overfitted data and misleading associations.[20] Another difficult finding was the lack of reporting and perhaps conducting of internal control, as it was frequently not possible to assess calibration or censoring appraisal.[10] Moreover, any omission of the methodological assessment was not related to the quality rating of the journal in which the paper was published: we found no substantial differences among studies stratified according to the journal of publication's impact factor, thus stressing the need for more careful attention from peer reviewers concerning studies reporting multivariable adjustments.

CLINICAL APPLICATION AND LIMITS OF MULTIVARIATE ANALYSIS

One of the most striking examples of the profound clinical impact of multivariate analysis is represented, among others, by the example of stent thrombosis (ST) and DES, reported by Lagerqvist[25] in 2007 in Nejm. Through an accurate propensity score model, the authors demonstrated the increased risk of ST for DES, data that have never been confirmed in randomised evidence.[26] As a result of the potentially dramatic clinical impact, the work caused a reduction of more than one-third of DES implantation, particularly in North America. This example stresses the crucial point of the limitations of multivariate analysis, even when accurately performed, because they could not account for non-recorded or evaluated features, thus leaving potentially fundamental clinical or interventional properties unanalysed.

In summary, multivariate models, if accurately performed, represent a useful way to analyse observational data, despite the intrinsic limits of their observational nature.

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UPDATE ON DRUG-ELUTING BALLOONS FOR PERCUTANEOUS CORONARY INTERVENTIONS

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ABSTRACT

Restenosis prevention continues to be a challenge to the interventional cardiologist. The introduction of stents has virtually eliminated the problems of elastic recoil, late negative remodelling and scaffolds unpredictable dissections, leaving neointimal hyperplasia as the primary cause of restenosis. Drug-eluting stents (DES), using antiproliferative drugs added to stents, serve to prevent the development of neointima hyperplasia. However, they can be associated with an irregular endothelialisation, requiring prolonged double antiplatelet therapy to reduce the risk of late and very late stent thrombosis. Moreover, incomplete suppression of neointimal hyperplasia at the stent margins or between the struts may limit the efficacy of DES, especially when they are used "off-label" in complex clinical and anatomic settings.

Drug-eluting balloons (DEBs) may represent a therapeutic alternative for the interventional treatment of coronary disease. With the use of this technology, the short-term transfer of antiproliferative drugs to the arterial wall appears feasible, thus potentially reducing the untoward effects of the prolonged drug release associated with polymer-based stent technologies, and avoiding the risk associated with having a permanent metallic cage. In the last few years, research in this field has been increasing, and several trials have already been published or are planned to determine the place in therapy of these devices. The present article will review the available *in vitro*, animal and human evidence regarding these devices at present, and discuss the emerging role and their future perspectives.

Keywords: Drug coated balloon, paclitaxel, in-stent restenosis, paclitaxel eluting balloon.

INTRODUCTION

With the aim to overcome the limitations of drug-eluting stents (DES), a new concept of coronary intervention has been introduced in the recent years: the use of drug-eluting balloons (DEB). Paclitaxel coated-balloon (PCB) angioplasty appeared with the objective to achieve a local and homogeneous high concentration of an antiproliferative agent at the site of endovascular interventions. Advantages of this approach over the use of DES include a more homogeneous drug distribution and the fact that this mode of local delivery does not require foreign material implantation. Moreover, the recently introduced concept of "combined treatment strategy" of bare metal stent followed by DEB has aroused the interest of interventional cardiologists. Therefore the information that has emerged in a short time has been incredible.

This review provides an update on drug-eluting balloons. We analyse in detail the DEB commercially available, including essential data about their physicochemical properties. Moreover, first clinical experiences with DEB in different scenarios are reviewed in detail.

CHARACTERISTICS OF PACLITAXEL-COATED BALLOONS

Since the initial research undertaken by Scheller et al.,[4] several companies started commercialising

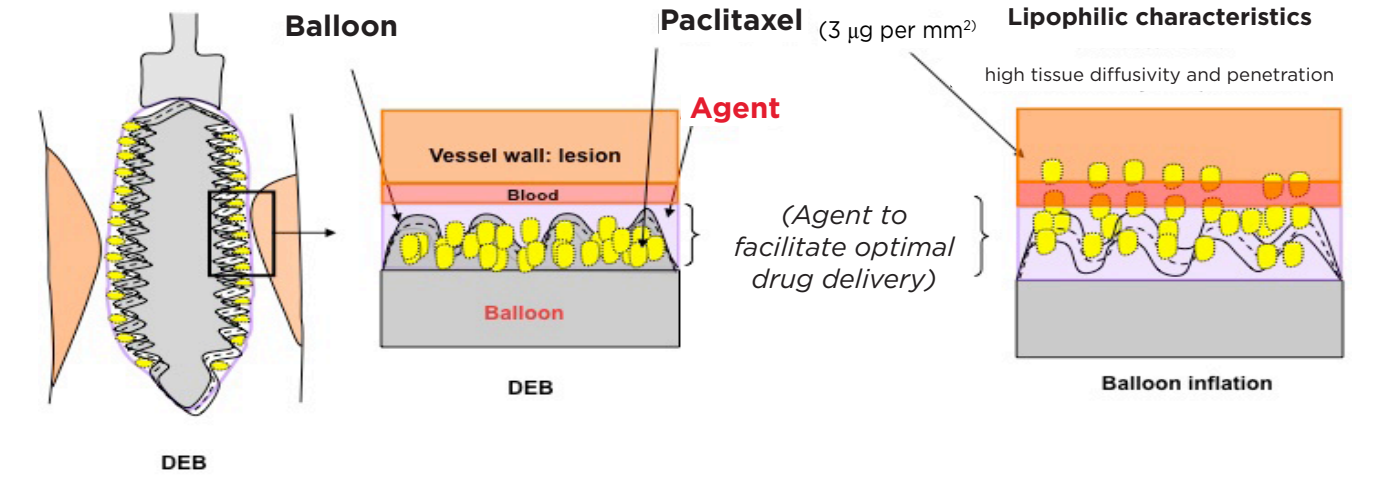

Figure 1. Drug-eluting balloon technology: the three components.

or developing drug-coated balloons (DCB). The best studied DEB, the SeQuent Please (B.Braun, Melsungen, Germany) and the Dior (Eurocor, GmbH, Germany), have given us insight into certain important properties of DCB (Figure 1). It has been proposed that the overall effectiveness of any DCB technology depends on the particular drug formulation and the coating method.[1]

Antiproliferative Agent

Paclitaxel was identified as the primary drug for DEB due to its high lipophilic property and ability to remain in the vessel wall for nearly a week.[2] The action of paclitaxel on vascular smooth muscle cells has been known since 1988. Paclitaxel is characterised by rapid intracellular uptake and irreversible binding to microtubules, inhibiting cell division and migration. The structural intracellular changes caused by paclitaxel explain its long-lasting effects.[3]

Compared with paclitaxel-eluting stents (PES), the concentration of paclitaxel on DEB is about three times higher with 3 µg/mm^2. This specific dose is the same for all DEB and this is based on *in vitro* studies that showed only about 10 to 20% of the paclitaxel is transferred from the balloon surface to the vessel wall.[4] 10% of the dose is lost while the catheter is advanced to the lesion through the haemostatic valve and the guiding catheter and most of the dose (70-80%) released at the target site is washed away in the blood stream during inflation. Thus, PCB delivers a dose to the target site in a very short time that is higher than the total dose released by stents over the course of the weeks. With this immediate drug release, there is no need for a polymer for drug administration, thus avoiding chronic inflammation and late thrombosis with first generation DES.

In the near future the lipophilic nature of the antiproliferative drug zotarolimus makes it a potential candidate for DCB applications. Zotarolimus-coated balloons were found to effectively reduce , proliferation in the porcine coronary overstretch model and showed profound anti-inflammatory effects.[5] Zotarolimus can be effectively formulated onto angioplasty balloons, ensuring delivery of high drug concentrations to the arterial target segments.[5]

Local Vascular Effects

It is well-known that restenosis due to neointimal hyperplasia is a slow process, suggesting the need for prolonged or repeated drug administration. Sustained drug release is considered to be essential for preventing restenosis by local drug delivery.[6] However, the concept of non-stent-based, local paclitaxel delivery was stimulated by the surprising observation that the short period of exposure of paclitaxel through the coronary arteries allows for taxane uptake sufficient to inhibit restenosis. A short incubation time (3 minutes) with paclitaxel almost completely inhibited vascular smooth muscle cell proliferation for up to 12 days.[7] The PCB releases the drug almost entirely in the first 48 hours, however, its biological effect has been discovered to persist for the first 14 days. This is very important because the process of restenosis is seen in the first days after the barotrauma induced by angioplasty, and paclitaxel primarily exerts its effect at that time.[7]

Formulation Used to Coat the Balloon. The Importance of Excipients

Current products range from those with no additive/

Name of PEB	Type of Coating	Formulation	Realease from balloon surface 30/60(s)	Vessel wall paclitaxel concentration & time of inflation	Company	Procedure
Paccocath™	Iopromide	3 µg paclitaxel/mm² balloon surface, admixed iopromide (Ultravist 370™)			Bavaria Medizin Technology	- BMS-ISR (RCT): PEB vs POBA (11)
SeQuent™ Please	Iopromide	3 µg paclitaxel/mm² balloon surface, modified Paccocath™	NA/93%	45-95 µg- 60 s	B. Braun, Melsungen, Germany	- BMS-ISR (RCT): PEB vs PES (14) - DES-ISR (RCT): PEB vs POBA (12, 13). PEB vs PES vs POBA(16) - *De novo* lesions (r) (16, 17)
Cotavance™	Iopromide	3 µg paclitaxel/ mm² balloon surface, modified Paccocath™	NA	NA	MEDRAD Inc, Warrendale, PA	NA
DIOR I	No carrier	Paclitaxel micro-crystals coated onto a 3-fold-microporous balloon surface structure	20/25%	1.5-6 µg – 60 s	Eurocor, GmbH, Germany	BMS/DES-ISR (r) (20) *De novo* lesions (RCT) (30)
DIOR II	Shellac	3 µg paclitaxel/mm² balloon surface, 1:1 mixture of paclitaxel and shellac	75/85%	167 µg – 30 s	Eurocor, GmbH, Germany	BMS/DES-ISR (r) (20, 21) *De novo* lesions (r) (31)
IN-PACT (FALCON)	Urea	FreePac™ paclitaxel-coated balloon catheters (Invatec, S.P.A., Italy)	NA	NA	Medtronic, Inc., Santa Rosa, California	BMS-ISR (r)(23) *De novo* lesions (RCT) (24)
Pantera Lux	Butyry trihexyl citrate (BTHC)	3 µg paclitaxel/ mm² balloon surface, matrix: BTHC	NA	165 µg – 30 s	Biotronik, Berlin, Germany	BMS/DES-ISR (r) (25, 26)
Elutax I	No carrier	2 µg paclitaxel/mm² balloon surface, formulated pure paclitaxel, coated on structured balloon surface	NA	NA	Aachen Resonance GmbH	ISR & *De novo* lesions: RCT: SeQuent™ Please vs Elutax I (8)
Protégé	No additive and very tight binding of the drug to the balloon membrane	Precise Paclitaxel volume administration at the precise location on the balloon surface between the wings prior to folding	NA	NA	Blue Medical, Helmond, the Netherlands	NA
Danubio	n-Butyryl tri-n-hexyl citrate (BTHC)	The SpeedPAX technology : BTHC and paclitaxel	NA	NA	Minvasys, Gennevilliers, France	NA

ISR: In-stent restenosis; NA = not available; s = seconds; µg = microgram; RCT= randomised clinical trial; (r) =registry.

Table 1. Paclitaxel-Eluting Balloons (PEB) commercially available.

carrier and very tight binding of the drug to the balloon membrane to those applied in conjunction with standard contrast agents or other additives. Different types of water-soluble matrix have been introduced by the manufactures, all relying on the same concept that has been firstly developed in the Paccocath DEB (Table 1). According to the initial investigation of comparative DEB performance in humans[8] and porcine model of coronary restenosis,[1,9,10] it seems that the most effective DEB in terms of antiproliferative effect could be related with the final tissue dosage, which depends on the formulation used to coat the balloon. It has been reported (Table 1) that the Pantera Lux DEB (drug concentration 165 μg) was more effective than SeQuent Please DEB (drug concentration 45-95 μg), and Elutax first generation (no data could be found in the literature concerning the delivery dose).[10] Moreover, SeQuent Please was more effective than Dior first generation (paclitaxel concentration 1.5-6 μg)[9] and Elutax first generation.[1] Thus, it seems that the highest drug retention in the vessel wall, the most effective DEB. Also it is important to note that evidence of delayed healing was observed in the most effective DEB groups.[10]

PACLITAXEL-ELUTING BALLOONS STUDIED IN CLINICAL TRIALS

The SeQuent Please (or its Predecessor Paccocath) (B. Braun, Melsungen, Germany)

The results of Scheller et al.[4] demonstrated that paclitaxel admixed to a small amount of the hydrophilic X-ray contrast medium, iopromide, emerged as a very effective coating matrix in numerous *in vitro* and *in vivo* experiments. The concentrations of paclitaxel achieved in iopromide-370 are about 20 times higher than in saline or other aqueous media because iopromide greatly enhances the solubility of paclitaxel. Scheller et al.[7] demonstrated that short exposure of the vessel wall to paclitaxel was sufficient to achieve an arterial wall concentration high enough for preventing restenosis. A very ambitious clinical study program investigating this balloon catheter was initiated in 2004; published results show good agreement with the Paccocath™ ISR study.[11] In randomised trials, PCB angioplasty (Paccocath, SeQuent Please) was superior to uncoated balloon angioplasty and PES for treatment of in-stent restenosis (ISR) in bare-metal stent (BMS)[11] and DES.[12,13,14,15] Moreover, for *de novo* lesions, PCB angioplasty resulted in good angiographic and clinical results.[16,17]

The Dior I and II (Eurocor, GmbH, Germany)

Both generations of Dior™ balloons share most general properties: the drug and the dose of paclitaxel, the same balloon designed with three-folds of microporous surface ensuring good contact with paclitaxel, and similar preparative process. However, the coating method was completely different. The first generation Dior balloon had a nanoporous surface containing microcrystals of pure paclitaxel that were then embedded on the vessel wall at the time of balloon inflation.[18] The second generation Dior balloon contains shellac as a paclitaxel carrier. Shellac is an inert substance that has already been approved by the FDA as a food additive. It is mostly composed of aleuritic acid, jalaric acid and shelloic acid. The microporous balloon surface contains a 1:1 mixture of paclitaxel and shellac. A balloon inflation time dependency study in the porcine model of coronary artery overstretch showed almost maximum tissue paclitaxel concentrations after shorter balloon inflation times of 30 seconds and release of 75% of the drug from the balloon surface, which resulted in an up to 100-fold higher drug concentration after 45 minutes when compared with the first generation Dior, and around the same delivery dose of the Sequent Please DEB. Moreover, tissue paclitaxel resulted in much lower concentration 12 hours after balloon inflation, a result comparable with other PCB in previous studies.[19] As it has been demonstrated the type of PCB coating had an impact on clinical results. In real life registries, second generation Dior DEB has shown low target lesion revascularization (TLR) and major adverse cardiac events (MACE) at mid term.[20,21]

In.Pact (Falcon) (Medtronic, Inc., Santa Rosa, California)

Various FreePac™ paclitaxel-coated balloon catheters (Invatec, S.P.A., Italy) have been introduced since early 2009. FreePac™ is a proprietary hydrophilic coating formulation with urea as matrix substance. Urea is a non-toxic, ubiquitous endogenous compound, commonly used in pharmacy and is supposed to enhance the release of paclitaxel during the short time of contact with the vessel wall. A comparison of the FreePac™ coating formulation on a balloon catheter with an uncoated balloon catheter (negative control) and the Paccocath™ coating (positive control) was performed in the coronary overstretch and stent implantation porcine model. In this study, similar mean residual drug content on the used balloons and similar amounts of paclitaxel were transferred to the vessel wall with

the Paccocath™ coating and the FreePac™ coating, 15-25 minutes after stent implantation.[22] The initial data from a registry of this novel paclitaxel urea coated angioplasty balloon in the treatment of coronary BMS in-stent restenosis showed promising results.[23] Moreover a randomised clinical trial with this DEB in small coronary vessels has revealed similar late loss at 6 months late loss compared to PES. Furthermore, DEB and PES were associated with similar rates of angiographic restenosis, MACE, and repeat revascularisation in small vessels.[24]

Pantera Lux (Biotronik, Berlin, Germany)

Pantera Lux™ (Biotronik AG, Germany) uses butyryltrihexyl citrate (BTHC) as a carrier for paclitaxel. BTHC is used in different medical devices and cosmetics and is approved for blood contact in blood bags. Preliminary clinical data have been published recently with promising results for the treatment of BMS restenosis.[25,26]

Elutax™ (Aachen Resonance, Germany)

This DCB uses pure paclitaxel without a matrix, coated on structured balloon surface. This balloon has a drug configuration with a concentration of 2 µg/mm^2 paclitaxel, without any excipient. To date, no data have been published in the literature concerning the delivery dose of this balloon. Comparative assessment of DCB (Pantera Lux, SeQuent Please and Elutax I) in an animal study with porcine model of coronary restenosis showed worse results in terms of antiproliferative effect of Elutax comparing with Pantera Lux and SeQuent Please DCB.[14]

EVIDENCE IN CLINICAL APPLICATIONS

In-Stent Restenosis (Table 2 & 3)

Paclitaxel-eluting balloon (PEB) is emerging as an effective treatment for in-stent restenosis in both BMS and DES.

Intervention Type	Trial Name	Type of comparison	Sample size (n)	Type of DEB	Angiographic and Clinical Outcomes		
					6 mo late loss	TLR	MACE
BMS-ISR		**RCT**					
	PACCOCATH-ISR I (11) & II trials (27)	DEB vs POBA	I (n= 52) I & II (n=108)	Paccocath™	0.03±0.48 vs 0.74±0.86 mm*	6 mo: 0 vs 23%* 5y: 9.3 vs 38.9%*	5y: 27.8 vs 5.3%*
	PEPCAD II (14)	DEB vs PES	n=101	SeQuent™ Please	0.17±0.42 vs 0.38±0.61 mm*	12 mo: 9 vs 22%*	
BMS-ISR		**DEB Registries**					
	Spanish Multicenter Dior registry (20)		n=65	Dior I & II		12 mo: 9.2%	12 mo: 12.3%.
	Valentines I trial (21)		n=168	Dior II		7.5 mo: 5.1%	
	World Wide Registry (16)		n=743	SeQuent™ Please		9 mo: 3.6%	9 mo: 5.3 %
	IN-PACT (FALCON) (23)		n=43	IN-PACT (FALCON)	- In-stent 0.07±0.37mm	6mo restenosis: 4.3%	
	PEPPER trial (26)		n=43	Pantera Lux	0.05±0.28 mm		12 mo: 11.8%

The European Society of Cardiology Guidelines for Percutaneous Coronary Intervention (2010) recommended that DEB should be considered for the treatment of in-stent restenosis after prior bare-metal stent (class 2 IIa, evidence B) (28).

ISR: In-stent restenosis; mo=month; y=year; RCT=randomised clinical trial; (r)=registry; POBA=plain old balloon angioplasty; * p<0.05

Table 2. Paclitaxel-Eluting balloons (PEB) for bare metal in-stent restenosis (BMS-ISR).

Bare metal stent restenosis:

In randomised trials, PCB angioplasty (Paccocath, SeQuent Please) was superior to uncoated balloon angioplasty (POBA) for treatment of ISR in BMS.[11] Similar positive results were found when comparing the SeQuent Please DEB with PES to treat BMS restenosis.[12] Superiority was demonstrated for angiographic and clinical endpoints and for the long term follow-up (Table 2).[27] Moreover, positive results have been reported in a "real, non-selected, population" in registries and for other DCB balloons.[16,20,21,23,26] Thus the European Society of Cardiology Guidelines for Percutaneous Coronary Intervention (2010) recommended that DEB should be considered for the treatment of in-stent restenosis after prior BMS (Class IIa, evidence B).[28]

Drug-eluting stent restenosis:

The optimal management strategy for patients with DES-ISR certainly remains unknown. Clinically, treatment of DES restenosis lesions seems to be associated with higher rates of adverse events and recurrent restenosis.[29] In randomised trials, PCB angioplasty (SeQuent Please) was superior to uncoated balloon angioplasty for treatment of in-stent restenosis (ISR) in DES.[12,13] Futhermore, the recently published ISAR-DESIRE 3 has revealed comparable results of DEB and PES in the treatment of DES restenosis. Both strategies showed to be superior to balloon angioplasty, (Table 3).[15] Despite DES restenosis is associated with adverse outcomes compared to BMS restenosis, four published multicentre and prospective registries using different DCB have reported promising results.[16,20,21,26]

De Novo Lesions (Table 4)

The efficacy of DEB in *de novo* lesions needs to be established. Potentially DEB may be particularly advantageous over DES in the treatment of *de novo* lesions by providing an immediate and homogenous drug uptake, avoiding inflammatory reaction to stent

Intervention Type	Trial Name	Type of comparison	Sample size (n)	Type of DEB	Angiographic and Clinical Outcomes		
					6 mo late loss	TLR	MACE
BMS-ISR		**RCT**					
Sirolimus/ Everolimus/ Paclitaxel ISR	PEPCAD DES (12)	DEB vs POBA	n=110	SeQuent™ Please	0.43±0.61 vs 1.03±0.77 mm*	6 mo: 15.3 vs 36.8%*	6 mo: 16.7% vs 36.8%*
Sirolimus-ISR	Habara S et al. (13)	DEB vs POBA	n=50	SeQuent™ Please	0.18±0.45 vs 0.72±0.55 mm*	6 mo: 4.3% vs 41.7%*	
Limus-ISR	ISAR-DESIRE 3 (15)	DEB vs PES vs POBA	n=137/131 /134	SeQuent™ Please	DEB 0.37±0.59 vs PES 0.34±0.61 mm, p=NA DEB/PES vs POBA 0.70 ± 0.60 mm*.	DEB 22.1 vs PES13.5%* DEB/PES vs POBA 43.5%*	DEB 23.5 vs PES 19.2%* DEB/PES vs POBA 46.3%*
BMS-ISR		**DEB Registries**					
	Spanish Multicenter Dior registry (20)		n=61	Dior I & II		12 mo: 14.8%	12 mo: 21.3%.
	Valentines I trial (21)		n=86	Dior II		7.5 mo: 10.8%	
	World Wide Registry (16)		n=464	SeQuent™ Please		9 mo: 9.6%	9 mo: 11.6%
	PEPPER trial (26)		n=38	Pantera Lux	0.19±0.29 mm		12 mo: 11.8%

ISR: In-stent restenosis; mo=month; y=year; RCT=randomised clinical trial; (r)=registry; POBA=plain old balloon angioplasty; * p<0.05

Table 3. Paclitaxel-Eluting balloons (PEB) for drug-eluting in-stent restenosis (DES-ISR).

Intervention Type	Trial Name	Type of comparison	Sample size (n)	Type of DEB	Angiographic and Clinical Outcomes		
					6 mo late loss	TLR	MACE
Small Vessel				RCT			
MRD= 2.54±0.47 mm	PICOLETO trial (30)	DEB vs PES	n=60	Dior I	Bailout BMS DEB group: 35.7%. ISR: 32.2% vs 10.3%*		35.7 vs 13.8%*
MDR= 2.15±0.2 7mm	The BELLO trial (24)	DEB vs PES	n=182	In-Pact (FALCON)	Bailout BMS DEB group: 20.1%. 0.08±0.38 vs 0.29±0.44mm ISR: 8.9 vs 14.1% p=ns	6mo: 4.4 vs 7.6% p=ns.	7.8 vs 13.2% p=ns
		DEB Registries					
MDR= 1.9±0.34 mm	Spanish Multicenter Dior registry (31)		n=103	Dior II (46%)	Bailout BMS required: 7.5%. 0.34±0.23 mm ISR 19.6%.	12 mo: 2.9%	12 mo: 5.8%
MRD= 2.36±0.18 mm	PEDCAD I (17)		n=118	SeQuent™ Please	Bailout BMS required: 26.9%. 0.28±0.53 mm ISR 18%.	12 mo 11.9%	12 mo: 15.3%
MRD= 2.5±0.4 mm	World Wide Registry (16)		n=390	SeQuent™ Please	Bailout BMS required: 26.9%. 0.28±0.53 mm ISR 18%.	12 mo 11.9%	12 mo: 15.3%
Bifurcated lesion		RCT					
Provisional T stent strategy	Stella et al. (32)	(A) DEB MB & SB & BMS MB vs (B) BMS MB & POBA SB (C) DES MB & POBA SB	n=117	Dior II	(A) MB proximal 0.58±0.65 MB distal 0.41±0.60 / SB 0.19±0.66 (B) MB proximal 0.60±0.65 MB distal 0.49±0.89 / SB 0.21±0.57 (C) MB proximal 0.13±0.45 MB distal 0.16±0.64 /SB 0.11±0.43* ISR: (A) 24.2% (B) 28.6%. (C) 17.5% p=0.45. MACE : (A) 20%. (B) 29.7%. (C) 17.5%. p=0.40.		
		DEB Registries					
Provisional T stent strategy	PEDCAD V (33)	DEB MB & SB BMS MB	n=28	SeQuent™ Please	Bailout BMS require SB: 14.3%. MB 0.38±0.46mm and SB 0.21±0.48mm. ISR: MB 3.8% and SB 7.7%. 2 late stent thrombosis at 6 and 8 mo	9mo TLR MB 3.8%.	
Other		DEB Registries					
	Valentines II (*)		n=103	Dior II	Bailout BMS require: 11.9%	6-9 mo:2.9%	6-9 mo:8.7%

MRD= Mean Reference Diameter; ISR: In-stent restenosis; mo=month; y=year; RCT=randomised clinical trial; (r)=registry; POBA=plain old balloon angioplasty; * p<0.05

(*) Angiographic results of the Dior Drug-coated Balloon fro the novo coronary lesions: Results from the Valentines II trial. Lob JP, Serra A, Malik F, et al. J Am Coll Cardiol Intv. (2013) 6.No2. Page S3.

Table 4. Paclitaxel-Eluting balloons (PEB) for *de novo* lesions.

struts or polymers, and preserving the normal vessel anatomy. DEB also provide a therapeutic option in very small vessels (<2.25 mm), for which DES sizes are not available. However, with this technology, flow limiting dissections and acute recoil may require the additional implantation of stents.

Small vessel disease:

There are few specific studies published in the literature that have assessed the role of DCB in small vessel coronary disease. The PEPCAD I was the first study (single-arm non-randomised trial) evaluating the safety and efficacy of the Sequent Please balloon for the treatment of small vessel disease, and showed good angiographic and clinical results, thus, demonstrating that DEB possibly yields the potential as treatment alternative for these types of lesions.[16] Moreover, this study reported a significantly higher late loss and restenosis rate in lesions treated with a combination of DEB and BMS, especially if geographic mismatch occurred (i.e. stent implanted in an area that was not treated with DEB).[16] Then, two randomised trials have reported different results. The recently published BELLO randomised trial reported that the In.Pact Falcon DEB was noninferior to PES in suppressing neointimal proliferation in small vessels. Furthermore, DEB and PES were associated with similar rates of angiographic restenosis, MACE, and repeat revascularisation.[24]

On the other hand, the PICCOLETO trial failed to demonstrate Dior I DEB equivalence to a PES for the treatment of small vessel disease, both in terms of angiographic and clinical restenosis.[30] It is important to note some procedural limitations of this study as plain balloon predilatation was done only in 25% of cases and bailout stent implantation in the DEB group was 35.6% with the occurrence of so-called "geographical mismatch", which led to restenosis in stented lesion sites that were not adequately pretreated with DEB. Another important fact that could explain the negative result of the PICCOLETO could be that this study was performed with Dior I while the SeQuent Please used in PEPCAD I and the In.Pact Falcon used in the BELLO Trial, probably could be considered superior to the Dior I in terms of tissue dosage (Table 1). The Spanish Dior Registry[31] used 49% Dior-II to treat really small vessel disease in a real-world population. The investigators in the Spanish Multicentre Registry study were particularly careful to use DCB as a delivery drug system, thus lesion predilatation was performed in all cases with a shorter plain balloon than Dior. Bailout stent implantation was only needed in 7.5% of cases, and in these cases investigators were particularly careful to ensure that any needed stent was implanted within the DEB-treated zone. This registry showed similar positive results to other published registries (Table 4).[16,17]

Bifurcated lesions:

To date, two approaches to treat bifurcated lesions with DEB have been described; i) sequential DEB treatment of the bifurcation branches followed by BMS implantation in the MB; ii) simple MV stenting followed by kissing DEB. Few results have been reported with inconsistent data.[32-34] In the first group, The PEPCAD V, a small prospective register, enrolled 38 patients with bifurcation lesions. SeQuent Please DCB, was used to dilate both main and side branch, with BMS deployment in the main branch (MB) by provisional T stent strategy. Only in case of more than 75% residual stenosis in the SB or reduced Thrombolysis in Myocardial Infarction (TIMI) flow, final kissing balloon dilation was performed. At 9-months, the percentage of restenosis was comparable to the historical data of DES treatment.[33] By contrast, the recently published Drug-eluting Balloon in Bifurcations Trial,[32] enrolled 117 patients in a multicentre randomised trial. The study aimed to compare three strategies based on the provisional T-stenting approach, firstly using Dior II DCB in both branches followed by BMS implantation in MB, versus standard BMS implantation versus standard DES implantation. Considering the primary endpoint, the DEB group showed similar late luminal loss as the BMS group, being both inferior to the DES group. No significant differences were found in MACE rate between the three groups (Table 4).

In the second group of strategy type, only one feasibility study of 14 patients reported procedural success of provisional stenting with an open-cell design BMS and final kissing balloon with second-generation DEB. At a mean follow-up of 234±81 days, no MACE was reported.[34] The German consensus group has recommended an approach of sequential regular balloon predilatation of the bifurcation branches, and if there is a good angiographic result, it is to be followed by DEB treatment in the MB and SB. Stent implantation was recommended as a bail-out strategy in case of major dissection or TIMI <III. Moreover if the SB has >75% residual stenosis or TIMI flow is reduced, a final kissing balloon dilatation with conventional balloons was recommended.[35]

Intervention Type	Trial Name	Type of comparison	Sample size (n)	Type of DEB	Angiographic and Clinical Outcomes		
					6 mo late loss	TLR	MACE
Diabetes		RCT					
MRD= 2.87±0.34 mm	(37)	DEB + BMS vs PES	n=84	SeQuent™ Please	0.51±0.61 vs 0.53±0.67 mm, p=ns. 6 mo ISR: 8.7 vs 10.3%, p=ns.		13.3 vs 15.4%, p=ns
CTO		DEB Registries					
	PEDCAD-CTO (38)	DEB + BMS vs PES	n=48	SeQuent™ Please	0.64±0.69 vs 0.43±0.64 mm, p=0.14. 6 mo ISR: 27 vs 20.8%, p=0.44.		14.6 vs 18.8%, p=ns
STEMI		RCT					
	DEB-AMI (39)	(A) BMS vs (B) DEB+BMS vs (C) PES	n=150	Dior II	(A) 0.74±0.57 (B) 0.64±0.56 (C) 0.21±0.32* ISR: (A) 26.2 (B) 28.6 (C) 4.7%*		(A) 23.5 (B) 20.0 (C) 4. 1%

ISR: In-stent restenosis; mo= month; y=year; RCT=randomised clinical trial; (r)=registry; POBA=plain old balloon angioplasty; * p<0.05.

Table 5 . Treatment strategy with Paclitaxel-Eluting balloons (PEB) plus bare metal stent (BMS) for the *de novo* lesions.

Drug-Coated Balloon Angioplasty Plus Bare-Metal Stent (Table 5)

For the *de novo* lesions, sequential application of DCB and not pre-mounted BMS for treatment of *de novo* coronary lesions resulted in efficient inhibition of neointimal hyperplasia. The sequence of application (DCB first vs. BMS first) did not seem to influence the outcome (6 months late loss 0.45±0.57 mm vs. 0.53±0.52 mm, p=0.83), except for better apposition in BMS first (p=0.013).[36]

In patients with diabetes, the treatment strategy with SeQuent Please DCB angioplasty plus BMS revealed similar results compared with PES.[37] In chronic patients, the use of PCBs in combination with BMS was tested in the Paclitaxel-Eluting Percutaneous Transluminal Coronary Angioplasty - Balloon Catheter in Coronary Artery Disease to Treat Chronic Total Occlusions (PEPCAD-CTO) trial. With 48 patients matched to a historical population with paclitaxel-eluting stents, the angiographic late loss, the need for TLR and MACE was similar between the two treatment strategies and there was no stent thrombosis within 12 months follow-up.[38] However, in the DEB-AMI randomised trial, (two-centre, single-blinded, three-arm study) STEMI patients were randomly assigned to group A: BMS; group B: Dior II DCB plus BMS; or group C: DES after successful thrombus aspiration. As is shown in Table 5, DCB followed by BMS implantation failed to show angiographic superiority to BMS only. Angiographic results of DES were superior to both BMS and DEB. Moreover, DEB before implantation induced more uncovered and malapposed stent struts than BMS, but less than after DES.[39] Therefore, what limited data exist to date do not suggest a clear role for this modality in the *de novo* lesions.

CONCLUSIONS

Preclinical and clinical investigation on the DEB performance in humans and in porcine models of coronary restenosis, suggest that efficacy of DEB in terms of antiproliferative effect and better clinical outcomes, relies on the achievement of sufficient bioavailability of paclitaxel at the vessel lesion site. Moreover, the final tissue dosage sufficient to result in successful angiographic results may depend on the formulation used to coat the balloon and on the type of the coronary lesion treated. Since there is no certain class effect, efficacy and safety have to be demonstrated for different types of DEB and in different subset of lesions.

Rigorous preclinical and clinical work is needed to establish safety and efficacy beyond the current stage. It has been demonstrated that to enhance the solubility of the lipophilic paclitaxel, DEB needs the use of a smaller amount of additives. In the second generation of DEB (SeQuent Please, Dior II, In-Pact Falcon and Pantera Lux) different types of water-soluble matrix (iopromide, shellac, BTHC, and urea) have been introduced by the manufacturers, all relying on the same concept that has been firstly developed in the Paccocath DEB. It has been reported for Dior II and Pantera Lux DEB a delivery dose similar to the SeQuent Please DEB. These promising preclinical results need to be better confirmed in clinical trials.

Despite clinical randomised trials and registries, DEB has demonstrated to be superior to uncoated balloon angioplasty and PES for the treatment of in-stent restenosis in BMS and DES. Currently, the treatment of BMS in-stent restenosis is the only guideline-approved indication for DEB use. For the *de novo* lesions the efficacy of DEB seems promising but needs to be established. However, DEB cannot overcome the mechanical limitation of acute recoil and flow-limiting dissections seen after post-balloon angioplasty. Furthermore, it is not clear whether DEB can avoid the late negative remodelling seen with noncoated balloons. The concept of "combined treatment strategy" of BMS followed by DEB has been recently challenged but further validation in appropriately designed trials is needed. Furthermore, the results of the DEB technology need to be compared in randomised trials against the second generation DES. Research in this field is active, and new trials are already planned to determine the place in therapy of these devices.

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PACEMAKER DEPENDENCE AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative for multimorbid patients not suitable for open heart surgery. The vicinity of the conduction system, especially the atrioventricular node and His bundle to the non-coronary and right coronary aortic cusp, predisposes these patients to conduction abnormalities. However, due to the shape of both available transcatheter aortic valves (CoreValve and Edwards SAPIEN valve) these rates are different. To date, there is no clear information about the true rate of atrioventricular block, the significance of left bundle branch block as well as the transient or permanent nature of these conduction disorders. Due to this, the rate of subsequent pacemaker implantation exceeds up to 50%, which itself may be associated with worse clinical outcomes. Thus, there is a need for further data from large-scale series with a glance to the true rate of clinically relevant conduction disorders.

INTRODUCTION

Calcific aortic stenosis is the most frequent expression of valvular heart disease in the Western world. Population-based observational studies have revealed that 1-2% of patients over 65 years have moderate to severe aortic stenosis.[1] Increased valve cusp thickness due to fibrosis and lipid accumulation, but without left ventricular outflow tract obstruction, is known as aortic valve sclerosis (Figure 1). It is a progressive disease that starts with initial changes in the cell biology of the valve leaflets, which develop into atherosclerotic-like lesions and aortic sclerosis, and eventually lead to calcification of the valve, causing left ventricular outflow tract obstruction. Even mild aortic stenosis is associated with adverse outcomes, with a 50% increased risk of cardiovascular death.[2] There are no known therapies that slow disease progression. Thus, current guidelines consider aortic valve replacement as a class I indication for symptomatic patients,[3,4] facing, however, the fact that one-third of patients are considered to have an unacceptably high risk for open surgery.[5] Current treatment options for those patients include medical treatment and percutaneous balloon aortic valvuloplasty, although neither has been shown to reduce long-term mortality of medically treated patients with symptomatic aortic stenosis, with a 1 and 5-year survival rate of 60% and 32% respectively, and only minor short-term benefits were reported after balloon aortic valvuloplasty.[6-8] The search for a less invasive treatment option for patients with severe aortic stenosis was pioneered by Andersen et al.,[9] subsequently, the feasibility

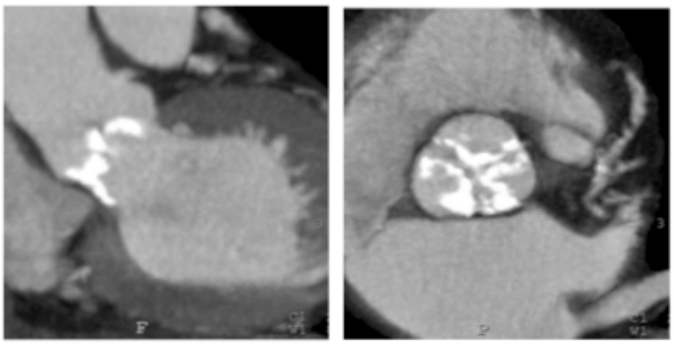

Figure 1. Calcific aortic valve stenosis in long-axis and short axis. The non-coronary cusp calcification extends to subvalvular regions, where the conduction system is located within the triangle of Koch.

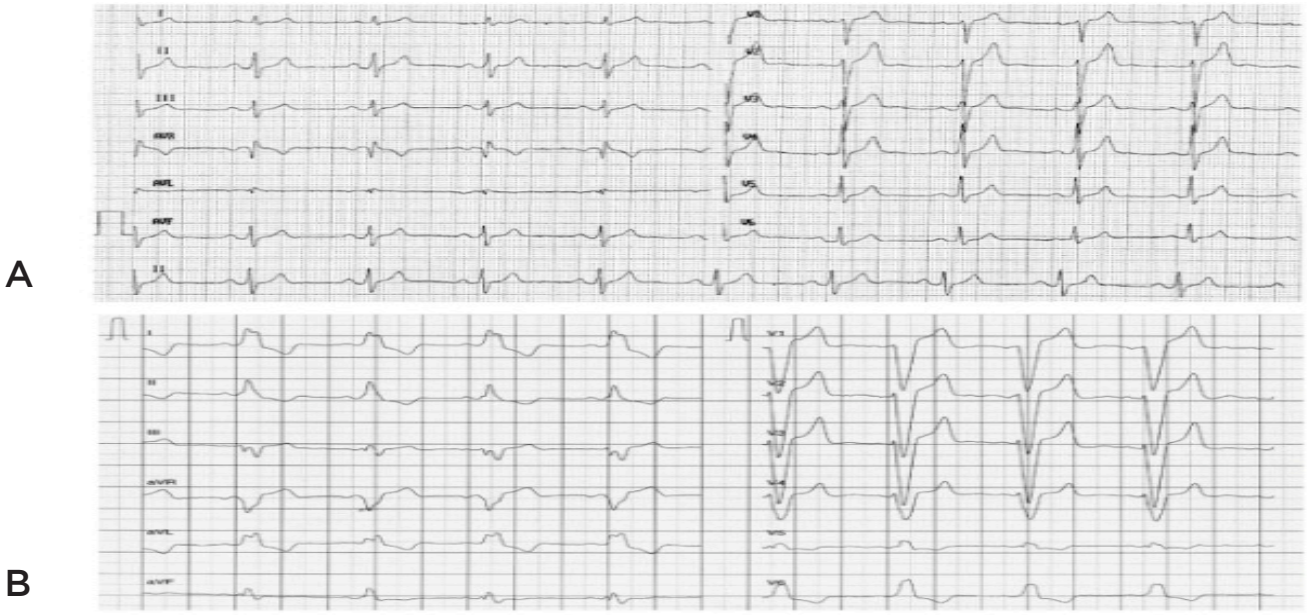

Figure 2. Surface electrocardiogram of a patient before (A) and 2 days (B) after implantation of a CoreValve (A).

of percutaneous prosthetic valve delivery was demonstrated by others[10-13] and in 2000 Bonhoeffer et al.[14] described the first successful implantation of a catheter-based stent valve in a pulmonary conduit. Transcatheter aortic valve implantation (TAVI) has recently been developed to minimise surgical risk in high-risk patients with severe symptomatic aortic stenosis who are refused for conventional open aortic valve replacement. The anatomical proximity of the conduction system to the aortic annulus atrioventricular block, with subsequent pacemaker requirement, was described in 6% of cases after surgical aortic valve replacement, but varies after TAVI between 5.7% and 42.5%, while new left bundle branch block occurs in up to 50-70%[15-19] (Figure 2). Better prediction of pacemaker requirement would be of considerable benefit in patients undergoing TAVI with respect to potential needs and duration of postoperative monitoring.

ANATOMICAL CONSIDERATION

The aortic valve is normally composed of three cusps or leaflets. The individual cusps are attached to the aortic wall in a semilunar fashion, ascending to the commissures and descending to the basal attachment of each cusp to the aortic wall. The valvar leaflets and their supporting sinuses, which together make up the root, are related to all four cardiac chambers. Within the right atrium, the atrioventricular node is located within the triangle of Koch. This important triangle is demarcated by the tendon of Todaro, the attachment of the septal leaflet of the tricuspid valve, and the orifice of the coronary sinus. The apex of this triangle is occupied by the atrioventricular component of the membraneous septum. The atrioventricular node is located just inferior to the apex of the triangle adjacent to the membranous septum, and therefore, the atrioventricular node is in close proximity to the subaortic region and membranous septum of the left ventricular outflow tract. Thus, pathologies involving the aortic valve can lead to complete heart block or intraventricular conduction abnormalities. The atrioventricular node continues as the bundle of His, piercing the membraneous septum and penetrating into the left through the central fibrous body. The branching bundle is intimately related to the base of the interleaflet triangle that separates the non-coronary and right coronary leaflets of the aortic valve.

CONDUCTION DISORDERS

Aortic valve disease has been associated with cardiac conduction system disease, as aortic stenosis and insufficiency have been associated with both prolonged atrioventricular conduction times and higher degrees of atrioventricular block.[20-22] Due to the vicinity of the aortic valve and atrioventricular node, as well as His bundle, complete atrioventricular block was reported in 5.7%, new left bundle branch block occurred in 18% with an association to complete atrioventricular block,

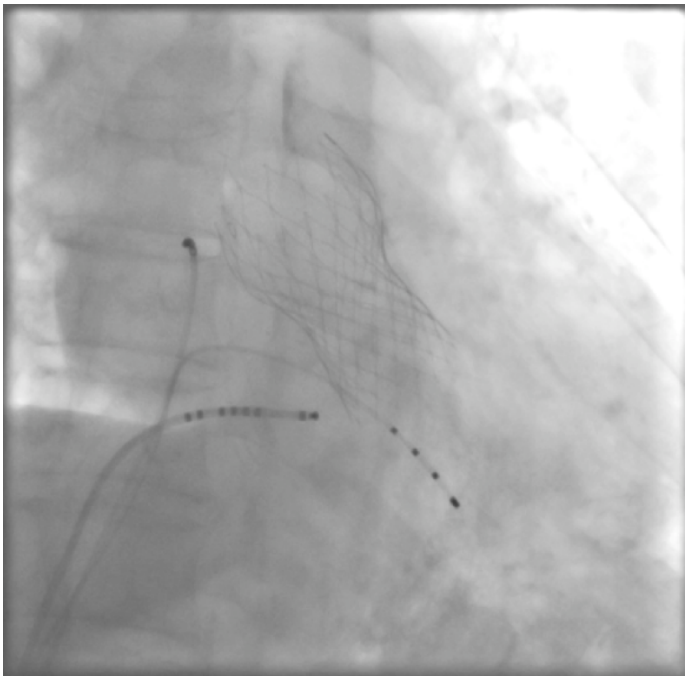

Figure 3. Setting of intracardiac measurements with a lead in right atrium, a lead in right ventricle and a lead in His bundle to measure intracardiac conduction.

syncope, and sudden cardiac arrest at long-term after open surgery.[23,24] Such conduction disturbances are presumed to result from surgical trauma to the cardiac conduction tissue during debridement of the calcified annulus.[23,24] Risk factors for complete atrioventricular block after surgical aortic valve replacement include previous aortic regurgitation, myocardial infarction, pulmonary hypertension, and postoperative electrolyte imbalance,[24,25] while among electrocardiographic criteria right bundle branch block was the strongest predictor for pacemaker requirement.[24,25] Several investigations report changes in surface electrocardiogram after TAVI.[15,26-31] The incidence of permanent pacemaker implantation after TAVI with the CoreValve system has been reported in 20% to 42.5%, and that of a new left bundle branch block in 50% to 70% [5,26-31]. Nevertheless, with the balloon-expandable, shorter Edwards SAPIEN prosthesis, which is placed in the aortic annulus without direct impact on left ventricular outflow tract, the incidence of atrioventricular conduction block requiring a pacemaker was reported between 0% to 6%, and new onset left bundle branch block of 3.3%.[32,33]

Differences to surgical aortic valve replacement might be due to the different techniques. In surgical approach the valve is replaced by another. Thus, the amount of conduction damage is predictable because the local trauma is nearly the same in all patients. However, in TAVI the amount of local damage is dependent of local calcification, the height of implantation in left ventricular outflow tract, the extent of trauma during index procedure (balloon valvuloplasty, balloon-to-aortic annulus relation, post-TAVI dilatation) and from further aortic annulus geometry. Degenerative calcification of the aortic and mitral annulus is probably a diffuse process, in which the cardiac conduction system is often involved and making it vulnerable to injury when exposed to mechanical compression by the nitinol frame of the CoreValve, which seems to completely expand within the first 7-10 days.[31] Jilaihawi et al. reported first that pacemaker requirement after TAVI correlates to left axis deviation at baseline, left bundle branch block, baseline thickness of the native non-coronary cusp and to diastolic interventricular septal dimension >17 mm.[30] Similarly, Piazza et al. revealed no prosthesis-related left bundle branch block when the proximal end of the valve frame was positioned <6.7 mm from the lower edge of the non-coronary cusp.[27] In the study by Marcheix et al. 30% of patients required pacemaker implantation due to persistent atrioventricular block,[34] whereas Zahn et al. reported a permanent pacemaker rate of 42.5% in the German Transcatheter Aortic Valve Intervention-Registry.[16] Different rates of pacemaker implantation might be due to different indications for pacing (e.g. complete atrioventricular block, new left bundle branch, prolonged atrioventricular conduction). However, to date there is no evidence about the occurrence of left bundle branch block. Additionally, there is no information about the true long-term occurrence of relevant conduction disturbances and the permanent or transient nature of conduction disorders. A comparison of hard endpoints like high-grade atrioventricular block would be more convincing. Other reasons for different pacemaker implantation rates might be the learning curve with high implantation techniques resulting in less compromise of the compact atrioventricular node.

Akin et al.[35,36] was the first to describe intracardiac conduction abnormalities for better discrimination of new electrocardiographic changes on surface electrocardiogram, and to predict critical conduction delays (Figure 3, 4). The evolution to complete atrioventricular block and to left bundle branch block took place over an observation period of 7 days. Similarly, PQ interval and QRS duration, as well as AH and HV intervals prolonged. In the series of Akin et al, complete atrioventricular block was seen

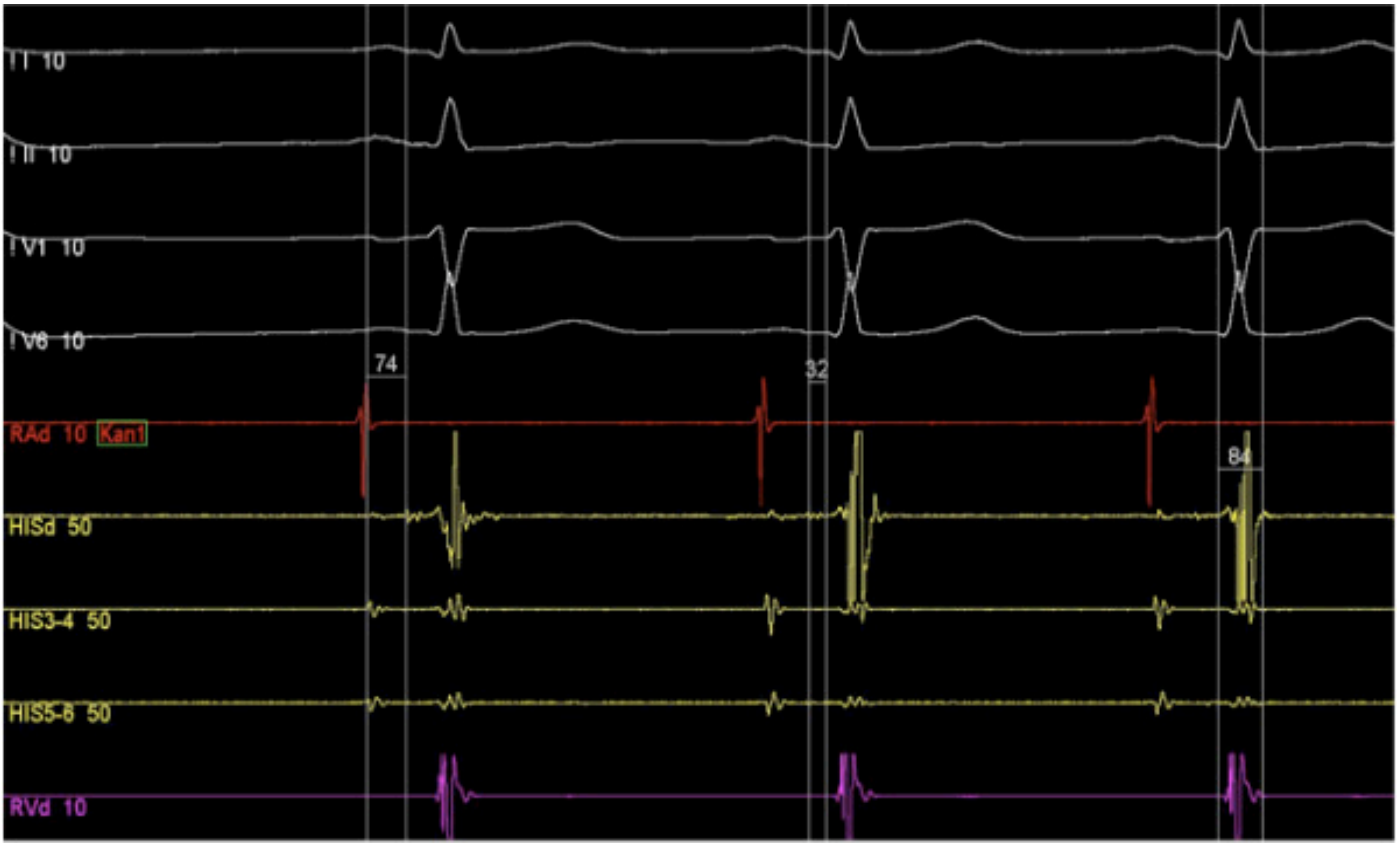

Figure 4. Intracardiac traces in a patient with normal AH and HV conduction.

in 13.3%, while 8.9% suffered from type II second-degree atrioventricular block; thus, 22.2% of patients developed an indication for permanent pacemaker implantation corroborating previous findings.[27-29,37-41] Their intracardiac measurements revealed that occurrence of first-degree atrioventricular block were predominantly due to prolongation of HV interval, which might be prognostically relevant.[42] Scheinman et al. have shown that patients with an HV interval greater than 100 msec are a at high risk to develop complete atrioventricular block.[42] Therefore, the possibility of progression of left bundle branch block to complete atrioventricular block should always be considered, and may explain the liberal use of pacemakers for conduction disorders observed in our series of TAVI patients. This liberal approach may be debatable, but in elderly patients with several comorbidities, preventive pacemaker insertion is justified by guideline recommendation.[43] Piazza et al. showed that some of the initial conduction delay after TAVI was partially reversible at 1 month follow-up and presumably related to inflammation and oedema around the conduction pathways;[27,31] Akin et al. could not identify a single case of conduction recovery.

The multivariate analysis of Akin et al. revealed that only PQ duration >200 msec, a left bundle branch block and QRS duration >120 msec immediately (within 60 minutes) after CoreValve implantation, seem to predict critical atrioventricular conduction delay. Other baseline clinical and electrocardiographic parameters had no impact. The occurrence of above electrocardiographic findings soon after TAVI may reflect the extent of trauma from the procedure. Interestingly, the exact determination of both the amount of valve calcification and the height of implantation turned out to be non-reproducible although both parameters have been claimed to impact on conduction physiology.[27,30] For example, the Edwards SAPIEN valve, shorter and less likely to extend into the left ventricular outflow tract, is obviously associated with a lower rate of complete AV block (0-6%).[33,44]

As demonstrated by Akin et al., we believe that, regardless of favourable anatomy, only the extent of trauma predict the occurrence of critical conduction delay after TAVI. However, to diminish trauma to the conduction system by TAVI using the CoreValve revalving system may reduce the risk of conduction abnormalities. Such strategies may include limiting the depth of the valve within the left ventricular outflow tract and keeping the number of pre and

post-valve implantation balloon valvuloplasties to a minimum. Additionally, operators should deploy the device only a few millimetres below the annulus and avoid impacting the septum. A modified implantation technique, however, may also require technical modifications to avoid malalignment of valves.

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UNITED STATES SEES RISE IN RADIAL ACCESS PCI OPERATIONS

U.S. has seen a 13-fold increase in threading through wrist procedure since 2007

- Feldman et al.

INTERVENTIONAL cardiologists in the US, rather than feeding a catheter towards the heart through the femoral artery in the groin, are increasily gaining access through the smaller radial artery in the wrist, according to a new anaylsis published online.

The proportion of radial PCI rose from 1.2% in 2007 to 16.1% in 2013, accounting for 6.3% of all procedures in the CathPCI registry during its 5-year period. Although frequently performed in Europe, Canada, and Asia, the increase was not uniform across the country, with radial PCI accounting for 24% of all procedures in the North East.

Nearly 2.8 million procedures from 1381 hospitals were analysed, with 178,643 procedures performed via the redial artery, though it was found approximately 13% of all hospitals included in the registry did not perform any transradial PCIs.

"This analysis of the largest contemporary multicentre PCI registry shows that there has been a 13-fold increase in adoption over 6 years in US clinical practice," Dr. Dmitriy Feldman of Weill Cornell Medical College, New York, and colleagues, write.

"In comparison with traditional femoral access, transradial PCI is associated with lower vascular and bleeding complication rates while maintaining procedural success."

As experience with radial access grows, fluoroscopy times approaching those of [femoral access] PCI could be strived for in the future.

- Feldman et al.

The reluctance from US interventionalists to take up the procedure is suggested to potentially be due to concerns about the learning curve of the procedure, and the need for quick, effective education.

The online report, published in *Circulation*, shows that compared to transfemoral procedures, patients undergoing radial PCI were more likely to be male, young, and have a high body mass index. This in turn reveals it is still underused in such groups as older women, and patients with acute coronary syndrome.

CLEARWAY™ CLEARS WAY FOR REDUCING INFARCT SIZE

PATIENTS experience a statistically significant relative reduction in infarct size if treated with the ClearWay RX local drug delivery balloon catheter, it was announced at the 62nd Annual American College of Cardiology Conference in San Francisco.

The year-long results of the Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction (INFUSE-AMI) trial showed the catheter was associated with lower mortality rates, while also reducing major adverse cardiac events, reducing infarct size by 16% after 30 days.

The results were found by measuring the size of the heart muscle impacted by a heart attack, via a highly sensitive cMRI, 30 days after patients were first treated with intralesional ClearWay RX/abciximab.

"ClearWay offers the interventionalists a reproducible, on-the-table treatment option for the preservation of heart muscle, resulting in reduced clinical events, and was associated with a mortality reduction," Dr. Michael Gibson, Co-Principal Investigator, said.

The drug delivery balloon catheter is a thin, microporous PTFE balloon, mounted on a 0.014 inch rapid exchange catheter. By atraumatically occluding blood flow during the local infusion, the therapeutic agent's concentration and removal time is maximised.

Mortality was also found to occur in patients with an infarct size greater than 17.1%, with the median size for both those patients treated with ClearWay RX/abciximab and those treated with an alternative, recorded at 15.1% and 17.9% respectively.

STENT ORIGINALLY USED ON CORONARY ISSUES LEADS TO DISAPPOINTING ERECTILE DYSFUNCTION RESTENOSIS RATE

ONE-THIRD of coronary artery stents, used to treat erectile dysfunction in an experimental trial, partically occluded after 1 year, according to a new study announced at the American Urological Association (AUA) 2013 Annual Scientific Meeting.

"For many of my patients, it's been a fabulous experience," said Director of the Institute of Sexual Medicine in San Diego, California, Dr. Irwin Goldstein.

Though the study appears to be both well-tolerated and safe, the researchers note that more information is required to observe if pudendal artery stenting is viable in treating men with vasculogenic erectile dysfunction, the same equipment having been used on millions of patients to effectively treat atherosclerosis of their coronary arteries.

Using zotarolimus-eluting cobalt chromium peropheral stents, the trial studied 45 atherosclerotic lesions of the internal pudendal artery on 30 men. After a year, restenosis was found in 11 of the 32 original lesions, a much higher rate than average concerning coronary artery stents.

Pudendal arteries are different from the coronary arteries for which the stents are designed, according to Dr. Tobias Köhler, as although blood flow to the heart is continous, the penis requires a large amount of blood for erections, and much less for the rest of the time. Bare-metal stents might work better in pudendal arteries, or perhaps stents that elute more medication.

> "For many of my patients, it's been a fabulous experience."
>
> *- Investigator Dr. Irwin Goldstein*

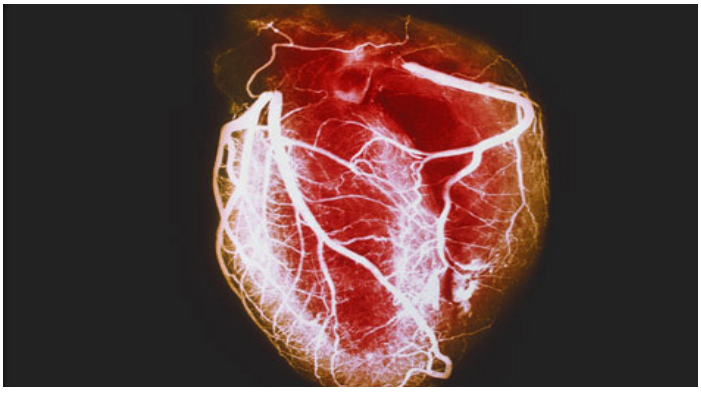
> "There has to be active involvement in lifestyle changes."
>
> *- Investigator Dr. Irwin Goldstein*

With current treatments for erectile dysfunction,, such as drugs and vacuum pumps, often leading to unfortunate effects at at times deemed inconvenient, Dr. Goldstein argues that none of the treatments deal with the actual cause of the dysfunction.

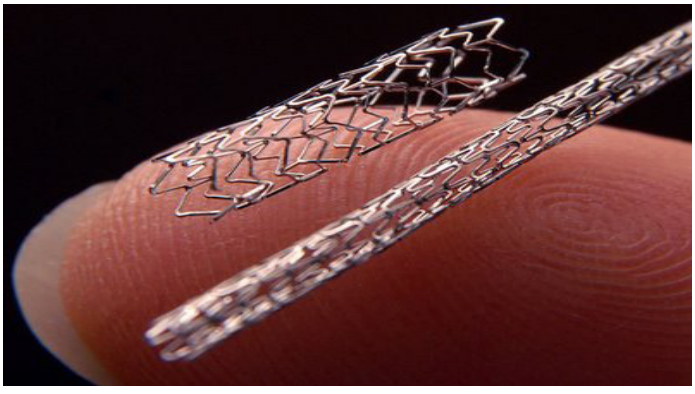
Though the investigators estimate that 3% of men with erectile dysfunction might be candidates for the treatment, Dr. Goldstein believes that the stent may not be enough. Much like those with coronary atherosclerosis, patients may need to focus on exercise, diet, and cholesterol,

"There has to be active involvement in lifestyle changes," Dr. Goldstein said, during an interview with *Medscape Medical News.* "If you're going to do this, you have to realise it's a systemic disease."

Though originally funding the trial, company Medtronic have cancelled its plans to pursue the research, with Dr. Köhler and colleagues searching for funding to launch a larger trial.



TECHNOLOGY: Data was taken with a sensitive cMRI



NEW GROUND: A new kind of stent is likely needed

US VETERANS TESTED WITH STATE OF THE ART STENTS IN TRIAL SHOWS CABG SURGERY MORE PREFERABLE TO DIABETICS

DIABETIC patients with multivessel coronary artery disease are better suited to coronary artery bypass graft (CABG) surgery than to angioplasty, despite the latest drug-eluting stents (DES) being employed, according to findings published in the *Journal of the American College of Cardiology*.

The VA CARDS study is described by Dr. Masoor Kamalesh from the Roudebush VA Medical Center in Indianapolis and colleagues to be the first to compare the most contemporary surgical techniques with the latest DES in a significant number of cases.

Following US veterans for at least 2 years, the prospective multicentre study focused on patients who had diabetes and multivessel disease including either the left anterior descending (LAD) coronary artery or the isolated proximal LAD.

"The overriding conclusion is that surgery is better, it's clearly the better way to go in diabetics," Dr. Makalesh said. "It is a state-of-the-art study."

In VA CARDS, the choice of stents was at the operator's discretion, thoug a single stent type per patient was recommended, while all commercially available DES were allowed following FDA approval.

Despite the fact the study was forced to be stopped due to slow recruitment, acquiring only 25% of the intended sample size, Dr. Makalesh believes the results are still meaningful, particularly when compared to other previous corrobarating studies.

One such example, the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, added significant weight to the argument in favour of surgery, though had only used first generation DES.

Though Dr. Kamalesh stated international trials were required, he added that the potential difficulties, such as different country's techniques for CABG and PCI depending on location, may require "a leap of faith to compare them."

CORONARY BIFURCATION STENTING HELPS HEALTH OUTCOMES

CORONARY bifurcation stenting with drug-eluting stents (DES) improves health-related functional outcomes, according to a UK report.

Data of 500 patients were examined for functional outcomes from simple versus complex bifurcation treatment, and was obtained from the British Bifurcation Coronary; Old, New, and Evolving Strategies (BBC ONE) randomised trial.

"Bifurcation coronary treatment is very effective at relieving symptoms of angina, irrespective of technique used," Dr. David Hildick-Smith from Sussex University Hospital in Brighton said, in speaking to Reuters Health. "Side branch should only be stented if necessary and if the physician has the appropriate experience for a two-stent strategy."

Scores for all Seattle Angina Questionnaire (SAQ) scales improved significantly following bifurcation percutaneous coronary intervention (PCI), yet there was no difference in the proportions of patients who were free from angina at follow-up between the simple and complex groups, recorded at 65% and 60% respectively.

> "Bifurcation coronary treatment is very effective at relieving symptoms of angina, irrespective of technique used."
>
> *- Dr. David Hildick-Smith*

Although it was known that simple versus complex stenting does not affect the event rate, the trial highlights it fails to affect the way symptoms improve.

"The lack of difference in symptomatic and functional outcomes between simple and complex approaches strengthens the argument that a default simple strategy is preferable in most cases, given its other proven advantages (reduced procedural duration, radiation dose, equipment costs, and so on)," the researchers conclude.

VIRTUAL ANGIOGRAPHIC IMAGING KEY TO REVOLUTIONISING 'UNDERUSED' FRACTIONAL FLOW RESERVE PROCEDURES

A STATE-OF-THE-ART tool to measure myocardial fractional flow reserve (FFR) using only angiographic images, and is able to detect any significant coronary lesions with a 97% accuracy rate, British researchers have announced.

The model of intracoronary physiology is based on a rotational coronary angiogram and fluid dynamics analysis, and does not require a pressure-sensitive intracoronary wire.

Lead author of the study, Dr. Paul Morris, states that FFR technology is still underused, with less than 10% of patients in the UK have FFR assessed prior to PCI.

"There is substancial evidence demonstrating that visual interpretation of coronary lesions, especially moderate lesions, can be misleading," Dr. Morris of the University of Sheffield, UK, said when speaking to *heartwire*.

"We would like to create a system that you don't have to be a PhD student to operate."

The researchers obtained 3D images of coronary lesions in patients suffering from established coronary disease using a rotational angiogram, applying computational fluid dynamics within the virtua artery to estimate pressures in 10 right and 12 left coronary arteries.

The results were then compared with traditional FFR measurements taken at the same time, assessing the ability to find sensitivity, specificity, positive predictive value, and negative predictive value. Findings showed an 86%, 100%, 100% and 97% accuracy rate respectively.

Despite FFR's advantages over other artery evaluation techniques, such as its ability to take into account collateral flow, which can render an anatomical blockage functionally unimportant, Dr. Morris believes there are multiple factors explaining the UK's reluctance towards FFR in clinical practice, including the time required to perform the procedure, and economical motivations.

Backing up the DEFER, FAME and FAME II studies in showing patients do better and long-terms costs are struck down through physiology-guided PCI, is published in the *Journal of the American College of Cardiology: Cardiovascular Interventions*.

INTRACORONARY AND IV ABCIXIMAB PROVED EQUALLY VIABLE

THE glycoprotein IIb/IIIa receptor antagonist, abciximab, may be given via the IV or intracoronary route during percutaneous interventions for ST-segment elevation myocardial infarction (STEMI), and have no effect on the outcome, according to researchers.

The AIDA STEMI trial, comparing the efficiacy and safety of bolus abciximab delivery between the two methods, meant the substudy could observe data through cardiac magnetic resonance (CMR) imaging, enabling "a comprehensive evalutaion of myocardial damage and reperfusion injury," according to author Dr. Ingo Eitel.

Using 795 of the 2,065 patients in the trial, the Germany-based team aimed to look further into the potential benefits of intracoronary abciximab on reperfusion, after noting a "statistically significant" reduction in new episodes of congestive heart failure in intracoronary patients, compared to those fed intravenously.

In speaking to *Reuters Health*, Dr. Eitel said CMR "revealed no differences in infarct size, myocardial salvage, left ventricular function, or extent of reperfusion injury between groups, confirming the lack of difference in clinical events."

Specifically, findings discovered the area at risk and the final infarct size did not differ between the intracoronary group and IV group, set at 16% and 17% respectively. Last year, in The Lancet, the research team had previously reported no difference in the primary endpoint of the study, composing of new congestive heart failure within 90 days, all-cause mortality, and recurrent infarction.

FEATURED SUPPLIERS

Alvimedica specialises in next-generation stents and catheters that are revolutionising interventional cardiology, boasting an interventional cardiology portfolio consisting of over 1,000 products in 10 product lines. Growing rapidly and planning to extend beyond the 30 countries in which it enjoys a sales presence, the company supports its portfolio with clinical trials worldwide.

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BUYER'S GUIDE

EVENTS

TCT Conference 2013

October 27-November 1, 2013

San Francisco, USA

Transcatheter Cardiovascular Therapeutics (TCT) is the world's largest educational meeting specialising in interventional cardiovascular medicine. For more than 20 years, TCT has been the centre of new cutting-edge educational content. TCT showcases the latest advances in current therapies and clinical research, and their long-standing commitment to life-saving innovation to translate into improved patient care.

TCT, the world's largest educational meeting specializing in interventional vascular medicine, is now partnered with the American College of Cardiology (ACC). TCT together with the ACC will offer invaluable opportunities for the medical community to discover the latest advances in the field, share clinical experiences, and exchange new ideas and information with colleagues from around the world.

CIT 2014

March 20-23, 2014

Shanghai, China

This congress is designed for interventional cardiologists radiologists, clinical cardiologists, basic scientists, vascular medicine specialists, surgeons, and other healthcare professionals with a special interest in the field of interventional vascular therapy and medicine.

By the end of the congress, participants should be able to:

Relate the results from important clinical trials and evidence-based medicine that guide the management of patients with atherosclerosis and structural heart disease.

Integrate new interventional techniques and procedures to the care of patients with complex coronary artery disease, peripheral vascular disease, structural heart disease, and heart rhythm.

Integrate appropriate pharmacological management in the care of patients undergoing diagnostic angiography and interventional therapies before, during, and after catheterisation.

Distinguish between new interventional technologies and propose their appropriate applications to patients with cardiovascular disease.

JIM 2014

February 13-15, 2014

Rome, Italy

The aim of the meeting is for participants to have the opportunity to be informed on the very latest innovation on interventional cardiology, and to approach new techniques through educational live cases.

Have a chance to show your best success or to discuss your worst complications in front of an outstanding panel in the Main Arena. Saturday morning will be devoted to cases review (approximately 10 minutes each, including Q&A) from Faculty and Attendance.

Deadline for submission is December 30, 2013

JIM 2014 Scientific Program will be submitted for EBAC CME Accreditation.

Once again the Meeting will take place in Rome, at the Ergife Palace Hotel. It combines a confortable accommodation solution with a large and efficient Congress Centre.

TCTAP 2014

April 22-25, 2014

Seoul, South Korea

In every April, thousands of influencial leaders in the field of cardiovascular medicine gather at TCTAP to discover emerging trends and technology, to learn the best practice in patient care, and to network with medical professionals from all over the world.

The TCTAP Best Young Scientist Award will be sought after, originally initiated in 2012 to acknowledge, recognise, and encourage mid-level young clinical investigators for their academic clinical research and case study presented at TCTAP. The highest scored presenters by the TCTAP scientific committee will recieve this award.

COURSES

TOBI 2013

September 12-13, 2013

Venice, Italy

Tobi is an absolutely-live course for a closed number of interventional cardiologists with tight interaction between participants, faculty, and operators.

Missions of TOBIto amplify the ability to perform complex coronary procedures in bifurcation and CTO lesions, to teach & discuss during extensively shown live cases performed by forefront operators: the most modern approaches and technical innovation, and to provide with concise lectures by world experts 'on-the-point' theoretical and practical knowledge.

Taiwan Transcatheter Therapeutics

January 11-12, 2014

Taipei City, Taiwan

Program includes: Highlights of TCT SF 2013, a PCI Live Transmission and Live Case Demonstration, an International Complex Case Competition, and a review dubbed Hot Topics in Percutaneous Interventions.

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INSIDE

Reviews of the
18th **EHA** Annual Congress
Stockholm, Sweden,

and the 39th **EBMT** Annual
Meeting, London, UK