EMJ EUROPEAN MEDICAL JOURNAL

INTERVENTIONAL CARDIOLOGY

ISSN 2053-423X — Vol 5.1 • July 2017 • europeanmedical-journal.com

CONTENTS

INTERVENTIONAL CARDIOLOGY

EDITORIAL BOARD

European Medical Journal Interventional Cardiology is published once a year.
For subscription details please visit www.europeanmedical-journal.com

Front cover and contents photograph: Paris, France, home of EuroPCR 2017. *© bloodua / 123rf.com*

AIMS AND SCOPE

- The European Medical Journal (EMJ) is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline
- EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe
- EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group
- EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research
- EMJ also publishes 16 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published annually, approximately 6 weeks after the relevant congress. Further details can be found on our website: www.europeanmedical-journal.com

EDITORIAL EXPERTISE

EMJ is supported by various levels of expertise:

- Guidance from an Editorial Board consisting of leading authorities from a wide variety of disciplines
- Invited contributors are recognised authorities from their respective fields
- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic
- An experienced team of editors and technical editors

PEER REVIEW

- On submission, all articles are assessed by the editorial team to determine their suitability for the journal and appropriateness for peer review
- Editorial staff, following consultation with either a member of the Editorial Board or the author(s) if necessary, identify three appropriate reviewers, who are selected based on their specialist knowledge in the relevant area
- All peer review is double blind
- Following review, papers are either accepted without modification, returned to the author(s) to incorporate required changes, or rejected
- Editorial staff have final discretion over any proposed amendments

SUBMISSIONS

- Contributors are identified and invited by editorial staff with guidance from the Editorial Board
- Following acceptance of an invitation, the author(s) and editorial staff formalise the working title and scope of the article
- Editorial staff will provide instructions to authors, or submission details can be found through our website: www.europeanmedical-journal.com
- Editorial staff are always keen to hear from healthcare professionals wishing to discuss potential submissions

REPRINTS

- All articles included in EMJ are available as reprints (minimum order 1,000). Please contact hello@europeanmedical-journal.com if you would like to order reprints

DISTRIBUTION AND READERSHIP

- EMJ is distributed through controlled circulation to healthcare professionals in the relevant fields across Europe

INDEXING AND AVAILABILITY

- EMJ is indexed on DOAJ, the Royal Society of Medicine, and Google Scholar®; selected articles are indexed in PubMed Central®
- EMJ is available through the websites of our leading partners and collaborating societies
- EMJ journals are all available via our website: www.europeanmedical-journal.com

INTERVENTIONAL CARDIOLOGY 5.1
JULY 2017

Staff members attend Medical Congresses as reporters when required.

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

Published by the European Medical Group
The MedBIC, Anglia Ruskin University, Chelmsford, CM1 1SQ

Welcome

We at EMJ would like to bid you a warm welcome to *EMJ Interventional Cardiology 5.1.* This edition is jam-packed with the latest news, guaranteed to pique the interest of anyone in the interventional cardiology field. Inside, you will be given an insight into the events of EuroPCR, the official annual meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). This review provides a digestible summary of the congress, perfect to either refresh your memory or update you on any information you missed out on. Additionally, dive into a wide selection of peer-reviewed articles covering the hottest topics within interventional cardiology in 2017. We are also lucky enough to share a variety of informative and thought-provoking interviews with our highly esteemed Editorial Board, as they reveal their hopes for the future of interventional cardiology, their current research, and some invaluable wisdom gained through years at the top of the discipline.

This year's EuroPCR congress brought together >12,000 participants in the 'City of Love', formally known as Paris, France. Our eJournal includes a series of abstract reviews to inform you of some of the exciting discoveries announced. We aim to provide you with truly ground-breaking, innovative information that inspires you to research further and keeps your passion for interventional cardiology alight.

> "We aim to provide you with truly ground-breaking, innovative information that inspires you to research further and keeps your passion for interventional cardiology alight."

Our Editor's Pick for this edition was penned by Yang and Takeuchi, who reviewed the present status of fully automated software with three-dimensional echocardiography with regard to the assessment of left ventricular volumes and left ventricular ejection fraction. Durante and Laforgia address the challenge of coronary bifurcation lesions, investigating drug-coated balloons that may improve provisional stent results. Cheung et al. provide an informative article, which discusses whether there is an optimum duration of dual antiplatelet therapy after drug-eluting stent implantation. Moreover, Wada et al. draw attention to the past, present, and future perspectives of stent or scaffold thrombosis, whilst highlighting pathophysiology and contributing risk factors for stents. These are just a handful of the articles featured in *EMJ Interventional Cardiology 5.1,* so make sure to continue reading so as not to miss out!

Producing this edition has been an absolute pleasure and we hope that you will find this latest edition to our eJournal collection as interesting, informative, and inspiring as we do. We look forward to seeing you at next year's EuroPCR congress!

Spencer Gore

Director, European Medical Journal

EMJ EUROPEAN MEDICAL JOURNAL

SUBSCRIBE

FREE TO OUR YOUTUBE CHANNEL

www.youtube.com/EMJreviews

CONGRESS HIGHLIGHTS
DISCUSSIONS
INTERVIEWS
WEBCASTS

europeanmedical-journal.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

Foreword

Dr Pierfrancesco Agostoni

Department of Cardiology, St. Antonius Hospital, Nieuwegein, Netherlands.

Dear Colleagues,

It is my utmost pleasure to welcome you to this edition of *EMJ Interventional Cardiology,* which features an impressive array of papers alongside its customary coverage of the EuroPCR Congress. As well as the huge range of research presented, this year's congress was also notable for commemorating the 40th anniversary of angioplasty. For those who could not attend, I encourage you to read the congress review section and learn more about the events that transpired there. Also within this feature are a number of reviews of abstract presentations that were made at the congress, which were provided by the presenters themselves. These include the clinical use of fractional flow reserve computed tomography and the 10-year clinical outcomes in patients who were treated with a first-generation drug-eluting stent.

> "...I was struck by the vast potential available to us as interventional cardiologists, and welcomed the opportunity to learn more about the backgrounds of these specialists in their field."

This publication features a selection of peer-reviewed articles that are highly topical and encompass a wide range of topics from the field of interventional cardiology. My Editor's Pick for this edition is by Yang and Takeuchi and is a thoroughly topical and thought-provoking read, especially for those with an interest in echocardiography. The authors have provided a glimpse into the promise of new technologies in this area. Additionally, I am pleased to present several more papers to you. These studies broach several issues I believe will be of interest, such as whether there is an optimal duration of dual antiplatelet therapy after drug-eluting stent implantation and a discussion on the repair of congenital heart defects.

Finally, you can enjoy reading a selection of interviews with my some of my colleagues who sit on the *EMJ Interventional Cardiology* Editorial Board. Reading their responses, I was struck by the vast potential available to us as interventional cardiologists, and welcomed the opportunity to learn more about the backgrounds of these specialists in their field.

I trust you will enjoy reading this new issue!

Warm regards,

Pierfrancesco Agostoni

Interventional Cardiologist, Department of Cardiology, St. Antonius Hospital, Nieuwegein, Netherlands.

EMJ EUROPEAN MEDICAL JOURNAL

European Medical Journal 2.1 2017 Available Now

Includes a selection of the latest articles for interventional cardiology, innovations, and more.

Featured inside:

FEATURE

Climate Change: What Can Doctors Do?

- Thomas Micklewright

ARTICLES

Editor's Pick: 3D Printing for Biomedical Applications: Where Are We Now?

- Carlos Miguel Chiesa Estomba et al.

Hide and Seek: The Game Between Chronic Lymphocytic Leukaemia Cells and B Cell Receptor Signalling Inhibitors

- Kumudha Balakrishnan et al.

Haemangioma: A Review of the Literature and an Unusual Case Report

- Ajaya Kumar

Transcatheter Repair of Congenital Heart Defects in the Young

- Sonia A. El-Saiedi et al.

Anaesthesia Techniques in Transfemoral Transcatheter Aortic Valve Implantation: A Brief Review

- Mehmet Aksoy et al.

New Drug Treatments for Osteoarthritis: What is on the Horizon?

- Fiona E. Watt, Malvika Gulati

Contemporary Drug-Eluting Stents and Vascular Response

- Anwer Habib et al.

Does Race/Ethnicity Have a Role in a Link Between Lower Urinary Tract Symptoms and Metabolic Syndrome?

- Seong Ho Lee, Sang Kon Lee

Antiphospholipid Syndrome and the Lungs

- Süreyya Yılmaz, Zülfükar Yılmaz

Cardiovascular Risk Factor Control in Type 2 Diabetes Mellitus and New Trial Evidence

- Peter M. Nilsson

State-of-the-Art Advances in Duchenne Muscular Dystrophy

- Henriette Van Ruiten et al.

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

EUROPCR ANNUAL CONGRESS 2017

PALAIS DES CONGRÈS
PARIS, FRANCE
16TH–19TH MAY 2017

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

This year's EuroPCR congress was held in the metropolitan city of Paris, France. EuroPCR is the official annual meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Known for its wide boulevards, fashion, and culture, Paris provided a magnificent backdrop for this year's meeting. Over 12,000 attendees came together in France's capital city to share the very latest research, developments, and best practice in treating cardiovascular conditions. Speaking at the opening ceremony, one of the EuroPCR course directors, Dr Jean Fajadet, Clinique Pasteur, Toulouse, France, announced: "EuroPCR has grown to become a platform for exchange and networking, helping us to help our patients. So, PCR brings together community initiatives within interventional medicine." In our congress review section, we provide a summary of the event, highlighting major news releases to ensure you do not miss out on anything.

The scientific programme this year was designed around four key aspects: Themes, Topics, Focus, and Formats. This enabled participants to find a theme they were interested in within a specific field focus and then choose an educational format that enabled them to maximise their learning experience. With the programme spanning >350 sessions, there was something for everyone. The programme also received significant input from the cardiology community, who submitted a wide variety of abstracts, clinical cases, images, innovative works, and late-breaking trials. Half the sessions at EuroPCR were based around these submissions. Feedback, garnered from social media and questionnaires, was utilised to design a unique, new series of sessions for younger interventional cardiologists. For example, the 'evidence-practice mismatch' sessions. These provided insight into cases where physicians may not adhere to guidelines in practice. Participants were provided with the opportunity to discuss these cases and come up with solutions.

Innovation was a thread that ran throughout the meeting, with clinical investigators at the forefront of innovation presenting their most recent findings. The importance of innovation was touched upon at the opening ceremony, with Dr Jean Fajadet noting: "So, to reach a point of being able to offer patients friendly

solutions to their problems requires a journey from research to implementation of innovation. That is a community that meets here as well." Furthermore, Innovators Day was held the day prior to EuroPCR to allow key innovation players in the European cardiovascular community the chance to network.

Another major feature of the meeting was the 40th anniversary of angioplasty. To honour this event, there was an exposition featuring the major milestones throughout the history of interventional cardiology. This exposition provided fascinating insight into the field and its development, and it highlighted some of the major players and driving forces behind shaping it. One intriguing display showcased early catheters and stents, which enabled viewers to visualise just how far the technology had developed. Another highlight was a short film on the first human percutaneous coronary angioplasty, carried out in 1977 by Andreas Grüntzig. Additionally, there was a feature providing details of the individuals behind some of the pioneering innovations in interventional cardiology, such as Dr Ibrahim Al-Rasdan (Kuwait), Dr Jorge Berlardi (Argentina), and Prof Ulrich Sigwart (Switzerland). There was a strong sense of community-created history in the exposition; attendees were encouraged to share their own stories and knowledge. For instance, there was a 'First Timers Map', which congress attendees could add to and provide details of the first people to carry out procedures in a country.

We hope you will take something of value away from perusing our highlights, and very much look forward to seeing many of you at next year's meeting, which will once again be hosted in Paris.

> "EuroPCR has grown to become a platform for exchange and networking, helping us to help our patients. So, PCR brings together community initiatives within interventional medicine."

Effect of Bivalirudin Versus Unfractionated Heparin on Infarct Size Reduction for PPCI in Large AMI

BIVALIRUDIN versus unfractionated heparin (UFH) was investigated to determine whether infarct size (IS) was reduced for primary percutaneous coronary intervention (PPCI) in large acute myocardial infarction (AMI). The results of this prospective, randomised, multicentre, open-label study were reported at the EuroPCR congress held in Paris, France.

The study enrolled 78 patients, randomised (1:1) to either bivalirudin or UFH. Patients randomised to the bivalirudin subgroup received 0.75 mg/kg (bolus) and 1.75 mg/kg per hour (infusion) for the procedure duration, as well as administration for 4 hours post-PPCI completion to maintain thrombin inhibition. UFH patients were assigned dosage as per standard practice at each institution. A value of ≥250 seconds was proposed for cases where active clotting time was considered to determine UFH dose. Four study centres participated.

> “...a substantial reduction in IS in PPCI by prolonged bivalirudin administration as opposed to UFH was not achieved.”

The primary endpoint, defined as IS, was measured using cardiac magnetic resonance (CMR) 5 days post-PPCI. No statistically significant reduction was noted for mean IS at 5 days, (bivalirudin 25.0±19.7 g versus UFH 27.1±20.7 g [p=0.75]).

Secondary endpoints were index of microcirculatory resistance (IMR), CMR-assessed microvascular obstruction and ejection fraction, and thrombin activity and cell injury biomarkers. Initial microvascular obstruction was lower for bivalirudin patients, 5.3±5.8 versus 7.7±6.3 g (p=0.17). There was no substantial difference in ejection fraction at 90 days. For biomarkers, thrombin-antithrombin complexes were reduced in the case of bivalirudin (-4.8 µg/L), versus UFH which increased (+1.9 µg/L [p=0.0003]). IMR, which was measured in 52 patients, was lower with bivalirudin when distal coronary artery pressures were similar (bivalirudin 43.5±21.6 versus 68.7±35.8 mmHg x s [p=0.014]).

In the acute phase, bivalirudin completely inhibited thrombin production ≤10 minutes from the completion of PPCI. UFH failed to prevent an increase in thrombin generation. Although IMR was decreased, IS was not; therefore, the primary study endpoint was not met and discontinuation of the trial resulted. Trial limitations, including the small sample

size (N=78), should be acknowledged and the results should be approached with care. In conclusion, a substantial reduction in IS in PPCI by prolonged bivalirudin administration as opposed to UFH was not achieved.

Pilot Trial of Rapidly Induced Therapeutic Hypothermia Shows Promising Results

A PILOT trial of rapidly induced therapeutic hypothermia in patients with anterior ST-elevation myocardial infarction (STEMI) without cardiac arrest found results that suggested it would be appropriate to commission a pivotal trial to further investigate efficacy. The results of the COOL AMI EU pilot trial were reported at the EuroPCR congress held in Paris, France.

This pilot study had its genesis in unpublished post hoc subgroup analyses of the COOL MI and ICE-IT clinical trials and combined analysis of RAPID MI-ICE and CHILL MI14; these analyses implied that, if rapid cooling was used to decrease core temperature before the opening of the infarct-related artery, patients might benefit from therapeutic hypothermia. The aim of the study was to consider safety and feasibility issues of faster and more profound cooling than in other clinical studies and to assist in the determination of sample size calculations for a larger pivotal trial.

Fifty patients with anterior STEMI were randomised 1:1 to either the control group or the cooling group. These two study groups were comparable in terms of BMI, age, sex, and risk factors for coronary disease. Patients in the cooling arm were cooled to 33.6°C, which was at least 1.1°C lower than in recent cooling trials, over the course of 20.5 minutes. Per protocol analysis showed that, in the cooling group, median infarct size/left ventricular mass was 16.7%, in comparison to 23.8% in the control group. Furthermore, mean left ventricular ejection fraction was 42% and 40% in the cooling and control groups, respectively. While this was not statistically significant, the authors felt this warranted further evaluation for efficacy in a pivotal trial. The only notable difference in adverse events was a greater incidence of self-terminating paroxysmal atrial fibrillation in the cooling group (32% versus 8; p=0.074); however, during the warming phase, this spontaneously resolved to sinus rhythm and required no further treatment.

This pilot study had its genesis in unpublished post hoc subgroup analyses of the COOL MI and ICE-IT clinical trials and combined analysis of RAPID MI-ICE and CHILL MI14...

As this was a pilot trial, limitations should be considered. One such limitation is that the trial was not sufficiently powered to detect differences in left ventricular ejection fraction and infarct size/left ventricular mass. It is calculated that the pivotal trial should enrol a total of 468 patients.

Utility of Post-Intervention Fractional Flow Reserve Measurement

AN ASSOCIATION between post-percutaneous coronary intervention (PCI) fractional flow reserve (FFR) measurements and clinical outcomes, using a specific rapid exchange FFR microcatheter with exchangeable guidewire capability, may reveal a novel role for FFR in catheterisation laboratories. The results of this study were reported in a press release from EuroPCR, dated 18th May 2017. Early results indicate that microcatheter-based FFR may be feasible in numerous clinical settings.

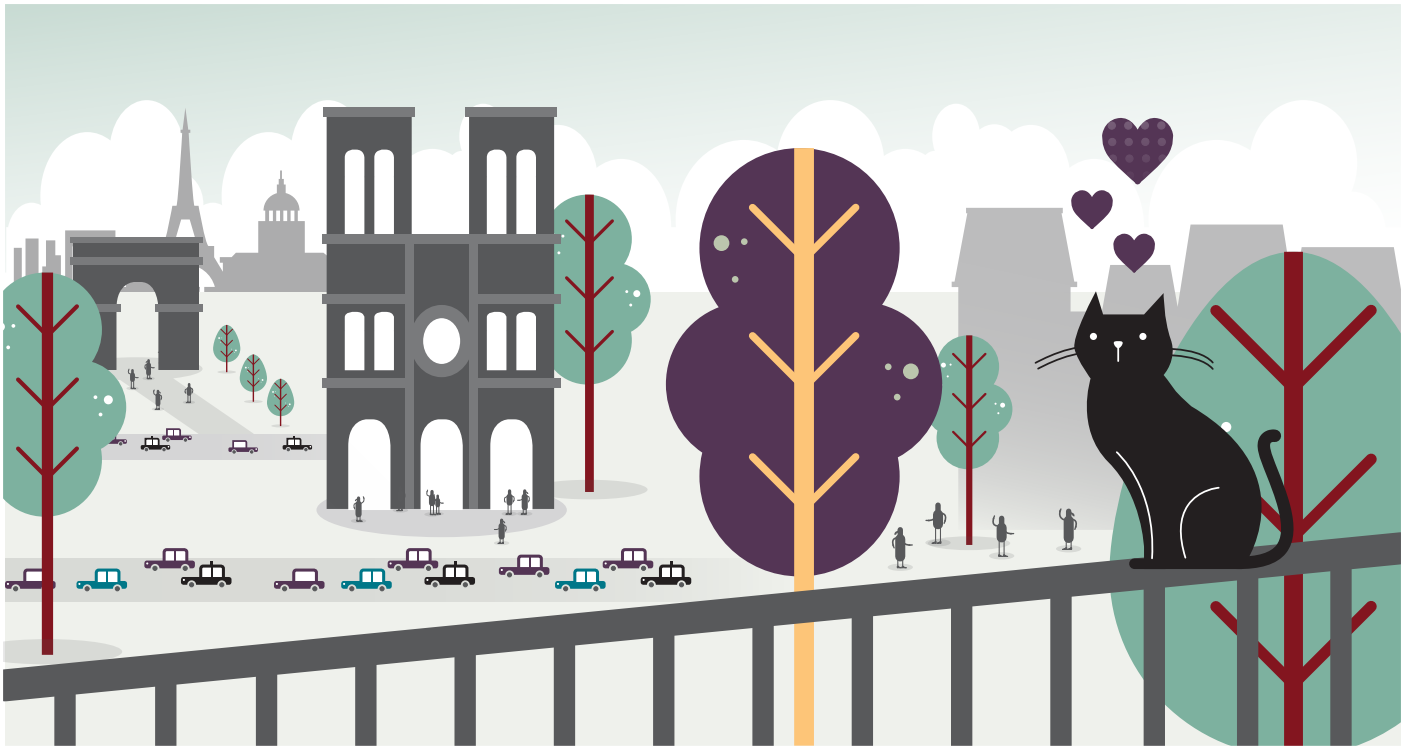
Preliminary results from the independent, physician-sponsored FFR-registry were unveiled at EuroPCR by investigators based at the Erasmus Medical Centre (Erasmus MC), Rotterdam, Netherlands. To determine the association between post-PCI FFR and clinical outcomes, >1,000 consecutive patients, who had been diagnosed with either stable angina or acute coronary syndromes (ACS) and been treated with PCI, were enrolled into the registry. Clinical outcomes were measured at several intervals: 30 days, 1 year, 2 years, and 5 years.

Initial analysis of 30-day data concluded that FFR measurements >0.90 led to a major adverse cardiovascular event (MACE) rate of 1.5%. Measurements of <0.9% lead to a MACE rate of 2.3% (p=non-significant). MACE rates increased as the FFR measurements lowered. Patient sub-groups with FFR measurements <0.9 could not demonstrate statistical differences between cohorts. However, FFR measurements of 0.86–0.90, 0.81–0.85, and ≤0.80, resulted in MACE rates of 2.0%, 2.6%, and 2.8%, respectively.

Dr Nicholas Van Mieghem, co-principal investigator, Director of Interventional Cardiology, Thoraxcenter, Erasmus MC commented: "The preliminary data from FFR-Search has the potential to significantly expand this technology's role in the cath lab in the future, which is why we are eager to see the important results of the primary endpoint at 2 years."

To determine potential causes for low post-procedural FFR, in 60 patients with an FFR value ≤0.85, intravascular high definition ultrasound analysis was carried out. In 84% of cases, stent under-expansion was the most common cause. This was followed by focal lesions distal to the stent (52%), focal lesions proximal to the stent (43%), and malposition of the stent (22%).

> "The preliminary data from FFR-Search has the potential to significantly expand this technology's role in the cath lab in the future, which is why we are eager to see the important results of the primary endpoint at 2 years."



Existing patients will continue to be monitored throughout the remaining duration of the trial, to determine a more conclusive understanding on the potential application of post-PCI FFR in clinical practice.

Efficacy of Percutaneous Coronary Intervention in Coronary Total Occlusion Patients

PERCUTANEOUS coronary intervention (PCI) achieves a high procedural success rate in patients with coronary total occlusion (CTO), according to results of the EURO-CTO trial presented in a EuroPCR press release dated 18th May 2017. The study found that bigger improvements in clinical symptoms were seen in CTO patients treated with this method compared to those who underwent the more commonly utilised optimal medical therapy, a finding that could lead to PCI becoming the primary treatment option for this group of patients.

> "The clinical symptoms and wellbeing of patients with CTO improve more efficiently with PCI than with optimal medical therapy. PCI should be the primary treatment option for these patients."

Currently only 7% of PCI procedures are for patients with CTO, a condition that occurs in ~20% of stable coronary artery disease patients. In contrast to non-occlusive lesions, a CTO is not accepted as an indication to perform PCI in current guidelines for managing coronary artery disease because of a lack of evidence on the benefits of PCI in CTO patients.

To gain a better insight into the efficacy and safety of PCI for CTO, the EURO-CTO trial enrolled 396 patients from 26 centres, who were then randomised to receive PCI or optimal medical therapy at a ratio of 2:1, respectively. Of the participants, 50% had single-vessel CTO and 30% had a non-CTO lesion treated before randomisation. Optimal medical therapy included anti-anginal drugs as well as standard secondary prevention methods. At follow-up, 9 patients moved from optimal medical therapy to PCI.

The results showed that in 86.3% of patients treated with PCI, the CTO was successfully opened. Additionally, there was a low procedural risk with this treatment method; no procedural deaths occurred and the 12-month major adverse cardiac and cerebrovascular events (MACCE) rate was 0.4%. PCI results were more favourable than optimal medical therapy, with more pronounced clinical symptoms, improved quality of life, and significantly greater absolute freedom from angina seen in PCI-treated patients.

"The clinical symptoms and wellbeing of patients with CTO improve more efficiently with PCI than with optimal medical therapy. PCI should be the primary treatment option for these patients," stated lead author Prof Gerald Walter, Director of the Cardiology Department, Klinikum Darmstadt, Darmstadt, Germany.

Deferred Revascularisation: Study Indicates Low Risk Based on Intracoronary Physiology Measures.

THE LARGEST real-world study on revascularisation in patients with stable angina and acute coronary syndrome (ACS) determined that deferring revascularisation on the basis of intracoronary physiology, using either fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR), was accompanied by low risk of substantial adverse coronary events. The results of this study were reported in a press release from EuroPCR, dated 16th May 2017.

Functional intracoronary measurements with pressure guidewires are largely carried out in coronary stenosis patients with a defined condition severity of 'intermediate' to determine the extent a stenosis has on blood flow restriction. For this particular subset of patients, there is restricted evidence on the safety of deferring vascularisation. Recent studies, DEFINE FLAIR and iFR SWEDEHEART, did not specifically report on patients whose procedures were deferred. However, data from the two trials did show positive outcomes for intermediate stenosis patients undertaking physiology-guided revascularisation.

The analysis in this study was derived from pooled data, originating from the two previously mentioned studies, and included information from 4,529 enrolled patients. The study's purpose was to determine the impact of deferring procedures. It was concluded that significantly fewer patients experienced interventions when iFR was used for measurement in comparison to FFR, (50% versus 45%; p=0.01).

In 2,130 patients with deferred myocardial revascularisation, the rate of major adverse cardiovascular events (MACE) was low (iFR; 4.12% and FFR; 4.05% at 1 year). The rate of MACE was lower in patients with stable coronary disease (SCD) compared to ACS (3.6% versus 5.9%; p=0.04).

"The findings support the safety of deferring revascularisation based on iFR or FFR," explained lead study author Dr Javier Escaned, Consultant Interventional Cardiologist, Hospital Clínico San Carlos, Madrid, Spain.

> "The findings support the safety of deferring revascularisation based on iFR or FFR."

Significant differences in event rate were observed for ACS and SCD when FFR was used as the method of assessment (ACS: 6.4% versus SCD: 3.4%; p=0.049). The variance was less defined for iFR (ACS: 5.4% versus SCD: 3.8%; p=0.37). Further data would be beneficial to better understand and further support the role of physiological evaluation in patients with ACS.

Switching Therapies Can Reduce Risk of Minor Bleeding Events

SWITCHING treatments after acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI) could improve outcomes, according to the results of a study reported in a EuroPCR press release, dated 16th May. This randomised study, led by Dr Thomas Cuisset, CHU Timone, Marseille, France, was the first to compare the two dual antiplatelet therapies (DAPT).

Prasugrel and ticagrelor are novel P2Y12 inhibitors that have been combined with aspirin to become the first-line initial DAPT following ASC. This treatment has been extended to 1 year. A reduction in ischaemia has been found during the first 30 days as a result of this DAPT regimen, yet during long-term maintenance treatment a significant increase in bleeding risk was reported.

Investigators in the TOPIC study administered a newer P2Y12 inhibitor administered with aspirin for 30 days after a PCI for ASC. Following this, maintenance DAPT with clopidogrel plus aspirin was used. The aim was to investigate whether this would lead to reduced risk of bleeding without any ischaemic adverse effects.

The study enrolled 646 ACS individuals who were undergoing PCI. These individuals were treated for 1 month with a new P2Y12 inhibitor plus aspirin. They were then randomised to either continue with this therapy or change to aspirin (75 mg) plus clopidogrel (75 mg). The combined primary endpoint was death, bleeding (classification of ≥2 with Bleeding Academic Research Consortium [BARC]), stroke, and urgent revascularisation. After 1 year, this was reported to be 52% lower for individuals who switched to aspirin plus clopidogrel, in comparison to individuals who continued to receive a new P2Y12 inhibitor plus aspirin (13.4% with switched DAPT versus 26.3% with unchanged DAPT; hazard ratio [HR]: 0.48; 95% confidence interval [CI]: 0.34–0.68; p<0.01).

Ischaemic events between the two dual antiplatelet regimens were reported to have no difference, as 9.3% of individuals had an ischaemic event on switched DAPT versus 11.5% individuals on unchanged DAPT (HR: 0.80; 95% CI: 0.50–1.29; p=0.36). Moreover, individuals who switched DAPT demonstrated a 70% lower bleeding rate, compared to those unchanged (4.0% versus 14.9% at 1-year; HR: 0.30; 95% CI: 0.18–0.50; p<0.01).

Dr Cuisset expressed his optimism for the study: "This strategy could be proposed in ACS patients. We think that this trial could change practice."

> "This strategy could be proposed in ACS patients. We think that this trial could change practice."

Excellent Clinical Outcomes Displayed for Two Transcatheter Aortic Valve Implantation Systems

EXCEPTIONAL safety and efficacy profiles for two self-expanding transcatheter aortic valve implantation (TAVI) systems were displayed in two clinical trials, the results of which were presented in a EuroPCR press release dated 16th May 2017.

Firstly, the ADVANCE clinical trial analysed the performance of the CoreValve™ System (Medtronic, Dublin, Ireland) in 465 real-world patients with severe aortic stenosis. At 5-year follow-up, the patients had sustained haemodynamic improvement (9.7 mmHg mean gradient at discharge; 8.8 mmHg mean gradient at 5 years), and 81% were classified as New York Heart Association (NYHA) Class I or II. Survival data in a higher-risk patient group were in line with other 5-year TAVI data in similar high-risk patient groups.

"As TAVI continues to be evaluated in lower-risk patients, the ability to demonstrate sustained valve durability over time is of increasing importance," stated Prof Axel Linke, Heart Center, University of Leipzig, Leipzig, Germany, principal investigator of the ADVANCE study.

To examine the CoreValve Evolut™ R TAVI system (Medtronic), a cohort of 1,038 patients with a mean Society of Thoracic Surgeons Predicted Risk of Mortality estimate of 5.5% were enrolled in the Evolut R FORWARD clinical study. This was a global, single-arm, prospective study covering 53 centres over four continents. At 30 days post-implant, a high survival rate (98.1%) and low rate of disabling stroke (1.8%) were displayed. Haemodynamic performance was also very high, with a reduction in the mean aortic valve gradient from 41.7±16.1 mmHg at baseline to 8.5±5.6 mmHg at discharge.

> "As TAVI continues to be evaluated in lower-risk patients, the ability to demonstrate sustained valve durability over time is of increasing importance."

"The FORWARD results with a large patient cohort are encouraging, as these data support the clinical safety and effectiveness of the Evolut R System," commented Prof Eberhard Grube, Center of Innovative Interventions (CIIC), University Hospital Bonn, Bonn, Germany.

Overall, these clinical trials add to the evidence that the CoreValve and Evolut R systems achieve high survival rates, excellent haemodynamics, and low rates of stroke in patients with severe aortic stenosis, providing confidence to heart teams in their ability.

Transcatheter Aortic Valve Implantation Demonstrates Lower Stroke Risk Than Surgical Aortic Valve Implantation

THE RISK of early neurological complications, such as stroke, has been found to be lower in individuals at intermediate risk for surgery when treated with transcatheter aortic valve implantation (TAVI) surgery compared with those treated with surgical aortic valve replacement. The findings from the large, randomised SURTAVI trial were shared on 18th May in a press release issued at EuroPCR 2017.

Individuals at intermediate risk for surgical mortality requiring aortic valve replacement are being treated with TAVI more frequently. However, long-term morbidity and an increased risk of death are also factors that individuals undergoing valve replacement are presented with.

The trial recruited 1,600 patients, all with intermediate surgical risk and severe, symptomatic aortic stenosis, and randomised them to aortic valve replacement with surgery or TAVI. Individuals who were suspected of displaying neurological events after their procedure were referred to a stroke specialist or neurologist for further evaluation.

At 30 days, it was reported that incidents of early stroke were lower in patients undergoing TAVI (3.3%), compared to individuals having surgical aortic valve replacement (5.4%; p=0.031). Patients treated with TAVI compared to surgery demonstrated lower stroke incidences at 2 years (6.3% versus 8.0%; p=0.143). Results also confirmed that 1-year mortality was similar for surgery individuals with stroke or encephalopathy at 30 days compared to TAVI patients.

> "This is the first time that there has been shown to be a lower stroke rate with TAVI compared to surgery."

Quality of life was also found to be lower at 30 days for patients with early stroke compared to individuals not having a stroke, based on the SF-36 physical summary. TAVI patients with stroke had a quicker improvement in quality of life; however, it was reported to be similar at 6 months regardless of procedure type.

Prof Pieter Kappetein, Erasmus MC, Rotterdam, Netherlands, expressed the importance of this study, explaining: "This is the first time that there has been shown to be a lower stroke rate with TAVI compared to surgery."

Exciting Results of Bioresorbable Stent Technologies Show Need for Further Development

BIORESORBABLE stent (BRS) technologies were a major topic of discussion at the EuroPCR Congress 2017, with a statement issued by the EAPCI and results of late-breaking trials displayed throughout the event, as described in a EuroPCR press release dated 19th May 2017.

Following questions regarding the safety of a particular BRS, EuroPCR issued a statement to encourage further developments in these devices. They stated that the continued development of BRS technologies was crucial in order to improve this approach for future patients. They outlined the encouraging results of devices evaluated during the congress but urged that current-generation BRS should not be used ahead of metallic drug-eluting stents in routine clinical practice until concerns about their limitations are assuaged.

> This is a clinical breakthrough as no other BRS technology has been successful in achieving such impressive results and, at the same time, degrading in 6 months with near complete resorption (mass loss) in 1 year.

The results of several BRS trials were reported at EuroPCR. The RENASCENT II study was a prospective multicentre trial assessing 9-month clinical and imaging outcomes of the APTITUDE® BRS (Amaranth Medical, Mountain View, California, USA) stent, a novel ultra-high molecular weight poly-L-lactide BRS.

This reported excellent results: no events in 60 patients treated for single lesion coronary artery stenosis at 1-year follow-up, and excellent wall apposition and full homogenous endothelial wall coverage was demonstrated with optical coherence tomography.

In the DESolve Nx Study, which sought to evaluate imaging outcomes and 4-year clinical and imaging results from the DESolve® Novolimus-Eluting Coronary BRS (Elixir Medical Corporation, Milpitas, California, USA), a mean lumen gain of 9% was shown at 6 months and an angiographic late luminal loss of 0.2 mm. The study was a prospective registry including 126 patients.

"This is a clinical breakthrough as no other BRS technology has been successful in achieving such impressive results and, at the same time, degrading in 6 months with near complete resorption (mass loss) in 1 year," stated lead author Dr Stefan Verheye, ZNA Middelheim, Antwerp, Belgium.

The positive results further underline the need for this approach to be developed in the future to complement other devices, to achieve optimal outcomes in patients.

Encouraging Trial Results for First Fully-Dissolving Heart Stent

RESULTS from two randomised clinical studies, ABSORB China and ABSORB Japan, were announced by Abbott, Chicago, Illinois, USA, on 16th May at EuroPCR 2017. These trials were comparing Absorb (Abbott), which is the first heart stent that completely dissolves, with XIENCE (Abbot). Dr Charles Simonton, Chief Medical Officer for Abbott's vascular business shared his views on these studies: "Three-year results from the ABSORB China and ABSORB Japan trials provide reassuring data about the longer-term efficacy and safety of Absorb."

Safety and efficacy results from the ABSORB China trial (N=475) continued to be favourable from 2 years to 3 years. Indeed, there were no new reports of stent thrombosis in either study arm since 2-year follow-up.

Furthermore, at 3 years, the cumulative rates of target lesion failure (TLF) were comparable between Absorb and XIENCE. There was no significant difference stated. Absorb TLF rates were 5.5% compared to 4.7% for XIENCE (p=0.68). With regard to stent thrombosis, there were also no statistically significant differences reported: 0.9% for Absorb versus 0.0% for XIENCE (p=0.50). Dr Simonton announced that: "Three-year results of the ABSORB China study supports that implanting Absorb in appropriately sized vessels positively affects patient outcomes."

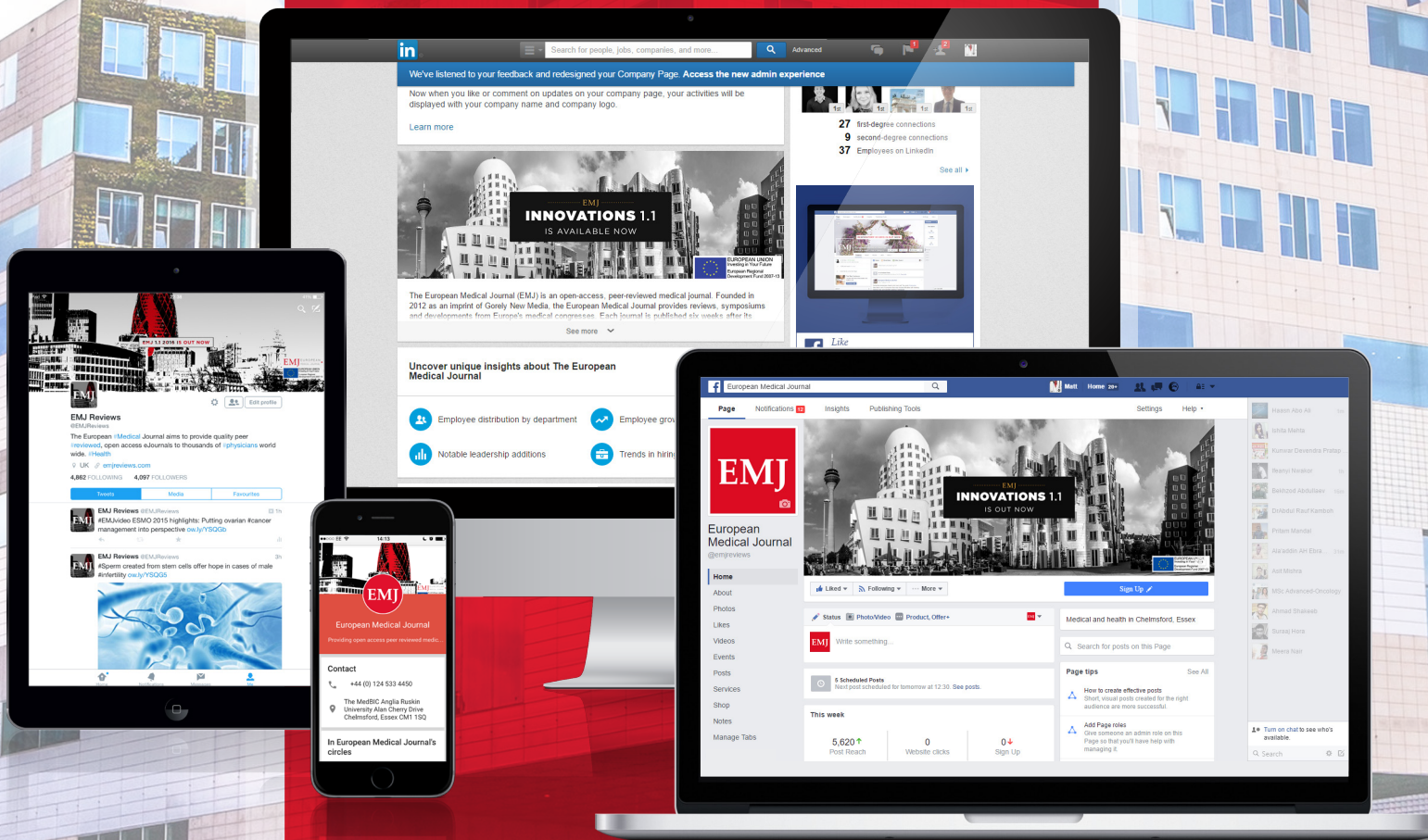
In the ABSORB Japan trial (N=400), the Absorb and XIENCE arms were comparable, and no statistical differences at 3 years for efficacy and safety were reported. It should be noted that current standards for the implantation of Absorb classify 14% of vessels treated in the trial to be too small. Safety events were similar across both arms between 2 and 3 years. TLF for Absorb and XIENCE were both 1.6% (p=1.00). At Day 810, one incidence of stent thrombosis occurred in the Absorb arm due to an under expanded scaffold.

Cumulative 3-year adverse events for Absorb were reported to be higher than XIENCE due to high adverse event rates during the initial first 2 years of the study; however, these were not statistically significant. The rate of probable/definite stent thrombosis for Absorb was 3.6% compared to 1.6% for XIENCE (p=0.35). Absorb TLF rates were 8.9%, whereas XIENCE TLF rates were 5.5% (p=0.23). The next set of results expected to be announced are from the ABSORB IV study.

> "Three-year results from the ABSORB China and ABSORB Japan trials provide reassuring data about the longer-term efficacy and safety of Absorb."

EMJ EUROPEAN MEDICAL JOURNAL

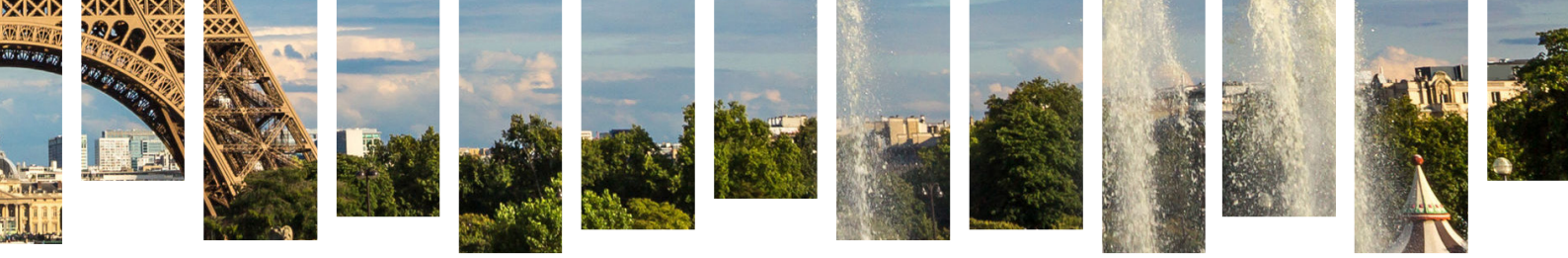
INTERACT WITH US ON SOCIAL MEDIA



europeanmedical-journal.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

LATEST **NEWS** • **CONGRESS** UPDATES • JOIN **DISCUSSIONS** • **AWARENESS** CAMPAIGNS



Magdy Abdelhamid

Professor of Cardiovascular Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt.

Q: What inspired you to pursue a career in cardiovascular medicine? What aspect particularly piqued your interest in this field?

A: When I was a student at the Faculty of Medicine, Cairo University, Giza, Egypt, I was interested in general medicine and I used to read a lot about internal medicine. I always contributed to discussions, especially on the topic of cardiovascular medicine, and after graduation I spent 2 months of my speciality as a house officer within the cardiology department. Since that time, my interest in cardiology continued to increase more and more, and I was then assigned my residency in this department.

Q: Could you give us a brief understanding of the roles and responsibilities that you have in your role at Cairo University, Egypt?

A: My responsibilities include:

- Teaching undergraduate and postgraduate students
- Supervision of candidates who register for Master's and doctorate degrees in cardiovascular medicine
- Clinical rounds in cardiology (outpatient and inpatient)
- Being the Director of the Catheterisation Laboratory (2010–2012)
- Being the Director of the Heart Failure Unit within the Cardiology Department, Cairo University
- Acting as the principal investigator at Cairo University for a multicentre international study, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA), the results of which may change the practice of medicine in management of stable coronary artery disease
- Acting as the principal investigator at Cairo University for the International Registry to assess mEdical Practice with lOngitudinal obseRvation for Treatment of Heart Failure (REPORT HF)

Q: How would you like to see the field of cardiovascular medicine develop over the next 10 years? Do you feel that this is achievable?

A: I would like to see the application of more innovative strategies for treatment of some cardiovascular diseases such as heart failure (HF); although we know the molecular and structural abnormalities associated with HF, we do not have a definitive treatment yet and still have high mortality and hospitalisation due to HF. Also, I hope to see more research related to stem cell therapy for cardiovascular disease.

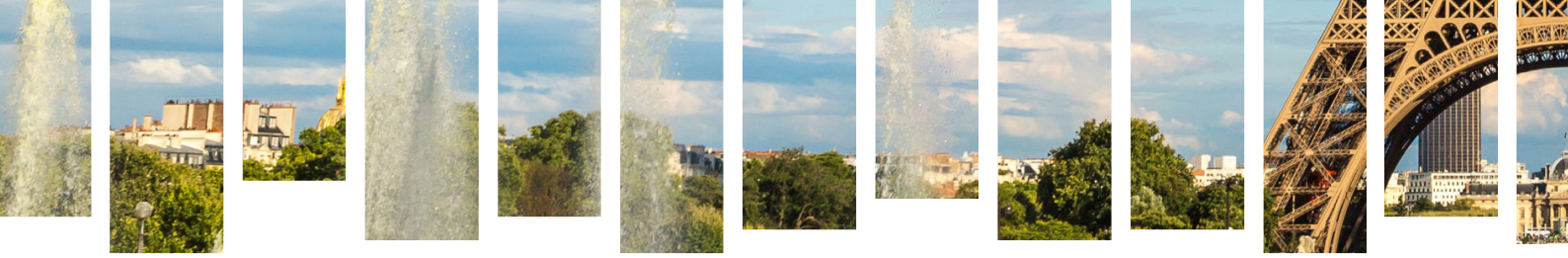
Q: What types of data would you like to see collected in order to evaluate mechanisms of intervention in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI)?

A: We need more randomised studies focussing on hot issues related to acute coronary syndrome (STEMI and NSTEMI).

Q: Could you explain the biggest challenges faced in achieving successful interventions in STEMI and NSTEMI? Are there ways in which policymakers can assist with these challenges?

A: Successful interventions are linked to the use of novel equipment and devices that can help in tackling difficult lesions, such as chronic total occlusion and left main and bifurcation lesions. Haemodynamic support using devices such as Impella® (Abiomed, Danvers, Massachusetts, USA) in critically ill patients is also important.

> "We need more randomised studies focussing on hot issues related to acute coronary syndrome..."



> I think it is important for healthcare professionals to be members of a society or a committee that will help them gain experience in their speciality, attend scientific meetings, and update their existing knowledge.

Q: Could you tell us more about your research comparing primary percutaneous coronary intervention (PCI) versus complete revascularisation in patients with STEMI?

A: Whether to adopt the culprit-only strategy during primary PCI or total revascularisation is a debatable issue, and the results of studies differ from one trial to another, but there are now ample data to suggest that PCI of the non-culprit vessel during or shortly after successful primary PCI is safe, but the benefit appears to be confined to reduction in ischaemia rather than improved endpoints such as death, myocardial infarction, or stroke.

Q: You are also a board member of the Egyptian Society of Cardiology. What duties does this role require and what are your main responsibilities?

A: It is a hard job because I am responsible for all international communications, in addition to the preparation and chairing of sessions for many scientific activities. I am the national co-ordinator in Egypt for the European registry for valvular heart disease. I am responsible for the monthly meeting agenda for the Board of the Egyptian Society of Cardiology in addition to many other assignments, and finally I was appointed chairman of the working group of heart failure in March 2017.

Q: How important do you feel it is for other healthcare professionals to be members of committees and societies?

A: I think it is important for healthcare professionals to be members of a society or a committee that will help them gain experience in their speciality, attend scientific meetings, and update their existing knowledge.

Q: What do you feel are your greatest accomplishments throughout your career?

A: I have received a number of awards and prizes, including:

- The Cairo University Incentive Award for Medicine (2003)
- The Certificate of Appreciation and Medal of Excellence, from the Egyptian Medical Syndicate in Cairo (2003) awarded for excellence in service to the medical community
- The Harvard Medical School Certificate for Excellent Performance and Successful Contribution to the Programme of Heart Failure, Brigham and Women's Hospital, Boston, Massachusetts, USA (1999)

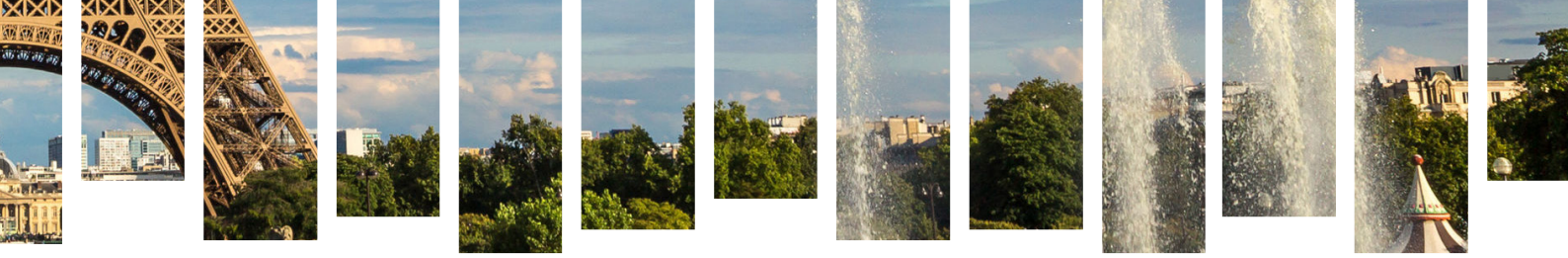
I am also currently:

- General Secretary of the Egyptian Society of Cardiology (March 2016–present)
- Secretary of the scientific committee upgrade for Cardiology, Egyptian Universities Promotion Committees (February 2013–present)
- Chairman of the working group of heart failure, the Egyptian Society of Cardiology, 2017

I have presented at several international conferences and have published many original manuscripts in several peer-reviewed journals. I have also contributed to cardiology books, including the Heart Failure Manual and the Egyptian Hypertension Society Guidelines (2002 and 2015, respectively).

Q: What advice would you like to give anyone hoping to specialise in the field of interventional cardiology?

A: Anyone hoping to specialise in the field of interventional cardiology should have an interest in the field, study hard from the beginning, follow their mentor, form a good relationship with their colleagues, and respect their patients and all medical staff.



Sanjog Kalra

Associate Director, Interventional Cardiology Training Program, Albert Einstein Healthcare Network, Philadelphia, Pennsylvania, USA.

Q: We understand that you have an interest in the revascularisation of chronic total occlusions. What particularly piqued your interest in this area?

A: I have always been drawn to challenges in clinical care. In my experience, when challenges are encountered, need and opportunity are not far away. Chronic total occlusions (CTO), one facet of the 'Complex and High Risk Intervention' subset of procedures, is one such area in need of extra support, as patients are often left untreated despite clear clinical indications for treatment due to a lack of knowledge, skills, and familiarity with newer technologies on the part of operators. This confluence of the opportunity to make an impact in the care of an undertreated population, the chance to develop additional skills in coronary intervention, and the prospect of participating in a developing sub-speciality within coronary intervention, has driven my interest in CTO and complex percutaneous coronary intervention (PCI).

Q: Could you give us a brief overview of your role as Associate Director of the Interventional Cardiology Training Program? Please give us an insight of your roles and responsibilities.

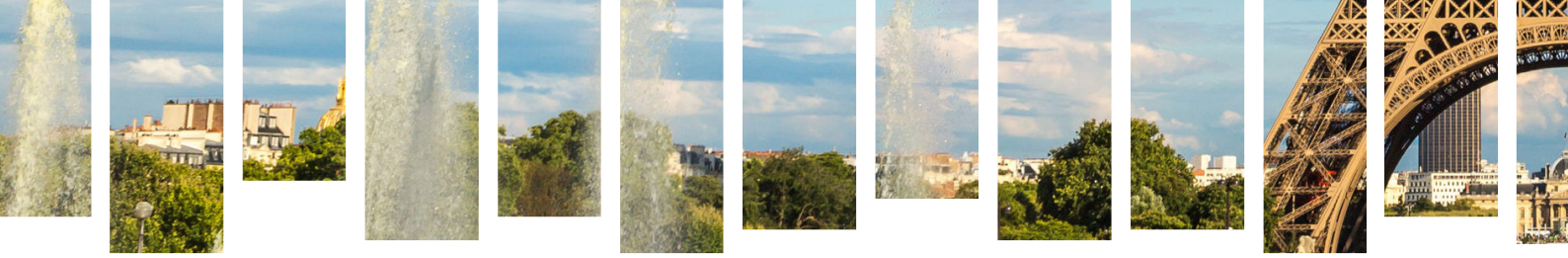
A: As the Associate Director of the Interventional Cardiology Training Program at our institution, I am privileged to help manage one of our most important duties as physicians, which is the training of our current and future colleagues. In this role, I manage the catheterisation laboratory (cath lab) rotation for all general cardiology fellows during their basic diagnostic catheterisation training, including their weekly cath educational conferences. For our interventional fellows, I am one of the five attending interventionalists at our institution who serve as teachers and mentors during their training. Participating in fellow education is undoubtedly one of the most cherished parts of my job.

Q: What is the importance of inspiring, relating to, and connecting with others within this field? How vital is the correct training, and how does this affect the future of interventional cardiology?

A: The Complex and High-Risk Interventional Procedure (CHIP) field within coronary intervention is growing rapidly. As the median age and medical complexity of patients presenting to cath labs steadily rises, interventionalists are being called upon to bring all of their knowledge, skills, and tools to bear to achieve success in these cases. Most critical of the tools at one's disposal is a network of colleagues (both near and far), with whom cases can be discussed and from whom learning can occur. These relationships, through which honest clinical and academic discussions can occur, are fundamental to the evolution of individual skills and to our speciality as a whole. Thankfully, through great national and international meetings and social media networks, these connections are easier to make and maintain.

Formal and comprehensive training is critical to the success of any interventionalist, particularly if one is interested in highly-specialised procedures, such as transcatheter valve replacements or CTO PCI. In formal training environments, proctors and mentors are able to gradually impart critical skills for success, all behind the safety of an 'iron shield' for the learner and the patient: an experienced set of hands and decision making algorithms that can prevent complications and deal with them efficiently when they arise.

> "I have always been drawn to challenges in clinical care. In my experience, when challenges are encountered, need and opportunity are not far away."



> As the field of interventional cardiology turns 40 this year, I find myself reflecting on the incredible growth that has occurred...

Q: Are there any innovative technologies that will be launched in the near future that particularly interest you, and could help the field of interventional cardiology progress?

A: As we become increasingly familiar with coronary physiology, structure, and function, the basis for intervention is changing from angiographic to ischaemic and imaging-based lesion assessment. Innovative technologies designed to identify the 'functional significance of lesions', including instantaneous wave-free ratio (iFR) and novel fractional flow reserve (FFR) devices are sure to drive a new wave of 'targeted interventions' to achieve maximal benefit for patients. In addition, novel intracoronary imaging systems, such as optical coherence tomography (OCT) and high definition intravascular ultrasound (IVUS), have already revolutionised our understanding of coronary structure and lesion characteristics. As these devices improve, perhaps with forward facing OCT catheters, virtual histology, equipped IVUS devices and computerised tomography (CT) FFR imaging, outcomes of coronary intervention may also continue to improve.

Q: Where would you like the field of interventional cardiology to be in the next 10 years? How achievable do you think this is?

A: As the field of interventional cardiology turns 40 this year, I find myself reflecting on the incredible growth that has occurred in our speciality since Andreas Grüntzig's revolutionary ideas and techniques. Even through the last 10 years, progress has been made from the first generation of drug-eluting stents, to today's highly sophisticated and improved devices; our field has seen tremendous technological advancements and improvements in outcomes. I am certain that disruptive innovations, such as the development of new, improved (and smaller) percutaneous haemodynamic support technologies will continue to occur and will improve the outcomes of patients with complex coronary disease and those with frank cardiogenic shock, in whom the results of our therapies remain suboptimal.

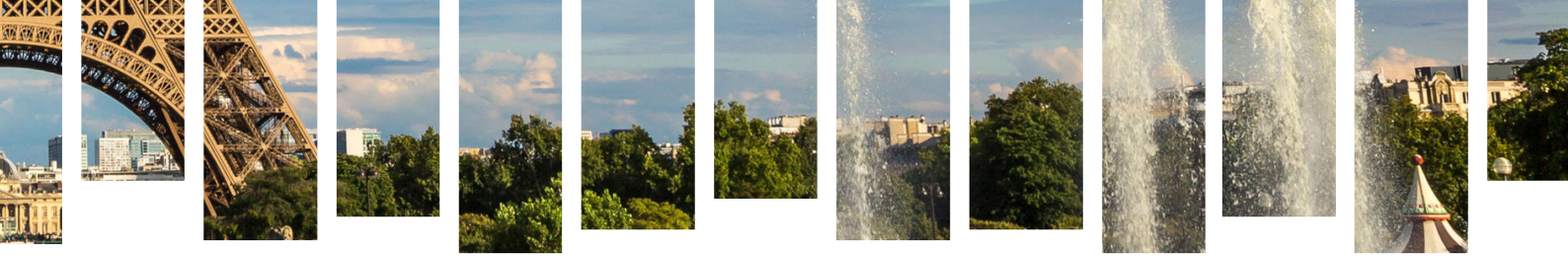
Q: Could you give us an insight into your research on haemodynamic support in high-risk percutaneous coronary intervention? How has this area changed since you began your career?

A: One of the greatest challenges in complex intervention has been the approach to patients whose haemodynamics are tenuous or unstable. In the treatment of these patients we often (and sometimes unavoidably) make patients ischaemic, which may transiently contribute to their instability. Haemodynamic support devices offer a potential avenue of stability for these patients that may allow durable and complete treatment of their coronary lesions.

One such group of patients are those with CTO and ischaemic cardiomyopathy. In CTO PCI, collateral channels are often used as conduits to reach and ultimately recanalise occluded vessels. With the transient occlusion of collaterals during gear delivery and manipulation in CTO PCI, haemodynamic embarrassment can occur, particularly in patients without adequate reserve. We are currently studying the use of haemodynamic support devices in this population as tools to maintain stability during these procedures. The results from this multicentre registry are forthcoming, including the outcomes of these procedures and insights into the patients most likely to benefit from the use of haemodynamic support technologies in CTO PCI.

Q: Out of all the achievements throughout your career, what would you say is your proudest accomplishment?

A: I am most proud of being selected as the first formally trained CHIP fellow at Columbia University, New York City, New York, USA (the birthplace of the CHIP training initiative). This tremendous privilege offered me the opportunity to train with true luminaries in our field, who instructed



me in the use of cutting-edge technologies and techniques to treat the most complex of coronary lesions. This training has shaped nearly every aspect of my current career, from my academic and research interests to my clinical practice. It has most importantly provided me with a community of senior colleagues whom I can rely on for advice and guidance at any time.

Q: Finally, if you could give yourself one piece of advice that you wish you had when you started your career, what would it be?

A: I was fortunate to have trained with truly exceptional mentors, who gave me a host of useful advice as I started my career. As a relatively new interventionalist, I often remind myself of these pearls each time I meet a high-risk patient whose particular complexities present unfamiliar challenges. Chief amongst them is the CHIP mantra: "The indications for treatment do not change just because the lesion is harder to treat". I remind myself of this principle daily and from it, I find the motivation to work as hard as I can to help and improve patient's lives.

Julinda Mehilli

Director, Interventional Cardiology, Munich University Clinic, Ludwig Maximilians University of Munich, DZHK, partner site Munich Heart Alliance, Munich, Germany.

Q: What was it that first attracted you to study interventional cardiology?

A: Interventional cardiology represents the field within cardiology in which accurate diagnoses and minimally invasive treatment of cardiac diseases are closely linked. Furthermore, it is a rapidly changing and growing field characterised by high-frequency innovations.

Q: Could you give us a short summary of the roles and responsibilities that you have in your role as the Director of Interventional Cardiology at the Ludwig Maximilians University of Munich?

A: There are four primary roles and responsibilities to note:

Firstly, in this position I am responsible for the standardisation of the workflow in the catheterisation laboratories. At the same time, I am responsible for the close interaction of this division with other divisions of cardiology, cardiac surgery, and the emergency care unit.

Secondly, I am responsible for keeping the quality of procedures performed up-to date and to increase the spectrum of procedures due to early uptake of innovations.

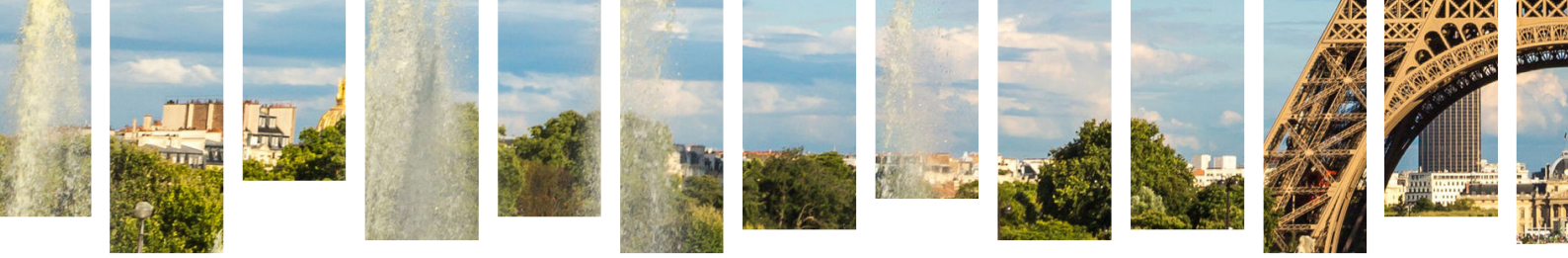
Thirdly, I am responsible for the structured education of the new generations of interventionalists.

Finally, I represent interventional cardiology outside the clinic, informing patients and general physicians about the possibilities it brings for the treatment of patients.

Q: In your opinion, what are the greatest issues cardiologists will face over the next decade? How would you like to see these issues dealt with?

A: The greatest issue to face will be treatment of a growing number of elderly multimorbid patients, which requires specialist expertise and interdisciplinary work. Moreover, it requires changes in the current infrastructure and workflow within and outside the clinics, as well as more specialised nursing personnel able to deal with this challenge.

> "The greatest issue to face will be treatment of a growing number of elderly multimorbid patients, which requires specialist expertise and interdisciplinary work."



Q: How do you believe policy makers and funding bodies could best direct their efforts to benefit interventional cardiologists?

A: Interventional cardiology is a tough 24/7 job. It is time-intensive and requires the expertise of the whole team including technicians and nurses; furthermore, it depends on the technical quality of the equipment. More specialised and adequately paid personnel, as well as flexible working hours, will increase the efficacy of work in this division. Less bureaucracy and greater willingness to invest, on a regular basis, in technical hospital equipment, as well as full digitalisation of patients' data, are directions the policy makers should focus on.

Q: You have recently published works that utilise large datasets. What benefits do you believe big data offers interventional cardiologists?

A: The truth lies in big numbers. Large datasets allow for clinically powered randomised trials, which are the instrument for testing new technologies and strategies in interventional cardiology.

Q: As one of the principal investigators of the Munich Heart Alliance (MHA), how important, in your opinion, is the formation of research networks?

A: Due to modern devices and drugs in cardiology, the outcome for patients after percutaneous cardiac interventions has been drastically improved. Large research networks are required to perform guideline-relevant trials. Furthermore, a direct translation from bench to bedside of innovative findings in medicine requires a close co-operation between research groups. These can be realised within a network like Munich Heart Alliance, a partner site of the German Centre for Cardiovascular Research (DZHK).

Q: Are there any challenges associated with the development of research networks and large-scale collaborations? If so, how do you believe these challenges can be managed?

A: Development of research networks is time-consuming and quite cost-intensive. Protected research time for physicians interested in research is required.

Q: Continuing the theme of big data and collaboration, are there any new ways of thinking or characteristics an interventional cardiologist needs in order to work within this model?

A: Interventional cardiologists are used to being collaborative and accurate in data documentation. Furthermore, being an invasive procedure, interventional cardiologists are particularly interested in documentation of the quality of work and possible events related to a procedure. I would say an interventional cardiologist thinks and has many characteristics of a clinical researcher in the way they work.

Q: Do you see any opportunities offered to the field of cardiology by wearable technologies?

A: Currently we lose a lot of time duplicating documentation in different databases, recording the same information about one patient. In addition, information exchange between different hospitals, departments, or healthcare professionals (general physicians and cardiologists) is based on paperwork or transferred in complex electronic ways. Wearable technologies help in transportation of digitalised patient data (virtual patients). Furthermore, it will increase the work efficiency within hospitals with no need for patient file transportation from one division to the other, aiding easy documentation of the procedures and implants (currently one patient in need of a stent implantation, pacemaker implantation, and a transcatheter aortic valve replacement will need three different passes!).

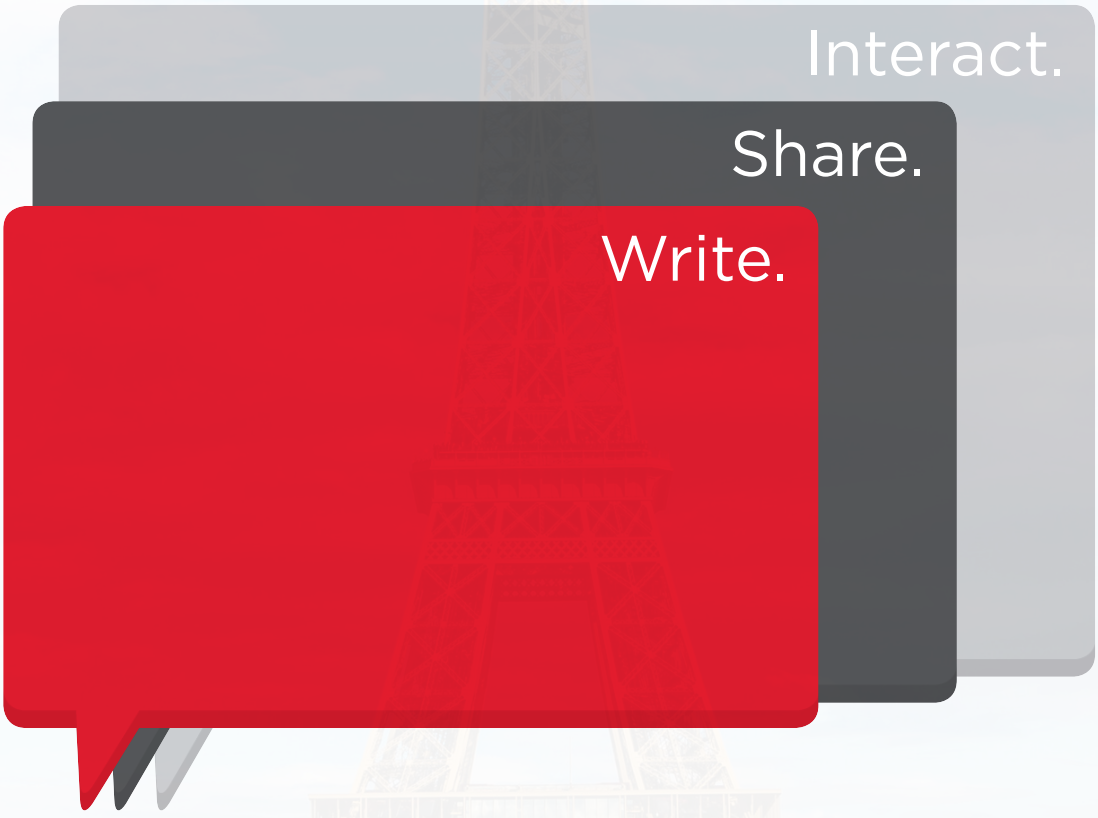
Q: What is the most important piece of advice you would give to someone hoping to specialise in interventional cardiology?

A: Be a hard-worker, be patient, curious, and open to innovations. Be flexible and be prepared to have less free time compared to a non-invasive physician!

> "Be a hard-worker, be patient, curious, and open to innovations."

EMJ EUROPEAN MEDICAL JOURNAL

Would you like to write for the EMJ blog?



Get involved today:
europeanmedical-journal.com/blog

europeanmedical-journal.com

EUROPEAN UNION
Investing in Your Future
European Regional Development Fund 2007-13

CLINICAL USE OF FFR_{CT} IN THE EVALUATION OF SYMPTOMATIC PATIENTS WITH INTERMEDIATE CORONARY ARTERY STENOSIS: CAN IT IMPROVE DIAGNOSIS AND REDUCE RADIATION RISK AND COST?

***Jeroen Sonck,[1] Kristof De Smet,[2] Johan De Mey[2]**

1. Department of Cardiology, Universitair Ziekenhuis Brussel, Jette, Belgium
2. Department of Radiology, Universitair Ziekenhuis Brussel, Jette, Belgium
**Correspondence to Jeroen.sonck@uzbrussel.be*

Disclosure: The authors have declared no conflicts of interest.
Citation: EMJ Int Cardiol. 2017;5[1]:34-35. Abstract Review No. AR1.

Keywords: Fractional flow reserve computed tomography (FFR_{CT}), non-invasive FFR, intermediate coronary artery disease (CAD), coronary CT angiography (CCTA), invasive coronary angiography cancellation, radiation risk, cost reduction.

Incidence of stable coronary artery disease (CAD) is expected to increase in the coming decades. Coronary angiography is the gold standard for the treatment of an acute coronary syndrome; however, its relevance as a first-line test in cases of stable CAD remains debatable. The European Society of Cardiology (ESC), American College of Cardiology/American Heart Association (ACC/AHA), and National Institute for Health and Care Excellence (NICE) guidelines on stable CAD suggest that non-invasive stress testing is the preferred diagnostic strategy among most stable patients. Only stable patients with the highest pretest probability, or those with signs of ischaemia on resting electrocardiogram (ECG), benefit from an immediate invasive approach.

Exercise stress testing, single-photon emission computed tomography (SPECT), and stress echocardiography are the most commonly used non-invasive tests, followed by cardiovascular magnetic resonance (CMR) and positron emission tomography (PET). These tests should identify the individuals who ought to undergo invasive coronary angiography. The major drawback for these non-invasive tests applies to their low specificity. The latter leads to an overuse of coronary angiography, with studies showing that <50% of patients sent for invasive angiography ultimately prove to have significant CAD.

Until recently, coronary CT angiography (CCTA) was commonly used to rule-out CAD depending on its high negative predictive value. The PROMISE and SCOT-HEART studies provided compelling evidence that CCTA is a safe tool for the diagnosis of stable CAD. Nevertheless, similar to other non-invasive tests, a substantial proportion of unnecessary invasive coronary angiographies (ICA) are executed as lesion severity, assessed by CCTA, shows an unreliable relationship to lesion-specific ischaemia and stenosis severity is often overestimated. As a result, invasive fractional flow-reserve (FRR) measurement is still the gold standard for the diagnosis of lesion-specific ischaemia in the cath lab.

Recently, a new tool has proven to be able to increase accuracy of CCTA in diagnosing obstructive CAD. Non-Invasive HeartFlow® FFR_{CT} (HeartFlow, Redwood City, California, USA) has been validated against invasive FFR in three trials: following the initial 2011 DISCOVER-FLOW study, the DeFACTO and NXT studies were published in 2012 and 2014, respectively. Subsequently, the outcome and resource trial, PLATFORM, proved that in patients with stable chest pain and planned invasive coronary angiography, care guided by CCTA and selective FFR_{CT} was associated with equivalent clinical outcomes and quality of life, as well as lower costs, compared with usual care over 1-year follow-up.

We performed a retrospective analysis of 48 patients, who presented with stable chest pain, positive exercise ECG, and intermediate (50–70%) CCTA stenosis, who were referred for

ICA and FFR examination. We determined the diagnostic accuracy of FFR_{CT} versus CCTA using FFR as the reference standard and evaluated the potential impact of clinical adoption of FFR_{CT} to guide clinical decision making. 'Unnecessary' ICA-FFR examinations were defined as ICA with measured FFR >0.80.

FFR_{CT} had higher diagnostic accuracy than CCTA (83% versus 29%) with higher positive predictive values (69% versus 29%) and a 6-fold reduction in false positives. Using an invasive FFR-guided therapy, 34/48 patients (71%) proved to have non-obstructive CAD (FFR >0.80) and were treated medically while only 14 patients (29%) had FFR ≤0.80 and were revascularised (8 percutaneous coronary interventions, 6 coronary artery bypass grafts). There were no major adverse cardiac events in the patients who were treated with optimal medical therapy. Use of a FFR_{CT}-guided strategy would have reduced unnecessary ICA-FFR procedures by 85%, thereby reducing the inherent risk of an invasive procedure. Assuming a cost of €1,000 per FFR_{CT} analysis, an overall cost reduction of 30% would have been achieved. Furthermore, radiation dose exposure would have been reduced by 63%, assuming an average dose of 2.1 mSv for CTA and 4.8 mSv for ICA.

In conclusion, utilisation of FFR_{CT} analysis in the evaluation of symptomatic patients with intermediate CTA stenosis results in fewer unnecessary invasive ICA-FFR examinations with significantly reduced costs, risks, and radiation dose exposure. These findings are in line with previously published data.

CORRELATION BETWEEN IFR AND FFR MEASUREMENTS AND ITS IMPACT ON THE LONG-TERM OUTCOME

***Jacek Bil,[1] Natalia Pietraszek,[1] Tomasz Pawłowski,[1] Robert J. Gil[1,2]**

1. Invasive Cardiology Department, Central Clinical Hospital of the Ministry of Interior, Warsaw, Poland
2. Institute of Experimental and Clinical Medicine, Polish Academy of Science, Warsaw, Poland
**Correspondence to biljacek@gmail.com*

Disclosure: The authors have declared no conflicts of interest.
Citation: EMJ Int Cardiol. 2017;5[1]:35-36. Abstract Review No. AR2.

Keywords: Fractional flow reserve (FFR), coronary artery disease, instantaneous wave-free ratio (iFR).

Instantaneous wave-free ratio (iFR) is a physiological index that can be obtained at rest without hyperaemic stimulation. iFR is conceptually different from fractional flow reserve (FFR), leading to lively scientific debate about this index.[1] Until recently, no data were available on the impact of iFR on clinical outcomes; there still are scarce data on the significance of the situation when these measurements (iFR and FFR) give different results.[2,3] Therefore, this poses a fundamental question: what should we do when one index is negative and the other one is positive? The aim of this study was to analyse the correlation between iFR and FFR measurements and its impact on long-term outcome.

We prospectively enrolled patients with stable coronary artery disease who qualified for FFR performance between January and August 2015. Patients had ≥50% stenosis in at least one coronary artery. FFR measurement was performed with the use of adenosine given in intracoronary (IC) boluses (120 µg, 240 µg, or 480 µg) or in intravenous infusion (140 µg/kg/min). Additionally, prior to FFR measurement, iFR measurement was performed. FFR and iFR measurements were performed with Verrata™ Pressure Guide Wire (Philips Volcano, Amsterdam, Netherlands). Clinical follow-up was planned at 12 months.

We enrolled 112 patients, in whom 267 iFR/FFR measurements were performed. The mean age of the population was 67±8 years. Diabetes mellitus was present in 31.25% of patients, hypertension in 62.5%, and 26.7% had a history of prior myocardial

infarction. Most measurements were performed in the left anterior descending artery and its branches (71.4%), followed by the left circumflex artery (48.2%), right coronary artery (44.6%), and left main artery (20.5%). One-vessel disease (1-VD) was found in 13.4% of patients, 2-VD in 61.6%, and 3-VD in 25%. Adenosine was given as IC boluses in 87.5% of cases.

Regarding the lesion severity, the correlation between iFR and FFR measurements was r=0.84 (p<0.01), r=0.82 (p<0.01), and r=0.79 (p<0.01) for 50–60%, 61–70%, and 71–89% of lesions, respectively. When analysing the advancement of the disease, the aforementioned correlation was as follows: r=0.85 (p<0.01), r=0.84 (p<0.01), and r=0.58 (p<0.01) for 1-VD, 2-VD, and 3-VD, respectively. Interestingly, we also found differences in correlation regarding the dose of adenosine given: r=0.83 (p<0.01), r=0.82 (p<0.01), and r=0.39 (p<0.01) for 120 µg IC, 240 µg IC, and 480 µg IC, respectively.

In our study, ˜35% of procedures ended with percutaneous coronary intervention/coronary artery bypass grafting. At 12 months, the major adverse cardiovascular events (MACE) rate was 6.5%, and the target lesion revascularisation rate was 4.7%. In logistic regression, patients had the best prognosis when both indexes were in agreement (both positive or both negative), and the worst prognosis was in the group with positive FFR and negative iFR, with an odds ratio of 2.93 for MACE.

Why are the results of this study important for physicians and patients? Firstly, this study shows that the use of high doses of adenosine is not necessary, and that further management based on such results does not improve the prognosis. Additionally, higher doses of adenosine are associated with an increased rate of adverse events. In terms of the possibility of changing medical practice, the results showed that stenting with positive FFR when other indexes (e.g. IFR) show no ischaemia is not always necessary.

REFERENCES

1. Toth GG et al. Standardization of Fractional Flow Reserve Measurements. J Am Coll Cardiol. 2016;68(7):742-53.

2. Götberg M et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med. 2017; 376(19):1813-23.

3. Davies JE et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med. 2017;376(19): 1824-34.

PRE-EXISTENT PROSTHESIS-PATIENT MISMATCH NEGATIVELY IMPACTS SURVIVAL FOLLOWING AORTIC VALVE-IN-VALVE PROCEDURE: RESULTS FROM THE VIVID REGISTRY

***Philippe Pibarot**

Québec Heart & Lung Institute, Département of Medicine, Laval University, Québec, Canada
**Correspondence to philippe.pibarot@med.ulaval.ca*

Disclosure: Research grants were received from Edwards Lifesciences and Medtronic.

Citation: EMJ Int Cardiol. 2017;5[1]:36-37. Abstract Review No. AR3.

Keywords: Transcatheter aortic valve replacement, aortic stenosis, valve-in-valve (ViV), Doppler-echocardiography.

BACKGROUND

Transcatheter valve-in-valve (ViV) implantation is a valuable alternative for the treatment of high-risk patients with degenerated bioprostheses. However, post-procedural high gradients are common following aortic ViV surgery and have been associated with increased mortality. We previously reported that small label size of the surgical valve was associated with increased mortality after ViV implantation.[1] However, it is unknown whether this association is, at least in part, related to a pre-existent permanent pacemaker (PPM), i.e. PPM

of the surgical valve.[2] The objective of this study was thus to examine the association between a pre-existent PPM and the occurrence of high post-procedural gradients and mortality survival after aortic ViV implantation.

PATIENTS AND METHODS

The Valve-in-Valve International Data (VIVID) Registry is a multicentre international registry of ViV procedures, which includes different transcatheter heart valve devices and valve positions.[3] This registry, which was started in 2010 by Dr Danny Dvir, prospectively collects data from centres in Europe, the USA, South America, Africa, Oceania, and the Middle East. In the study that we presented at EuroPCR 2017 in Paris, France, we reported the results of an analysis of the data of 1,168 patients included in this registry. Pre-existent PPM of the surgical valve was defined using the predicted valve effective orifice area (EOA), which is calculated by dividing the normal reference value of EOA for each given model and size of implanted prosthetic valve by the patient's body surface area. PPM was then graded using the criteria proposed by VARC-2:[4] i) overall PPM: indexed EOA <0.85 cm^2/m^2 if BMI is <30 kg/m^2, or <0.7 cm^2/m^2 if BMI is ≥30 kg/m^2; ii) severe PPM: indexed EOA <0.65 cm^2/m^2 if BMI is <30 kg/m^2, or <0.6 cm^2/m^2 if BMI is ≥30 kg/m^2. The primary study endpoint was 1-year mortality.

KEY FINDINGS

Among the 1,168 patients included in this analysis, 89 (7.6%) had a severe pre-existent PPM and these patients more frequently had high residual post-procedural gradients (mean gradient ≥20 mmHg). Patients with a severe PPM had significantly (p<0.001) higher 30-day (10.3% versus 4.3%) and 1-year mortality rates (28.6% versus 11.9%) compared to patients without a severe PPM. After adjusting for label surgical valve size, Society of Thoracic Surgeons (STS) score, renal failure, and diabetes, the presence of a pre-existent severe PPM remained associated with increased risk of 1-year mortality (odds ratio: 1.77; p=0.04).

CONCLUSIONS AND CLINICAL IMPLICATIONS

A pre-existent PPM of the failed surgical valve is independently associated with higher incidence of post-procedural gradients and with a 2.4-fold increased risk of mortality following ViV implantation. These findings provide strong support for the prevention of a severe PPM at the time of surgical valve replacement. They also emphasise the importance of systematic integration of the assessment of pre-existent PPM in the risk stratification and decision-making processes prior to ViV surgery. This identification of PPM can easily be achieved by calculating the predicted indexed EOA. The risk-benefit ratio should be carefully assessed in patients with evidence of severe PPM. Stent fracture of the surgical valve can be performed with the use of an oversized balloon prior to ViV surgery in these patients. This procedure has been proposed to reduce the detrimental haemodynamic and clinical impact of pre-existent PPM, but it requires further validation. The findings of this study also provide an impetus to manufacturers for the development of surgical bioprostheses with expansible stents.

To conclude, the best mechanic cannot convert a Ford Escort into a Ferrari. Similarly, the best interventional cardiologist cannot change a severely mismatched bioprosthesis into an aortic valve with exceptional haemodynamic performance.

REFERENCES

1. Dvir D et al.; Valve-in-Valve International Data Registry Investigators. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA. 2014;312(2):162-70.

2. Pibarot P, Dumesnil JG. Valve prosthesis-patient mismatch, 1978 to 2011: from original concept to compelling evidence. J Am Coll Cardiol. 2012;60(13):1136-9.

3. Simonato M et al. Transcatheter Replacement of Failed Bioprosthetic Valves: Large Multicenter Assessment of the Effect of Implantation Depth on Hemodynamics After Aortic Valve-in-Valve. Circ Cardiovasc Interv. 2016;9(6):pii: e003651.

4. Kappetein AP et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur J Cardiothorac Surg. 2012;42(5):S45-60.

THE NEW SMART NEEDLE TECHNIQUE: A NEW TOOL FOR DIFFICULT ARTERIAL PUNCTURES

***Paolo Pantaleo, Alessandro Elicio**

Istituto Clinico Ligure di Alta Specialità, Rapallo, Italy
**Correspondence to ppantaleo@gvmnet.it*

Disclosure: The authors have declared no conflicts of interest.
Citation: EMJ Int Cardiol. 2017;5[1]:38-39. Abstract Review No. AR4.

Keywords: Arterial cannulation, superficial femoral artery antegrade approach, below-the-knee (BTK) procedures.

INTRODUCTION

Antegrade superficial femoral artery puncture is by far the preferred approach in performing below-the-knee (BTK) percutaneous interventions. However, locating the proper arterial site is sometimes difficult, either because of excessive fat deposition in the groin or because of a hardly perceptible pulse due to severe obstructive lesions of the iliac or common femoral vessels. As a result, direct puncture can be frustrating, time-consuming, and often a cause of unjustified procedure prolongation and patient discomfort.

Angiographic visualisation of the target vessel using a different arterial access (contra-lateral leg, upper arm) is a frequently used option. However, this approach consistently prolongs procedure time, along with radiologic exposure; this implies an adjunctive arterial puncture, therefore increasing the likelihood of unnecessary complications and increasing contrast utilisation. As an alternative, the vessel can be visualised by an echo scan, which requires the presence of a dedicated sonographer in the cath lab, or an echo experienced interventionalist,[1] conditions that are not necessarily met in all cath labs.

We developed an easy, innovative technique that proved to be successful in the large majority of challenging cases reported here.

METHODS

All BTK procedures performed in our centre in the last 5 years have systematically employed an antegrade isocurrent approach, possibly combined with retrograde pedal or posterior tibial puncture in more challenging cases. Furthermore, to optimise timing and contrast utilisation and to minimise embolic complications, diagnostic and interventional procedures are performed using the ACIST-CVi® contrast injection system (ACIST Medical Systems, Inc., Eden Prairie, Minnesota, USA), which provides continuous haemodynamic monitoring and enables real-time pressure reading (Figure 1).

For the arterial puncture, we used a 70 mm 18G Cook needle (B. Braun Melsungen, Melsungen, Germany) directly connected to the arterial line of the CVi device. The needle is advanced through the skin about 1 inch proximally to the inguinal ligament with a 45° angle and a slightly medial orientation pointing at the homolateral big toe. As the needle enters the target vessel, the arterial pressure wave appears on the monitor screen, confirming cannulation (Figure 2). A few millilitres of contrast medium are then injected directly through the needle from the ACIST pump, allowing instant visualisation of the selected vessel. The procedure is then completed by advancing a guidewire according to the standard Seldinger technique.

RESULTS

Out of a total of 276 BTK consecutive procedures performed in the last 5 years, 24 were performed with the standard Seldinger[2] approach and 252 with the new smart needle technique. The Seldinger technique was performed essentially by junior interventionalists, before they were trained in the new procedure.

The reasons for choosing the latter were not related to excessive fat deposition, inability to feel the pulse, or inability to enter the artery; all the patients were approached with the same technique

due to the high success rate, independent from the anatomical properties.

The success rate of our method has been almost 100%; the only exceptions were vessel occlusions undetected by the preprocedural echo scan or extensive wall calcifications confirmed by angiography performed through the Cook needle; <1% of complications occurred unrelated to the technique but after sheath removal (12 haematomas, 8 pseudoaneurysms, no vessel dissections).

COMMENT

The new smart needle technique has proved to be highly successful and user friendly; the same procedure allows a direct visualisation of the selected artery, thus preventing unplanned cannulation either of the profunda or the common femoral artery. We recommend this easy, cheap, and effective approach in order to simplify the femoral artery puncture both for skilled and for less experienced BTK operators.

REFERENCES

1. Mustapha JA et al. Ultrasound-guided Arterial Access: Outcomes Among Patients With Peripheral Artery Disease and Critical Limb Ischemia Undergoing Peripheral Interventions. J Invasive Cardiol. 2016;28(6):259-64.

2. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography; a new technique. Acta radiol. 1953; 39(5):368-76.

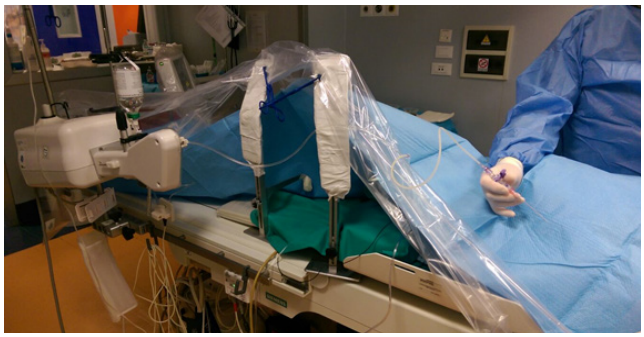


Figure 1: ACIST System connected to a Cook needle through the dye-saline injector/arterial line monitor.

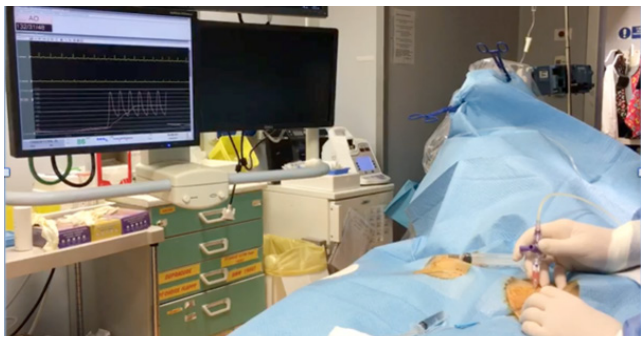


Figure 2: As soon as the arterial vessel has been cannulated, the arterial line appears all of a sudden on the previously flat curve in the polygraphic monitor.

TRANSCATHETER TRICUSPID VALVE REPAIR WITH AN ADJUSTABLE DEVICE: INITIAL RESULTS FROM THE MULTICENTRE FIRST-IN-MAN TRIAL

***Georg Nickenig,[1] Ralph Stephan von Bardeleben,[2] Karl-Heinz Kuck,[3] Ulrich Schaefer,[4] Jörg Hausleiter,[5] Stephan Baldus,[6] Alec Vahanian,[7] Azeem Latib,[8] Robert Schueler[1]**

1. Heart Center, University Hospital Bonn, Bonn, Germany
2. University of Mainz, Mainz, Germany
3. St. Georg Hospital Hamburg, Hamburg, Germany
4. University Heart Center Hamburg, Hamburg, Germany
5. University of Munich, Munich, Germany
6. Heart Center, University of Cologne, Cologne, Germany
7. Bichat-Claude Bernard Hospital, Paris, France
8. San Raffaele Hospital, Milan, Italy
**Correspondence to georg.nickenig@ukbonn.de*

Disclosure: The authors have declared no conflicts of interest.
Citation: EMJ Int Cardiol. 2017;5[1]:39-41. Abstract Review Number: AR5.

Keywords: Tricuspid regurgitation (TR), interventional annuloplasty, tricuspid valve.

The Edwards Cardioband™ Mitral Valve Repair System (Edwards Lifesciences Corporation, Irvine, California, USA) enables transcatheter implantation of an adjustable repair device in mitral or tricuspid valve position. The safety and performance for treatment of functional mitral regurgitation have been documented. We now report the initial safety and feasibility results for treatment of functional tricuspid regurgitation (TR).

Twenty consecutive patients with symptomatic TR Grade 3 or 4 were enrolled at five sites in Europe between October 2016 and April 2017. A comprehensive echocardiographic and computed tomography (CT) cardiac screening protocol was used in all patients to assess technical feasibility and to define anatomic landmarks, especially to evaluate the vicinity of the right coronary artery to the tricuspid annulus. All echocardiographic data were analysed by an independent core-lab. To date, 20 patients at high surgical risk (EuroSCORE II: 5% [2–13]) were prospectively analysed. In the cohort, 75% of patients were female, the mean age was 75 years (range: 56–84), and 95% of patients presented in New York Heart Association (NYHA) Class III–IV at baseline. A large proportion of treated patients presented with more-than-severe TR, so-called torrential TR, with vena contracta diameters of >1.5 cm as evaluated by transthoracic echocardiography.

Acute procedural success was defined as successful access, deployment, and positioning of the Edwards Cardioband implant and septo-lateral reduction during the procedure and at discharge, was achieved in all patients. The septo-lateral diameter was reduced by ˜27% in all patients after size adjustment of the Edwards Cardioband device. The reduction of septo-lateral diameters remained stable at 30-day follow-up. Echocardiography at 1-month follow-up showed a 44% reduction in Proximal Isovelocity Surface Area effective regurgitant orifice area (PISA EROA) (from 0.9±0.5 cm^2 to 0.5±0.3 cm^2) and a 29% reduction in vena contracta (from 1.4±0.2 mm to 1.0±0.5 mm).

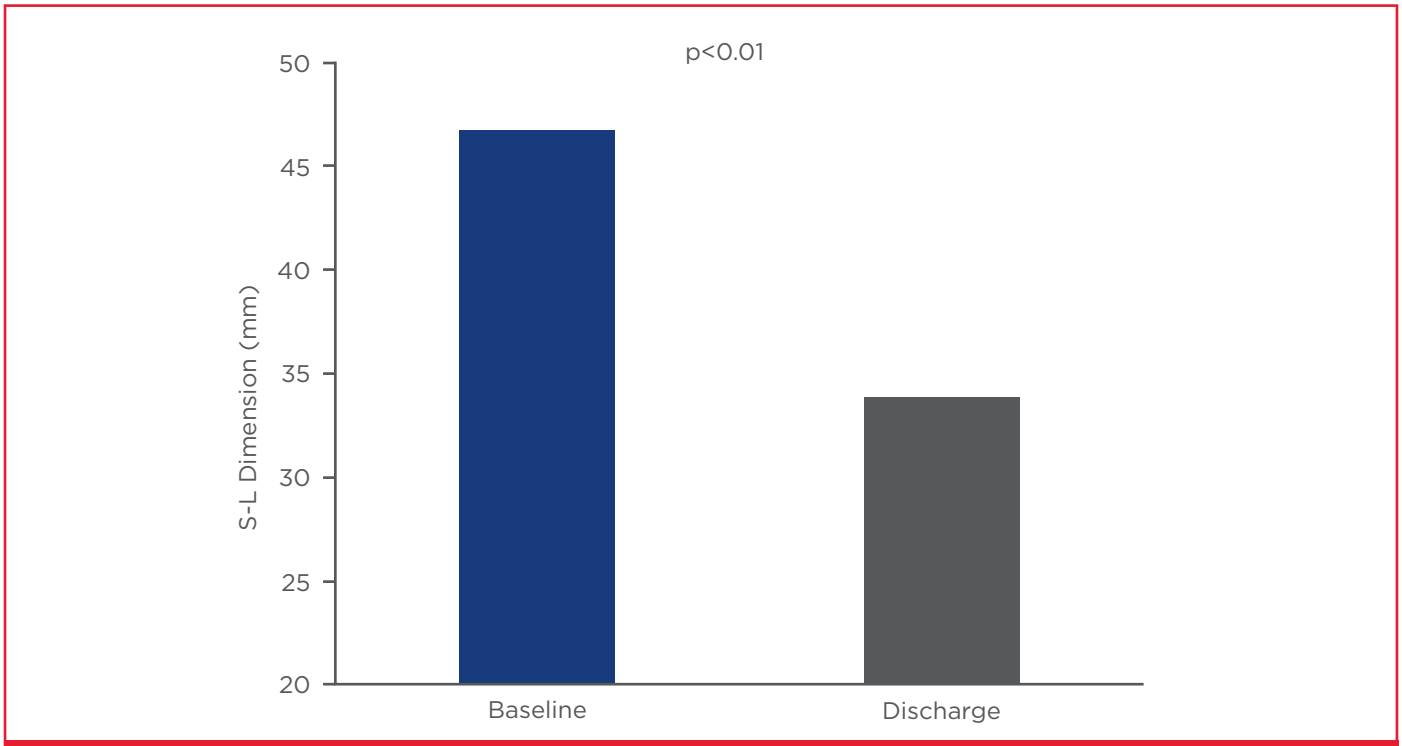


Figure 1: Acute changes in S-L diameter after tricuspid annuloplasty with the Edwards Cardioband device.
S-L: septo-lateral.

At 30 days, 73% of patients were in NYHA functional Class ≤2 and quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire, had significantly improved. Two patients died during the first 30 days after the procedure: the deaths were not directly related to the device or the procedure itself. No further major adverse events were reported for the first 30 days after the procedure.

Although the procedure is challenging for both interventional and imaging cardiologists, it is safe and effective for the reduction of functional TR. Patient selection using multimodality imaging is crucial. Intraprocedural echocardiographic guidance, specifically the use of three-dimensional echocardiography and real-time multiplanar reconstruction views, calculated from three-dimensional volumes of the tricuspid annulus, facilitate the procedure.

Of note, the development of a meaningful definition of the most relevant clinical endpoints for TR patients is urgently needed. Furthermore, TR assessment and grading algorithms need refinement.

Early 30-day outcomes suggest a high feasibility and a good safety profile of the Edwards Cardioband Mitral Valve Repair System in selected patients with significant and symptomatic functional TR. Effective acute reduction in TR severity was achieved in all patients and resulted in a significant reduction of septo-lateral diameters in all patients. Further long-term effects of the Edwards Cardioband Mitral Valve Repair System on TR and functional outcomes have to be validated in the ongoing first-in-man trial.

PREMATURE TICAGRELOR DISCONTINUATION IN PATIENTS UNDERGOING CORONARY REVASCULARISATION IN ROUTINE CLINICAL PRACTICE

Thomas Zanchin,[1] Fabrice Temperli,[1] Alexios Karagiannis,[2] Konstantinos Koskinas,[1] Markus Raesaenen,[3] Christian Zanchin,[1] Stephan Windecker,[1] *Lorenz Raeber[1]

1. Department of Cardiology, Bern University Hospital, Bern, Switzerland
2. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
3. Wihuri Research Institute, Biomedicum Helsinki, Helsinki, Finland
**Correspondence to lorenz.raeber@insel.ch*

Disclosure: Stephan Windecker reports having received research contracts to the institution from Abbott, Biotronik, Boston Scientific, Medtronic, Edwards, and St. Jude Medical. Lorenz Räber has received grants to the institution from St. Jude Medical. The other authors report no conflicts of interest.
Citation: EMJ Int Cardiol. 2017;5[1]:41-43. Abstract Review No. AR6.

Keywords: Coronary artery disease, percutaneous coronary intervention (PCI), antiplatelet therapy.

INTRODUCTION

Ticagrelor directly and reversibly inhibits the platelet P2Y12 receptor and exhibits a more potent and more predictable antiplatelet effect compared to clopidogrel.[1] The use of ticagrelor for the treatment of acute coronary syndrome patients has been shown to reduce death, myocardial infarction, and stroke, which has resulted in its approval for clinical use by the European Medicines Agency (EMA) in 2010.[2] However, although the safety and efficacy of ticagrelor is well established, the tolerability of ticagrelor appears to be impaired.[3] In Phase III trials, premature therapy discontinuation has been consistently reported to be 2–5% more

frequent among ticagrelor-treated individuals compared to clopidogrel-treated individuals.[4] As non-adherence to cardiovascular medication is a recognised and common problem that has been shown to be associated with impaired long-term outcomes,[5] we aimed to elucidate the frequency, reasons, and clinical implications of ticagrelor discontinuation in routine clinical practice.

METHOD

As of January 2009, all patients undergoing percutaneous coronary intervention (PCI) at Bern University Hospital, Bern, Switzerland, have been prospectively entered into the Bern PCI Registry.[6,7] The present analysis included all consecutive patients treated with ticagrelor who were enrolled between November 2011, when ticagrelor was introduced in Switzerland, and June 2014. Exclusion criteria were balloon treatment only and enrolment in a new clinical trial before 1-year follow-up. Demographic and clinical characteristics, procedural information, in-hospital outcomes, and 1-year follow-up data were systematically collected. A clinical event committee consisting of two cardiologists (and a third referee for cases of disagreement) adjudicated all events using original source documents.

RESULTS

Out of 4,837 consecutive patients prospectively enrolled into the Bern PCI Registry between November 2011 and June 2014, 1,278 patients were treated with ticagrelor. Within the recommended 1-year therapy duration, 152 patients (11.9%) prematurely changed to clopidogrel or prasugrel, and 60 patients (4.7%) prematurely discontinued ticagrelor therapy without replacement. Ticagrelor discontinuation occurred more frequently at a higher age, in female patients, in patients with renal failure, and following a history of previous PCI, and was less frequent among smokers.

The underlying reasons for premature ticagrelor therapy discontinuation were adverse effects (49%), oral anticoagulation (19%), preference by the general practitioner (10%), medical intervention (5%), and financial reasons (2%). Bleeding, dyspnoea, and gastrointestinal symptoms were responsible for 88% of adverse effects leading to premature ticagrelor discontinuation. Female sex and bleeding events were independent predictors for premature ticagrelor discontinuation, while smoking emerged as a predictive factor for adherence.

A total of 31 patients (2.4%) prematurely stopped ticagrelor therapy because of dyspnoea, of which 24 patients (77%) reported an immediate amelioration, while in 7 patients (23%) no improvement was observed. Patients with definite ticagrelor related dyspnoea more frequently had a previous PCI, a previous myocardial infarction, and were more often treated for stable angina.

With respect to clinical outcomes, there were no differences in all-cause death, cardiovascular death, myocardial infarction, target-vessel revascularisation, and the occurrence of stent thrombosis between patients who remained on ticagrelor and patients who prematurely discontinued ticagrelor. Patients who prematurely discontinued ticagrelor therapy suffered more frequently from Bleeding Academic Research Consortium (BARC) Type 2–5 and TIMI minor or major bleedings.

CONCLUSION

In this cohort study of patients undergoing PCI in routine clinical practice and treated with ticagrelor, premature discontinuation affected 16% of patients and did not associate with adverse cardiovascular outcomes. Adverse effects, onset of oral anticoagulation, and general practitioners' preference were the leading reasons for discontinuation.

REFERENCES

1. Cannon CP et al.; DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome. primary results of the DISPERSE-2 trial. J Am Coll Cardiol. 2007;50(19):1844-51.

2. Wallentin L et al.; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.

3. Gaubert M et al. Effect of ticagrelor-related dyspnea on compliance with therapy in acute coronary syndrome patients. Int J Cardiol. 2014;173(1):120-1.

4. Bonaca MP et al. Long-term Tolerability of Ticagrelor for the Secondary Prevention of Major Adverse Cardiovascular Events: A Secondary Analysis of the PEGASUS-TIMI 54 Trial. JAMA Cardiol. 2016;1(4):425-32.

5. Chowdhury R et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940-8.

6. Zanchin T et al. Preprocedural High-Sensitivity Cardiac Troponin T and Clinical Outcomes in Patients With Stable Coronary Artery Disease Undergoing Elective Percutaneous Coronary Intervention. Circ Cardiovasc Interv. 2016;9(6):e003202.

7. University Hospital Inselspital, Berne. CARDIOBASE Bern PCI Registry. NCT02241291. https://clinicaltrials.gov/ct2/show/NCT02241291.

OBSERVED VERSUS PREDICTED MORTALITY AFTER MITRACLIP® TREATMENT IN PATIENTS WITH SYMPTOMATIC HEART FAILURE AND SIGNIFICANT FUNCTIONAL MITRAL REGURGITATION

Cosmo Godino,[1] *Andrea Scotti,[1] Marianna Adamo,[2] Alessia Giannattasio,[1] Antonio Sisinni,[1] Mauro Chiarito,[1] Francesco Melillo,[1] Alessandro Beneduce,[1] Carlo Andrea Pivato,[1] Luca Arrigoni,[1] Anna Salerno,[1] Alberto Cappelletti,[1] Valeria Magni,[1] Stefano Stella,[1] Gabriele Fragasso,[1] Matteo Montorfano,[1] Eustachio Agricola,[1] Federica Ettori,[2] Alberto Margonato,[1] Antonio Colombo[1]

1. Cardiothoracic Vascular Department, San Raffaele Scientific Institute, Milan, Italy
2. Cardiac Catheterization Laboratory, Cardiothoracic Department, Spedali Civili, Brescia, Italy
**Correspondence to a.scotti@hotmail.com*

Disclosure: The authors have declared no conflicts of interest.
Citation: EMJ Int Cardiol. 2017;5[1]:43-45. Abstract Review No. AR7.

Keywords: MitraClip®, mitral regurgitation, heart failure, score.

The aim of this study was to compare the survival observed in patients with moderate-to-severe functional mitral regurgitation (FMR) and moderate-to-severe symptomatic heart failure (HF) treated with MitraClip® and the survival predicted by available HF scores: the Seattle HF Model (SHFM),[1] the HF calculator of the meta-analysis global group in chronic HF (MAGGIC),[2] and the Cardiac and Comorbid Conditions HF (3C-HF)[3] score. From 2008–2015, 171 patients with moderate-to-severe HF received MitraClip at two institutions. Patients were stratified in two subgroups according to the aetiology into non-ischaemic FMR (n=64) and ischaemic FMR (n=107). We compared the observed survival with that predicted by these scores at different time points for the overall population and for the two subgroups.

We found that: i) the survival predicted by the SHFM and the MAGGIC scores were consistent with those observed after MitraClip, with a trend of higher observed survival compared to that predicted by the MAGGIC, ii) the survival predicted by the 3C-HF score was lower than that observed after MitraClip (Figure 1), and iii) the results were consistent in the subgroup analysis for non-ischaemic and ischaemic FMR aetiology, with non-ischaemic patients showing the highest observed survival rates compared to the 3C-HF scores (Figure 2).

The SHFM and the MAGGIC scores are both validated in groups of patients without a predominance of severe MR and it is known that severe MR confers an increased risk of mortality.[4] Therefore, we can speculate that the score would have underestimated the mortality and we expected

that the observed survival would be lower than that predicted, because all patients included in our study were affected by severe MR. Instead, the observed survival after MitraClip was comparable with that predicted by the SHFM and MAGGIC scores, and therefore we can suppose that a certain benefit in terms of greater survival could have been conferred by the MitraClip procedure.

Considering that the 3C-HF score takes into consideration severe valve heart disease in the variables that contribute to outcome prediction, the observed survival after MitraClip is significantly higher than that predicted by the 3C-HF score and this can support the aforementioned hypothesis of outcome improvement after MitraClip, especially in non-ischaemic patients who seem to benefit the most from this procedure. Of course, a prospective, randomised, controlled trial is required to confirm these speculations.

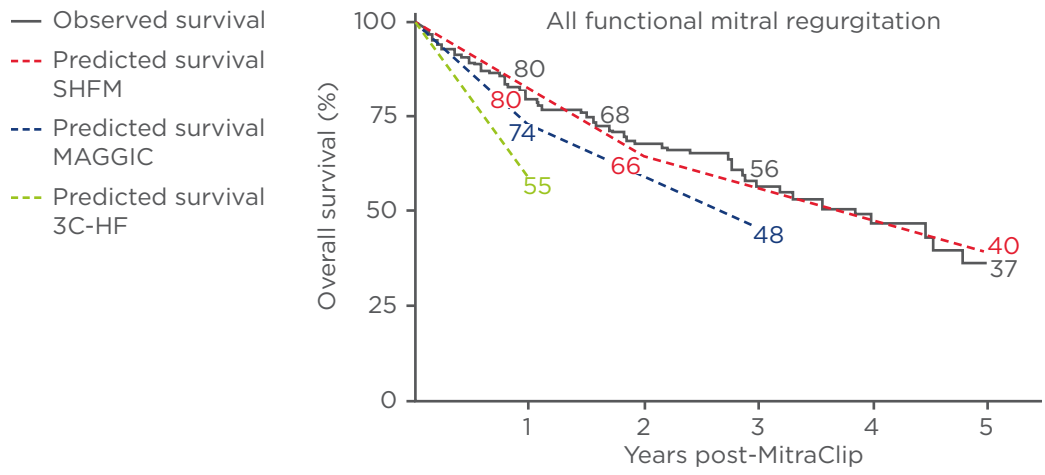


Figure 1: Kaplan–Meier analysis of overall survival compared to the predicted by the available HF scores in all FMR patients.
SHFM: Seattle Heart Failure Model; MAGGIC: meta-analysis global group in chronic heart failure; 3C-HF: Cardiac and Comorbid Conditions Heart Failure score; HF: heart failure; FMR: functional mitral regurgitation.

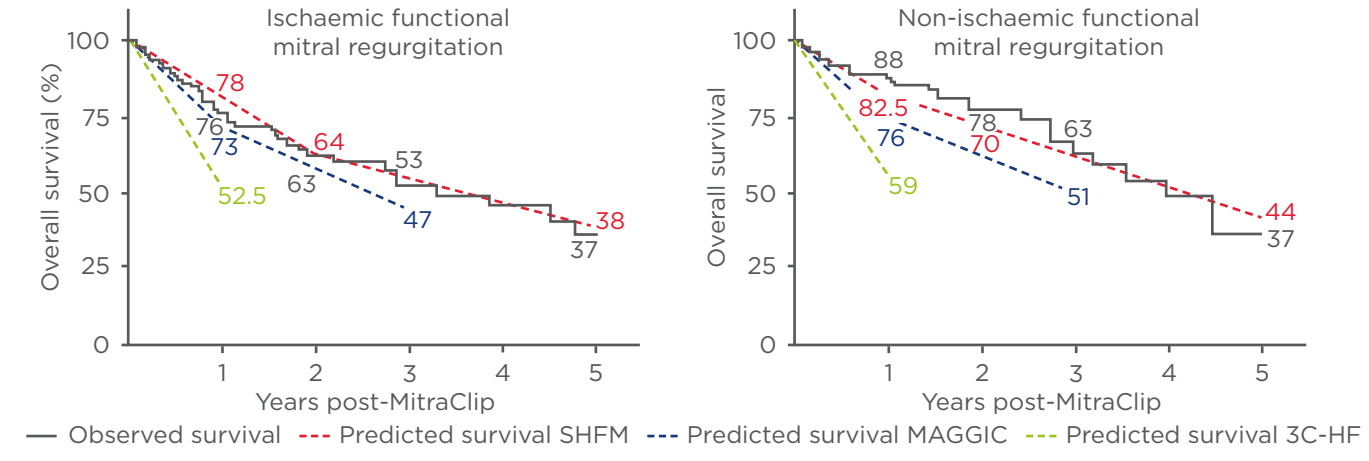


Figure 2: Kaplan–Meier analysis of overall survival compared to the predicted by the available HF scores in ischaemic (left) and non-ischaemic (right) functional mitral regurgitation patients.
SHFM: Seattle Heart Failure Model; MAGGIC: meta-analysis global group in chronic heart failure; 3C-HF: Cardiac and Comorbid Conditions Heart Failure score.

In conclusion, the survival outcome of patients with FMR and HF, after the MitraClip procedure, was better than that predicted by the 3C-HF score and similar to that predicted by the SHFM and MAGGIC scores.

REFERENCES

1. Levy WC et al. The Seattle Heart Failure Model Prediction of Survival in Heart Failure. Circulation. 2006;113(11):1424-33.

2. Pocock SJ et al. Chronic heart failure Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34(19):1404-13.

3. Senni M et al. Predicting heart failure outcome from cardiac and comorbid conditions: The 3C-HF score. Int J Cardiol. 2013; 163(2):206-11.

4. Enriquez-Sarano M, Sundt TM 3rd. Early surgery is recommended for mitral regurgitation. Circulation. 2010;121(6):804-12.

ANGIOGRAPHIC CORONARY ARTERY DISEASE BURDEN AND 10-YEAR CLINICAL OUTCOMES IN PATIENTS TREATED WITH FIRST-GENERATION DRUG-ELUTING STENT

***Kyohei Yamaji,[1] Thomas Zanchin,[1] Christian Zanchin,[1] Thomas F. Lüscher,[1] Franz Eberli,[3] Peter Jüni,[4] Stephan Windecker,[1] Lorenz Räber[1]**

1. Department of Cardiology, Bern University Hospital, Bern, Switzerland
2. Department of Cardiology, University Hospital Zurich, Zurich, Switzerland
3. Department of Cardiology, Triemlispital, Zurich, Switzerland
4. Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital; Department of Medicine and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada
**Correspondence to kyohei@yamaji.info*

Disclosure: Stephan Windecker reports to have received research contracts to the institution from Abbott, Biotronik, Boston Scientific, Medtronic, Edwards, and St. Jude Medical. Peter Jüni has received research grants to the institution from Astra Zeneca, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company, and serves as an unpaid member of the steering group of trials funded by Astra Zeneca, Biotronik, Biosensors, St. Jude Medical, and The Medicines Company. Lorenz Räber has received grants to the institution from St. Jude Medical. The other authors report no conflicts of interest.
Citation: EMJ Int Cardiol. 2017;5[1]:45-46. Abstract Review No. AR8.

Keywords: Coronary artery disease (CAD), percutaneous coronary intervention (PCI), clinical outcomes.

Angiographic SYNTAX score was widely used to assist clinical decision between percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) by scoring coronary artery disease burden.[1,2] While the burden of coronary artery disease (CAD), assessed by the angiographic SYNTAX score, was reported to be associated with greater mortality at 5 years,[3-6] the predictive ability of the SYNTAX score on long-term outcomes (>5 years) has not been established. The authors extended the clinical follow-up to 10 years in patients enrolled in the SIRTAX study[7] and evaluated the impact of SYNTAX score on long-term outcomes at 10 years.

The SYNTAX score was retrospectively calculated in 858 patients enrolled in the SIRTAX trial (median: 11, interquartile range [IQR]: 7–17). Since patients were included in the randomised controlled trial, SYNTAX score was relatively low compared with the all-comer population. Patients with previous CABG (n=92), those without suitable angiography (n=47), and those without creatinine clearance data available (n=15) were excluded. The follow-up rate was high but not complete (763 patients, 88.9%) at 10 years.

During the 10-year follow-up, 174 (21.9%) patients died, myocardial infarction (MI) occurred in 76 (9.8%) patients, target lesion revascularisation (TLR) in 157 (19.7%) patients, target vessel revascularisation (TVR) in 202 (25.4%) patients, and non-TVR in 153 (19.9%) patients, respectively. Rates of clinical events between 5 and 10 years were lower than those within 5 years, except for all-cause death (9% at 5 years and 22% at 10 years).

The SYNTAX score emerged as an independent predictor for all-cause mortality (adjusted hazard ratio [HR] [per 10]: 1.23; 95% confidence interval [CI]: 1.004–1.50; p=0.046), TLR (adjusted HR: 1.37; 95% CI: 1.12–1.68; p=0.003), and TVR (adjusted HR: 1.37; 95% CI: 1.14–1.64; p<0.001), and was associated with a trend toward greater adjusted risks for MI (adjusted HR: 1.30; 95% CI: 0.97–1.74; p=0.08) and non-TVR (adjusted HR: 1.22; 95% CI: 0.98–1.52; p=0.08), respectively.

The authors performed stratified analyses according to the median patient age of 62 years (≥62 years: 435 patients; <62 years: 423 patients). The SYNTAX score was higher in older patients compared to younger patients (11 [7–17.75] versus 9 [5.75–15.0]; p<0.001). The SYNTAX score independently predicted non-TVR in the younger group (adjusted HR [per 10]: 1.67; 95% CI: 1.20–2.32, p=0.002) but not in the older patient group (adjusted HR: 1.04; 95% CI: 0.75–1.44; p=0.82; p interaction=0.049) with significant interaction. Conversely, there was no significant interaction between SYNTAX score and age category for all-cause mortality, MI, TLR, and TVR.

The study has important limitations. The follow-up rate of 88.9% at 10 years was not complete. The majority of events, except for all-cause mortality, were observed within 5 years. Thus, the reported association of SYNTAX score on clinical outcomes might be mainly driven by earlier events, although it was notable that all-cause mortality rate increased from 9% at 5 years to 22% at 10 years.

The authors concluded that the SYNTAX score was independently associated with 10-year risks of all-cause mortality, TLR, and TVR. Among young, but not elderly patients, the SYNTAX score independently predicted non-TVR.

REFERENCES

1. Sianos G et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005;1(2):219-27.

2. Serruys PW et al. Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. N Engl J Med. 2009;360(10):961-72.

3. Girasis C et al. SYNTAX score and Clinical SYNTAX score as predictors of very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: a substudy of SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization (SIRTAX) trial. Eur Heart J. 2011;32(24):3115-27.

4. Iqbal J et al. Predicting 3-Year Mortality After Percutaneous Coronary Intervention: Updated Logistic Clinical SYNTAX Score Based on Patient-Level Data From 7 Contemporary Stent Trials. JACC Cardiovasc Interv. 2014;7(5):464-70.

5. Franzone A et al. Angiographic complexity of coronary artery disease according to SYNTAX score and clinical outcomes after revascularisation with newer-generation drug-eluting stents: a substudy of the BIOSCIENCE trial. EuroIntervention. 2016;12(5):e595-604.

6. Ikeno F et al. SYNTAX Score and Long-Term Outcomes: The BARI-2D Trial. J Am Coll Cardiol. 2017;69(4):395-403.

7. Yamaji K et al. Ten-year clinical outcomes of first-generation drug-eluting stents: the Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) VERY LATE trial. Eur Heart J. 2016;37(45):1-10.

EDITOR'S PICK

This paper, courtesy of Yang and Takeuchi, provides a timely and well-considered update on the current status of fully-automated software with three-dimensional echocardiography for quantifying left ventricular function. It is inspiring to see how far this technology has developed in recent years, and we look forward to observing its progression in the future and the potential benefits this development will bring to patient management.

CURRENT STATUS OF FULLY AUTOMATED SOFTWARE WITH THREE-DIMENSIONAL ECHOCARDIOGRAPHY FOR THE QUANTIFICATION OF LEFT VENTRICULAR FUNCTION

Li-Tan Yang,[1,2] *Masaaki Takeuchi[1]

1. Department of Laboratory and Transfusion Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan
2. Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
**Correspondence to takeuchi@med.uoeh-u.ac.jp*

Disclosure: The authors have declared no conflicts of interest.
Received: 01.03.17 **Accepted:** 24.04.17
Citation: EMJ Int Cardiol. 2017;5[1]:48-54.

ABSTRACT

Echocardiography has an important role in the diagnosis, treatment, and management of patients who require transcatheter valvular interventions. Left ventricular ejection fraction (LVEF) is a very popular parameter for the assessment of LV function. Although several cut-off values of LVEF have been used for decision making in patients with valvular heart disease, less attention has been paid to its accuracy and reliability. Observer variability is a significant concern, and >10% differences in LVEF measurements between two sonographers could occur in the same two-dimensional echocardiography datasets. The adoption of fully automated LV quantification software with three-dimensional echocardiography (3DE) might be one potential solution to eliminate this problem. We will review the current status of fully automated software with 3DE for the assessment of LV volumes and LVEF.

Keywords: Left ventricular ejection fraction (LVEF), three-dimensional echocardiography (3DE), fully automated software.

INTRODUCTION

Patients with severe aortic stenosis (AS) or mitral regurgitation (MR) with multiple comorbidities present as high-risk surgical candidates. Owing to the rapid advancement in transcatheter interventional technology, they could benefit from percutaneous aortic valve replacement (PAVR) or MitraClip® instead of a traditional operation. In the current guidelines, a decrease in the left ventricular ejection fraction (LVEF) is a Class I indication for surgical intervention in AS or MR, with the cut-off being 50% and 60% for AS and MR, respectively.[1] LVEF is usually determined by biplane Simpson's formula with two-dimensional (2D) transthoracic echocardiography (TTE)[2] though errors in

LVEF values could occur due to measurement (manual tracing of the endocardial border) and recording variability.

CLINICAL CASE

An 80-year-old woman with severe asymptomatic AS (peak transaortic valve velocity: 4.5 m/s; mean pressure gradient: 44 mmHg) presented to the heart valve clinic for regular follow-up. The TTE report showed her LVEF had decreased to 45% (Figure 1A) from 55% when measured 6 months ago by a different sonographer (Figure 1B). As per the recommendations for management of valvular heart disease, she now carries a Class I indication for aortic valve replacement.[1] Due to her prohibitive risk for surgical intervention, she would be a candidate for PAVR. A valid question that arises in this context is 'Should this patient immediately undergo PAVR?'

Before considering the operative procedure, we need to determine if the apparent reduction of LVEF is a true impairment. In this case, no obvious changes in LVEF (53% and 54%) were observed using three-dimensional echocardiography (3DE) guided Simpson's method with 2DE images extracted from 3DE (Figure 1C and 1D). Acquisition of the same cut views of 2DE images during serial examination is often difficult because subtle changes of transducer position and angulation make different cut-planes, which results in over and underestimation of LV volumes and ejection fraction. Since 3DE datasets encompass the whole part of the left ventricle, it is possible to obtain the same 2DE cut views extracted from serial 3DE datasets. This case illustrates that it is important to rule out observer and recording variability as a cause of false positives.

Sonographers differ in their individual practices in endocardial border tracing, resulting in different LVEF values in the same 2DE image. Additionally, repeated echo examinations account for the greatest source of variability because subtle differences in serial 2DE recording images might influence measurements of LVEF.[3,4]

Although cardiac magnetic resonance (CMR) is a reference standard for the quantification of LV volumes and ejection fractions with high accuracy, it is not possible to perform CMR in every patient due to cost, availability, and some contraindications. A potential solution to this common clinical dilemma could be application of fully automated quantification software with 3DE. Fully automated analysis eliminates measurement variability between different observers. We reviewed the current status of 3DE fully automated software for quantification of LV function.

HOW THREE-DIMENSIONAL ECHOCARDIOGRAPHY FULLY AUTOMATED SOFTWARE WORKS

Currently, there are two models of 3DE fully automated software available (eSie LVA™, Siemens Medical Solutions, Mountain View, California; and HeartModel^{AI}, Philips Healthcare, Andover, Massachusetts, USA), both of which operate under the knowledge-based workflow. At the outset, while beginning to develop the auto-contouring programme, experts analysed and marked endocardial borders in >1,000 subjects with varying shapes of the left ventricle. This was used as a databank of different LV shapes.[5] When this algorithm is used, the software locates the LV templates that best match the new LV volume and generates the endocardial contour. Before analysis, the end-diastolic volume (EDV) is determined from the R wave on the electrocardiogram and the end-systolic volume (ESV) from the frame with the minimal volume by motion analysis.[5-7] 3D LV rendering of LV casts, as well as time-volume curves, is then displayed with EDV, ESV, and EF (Figure 2). Manual editing of the LV endocardial border on apical cutting planes derived from the 3DE dataset is still allowed if the user is not satisfied with the automatically generated contours.

Accuracy of the Three-Dimensional Echocardiography Fully Automated Software

Current available validation studies utilising 3DE fully automated software show good-to-excellent correlation (correlation coefficient [r]=0.85–0.96) and acceptable accuracy compared to CMR imaging as a reference.[5,7,8] Chang et al.[5] performed a direct comparison of LV volumes and LVEF between 3DE with Siemens fully automated software and CMR in 91 patients, who were largely normal (38.5%) or having ischaemic cardiomyopathy (29.4%). There were 41 mL, 7 mL, and 8% underestimations against CMR with the corresponding 95% limit of agreement (LOA, 2 standard deviations): ±37 mL, ±33 mL, and ±13% for LVEDV, LVESV, and LVEF, respectively.[5] The r value of LV parameters against CMR is 0.91–0.94. Thavendiranathan et al.[7] validated LV volumes and LVEF utilising Siemens fully automated software against CMR in 67 patients with sinus rhythm.

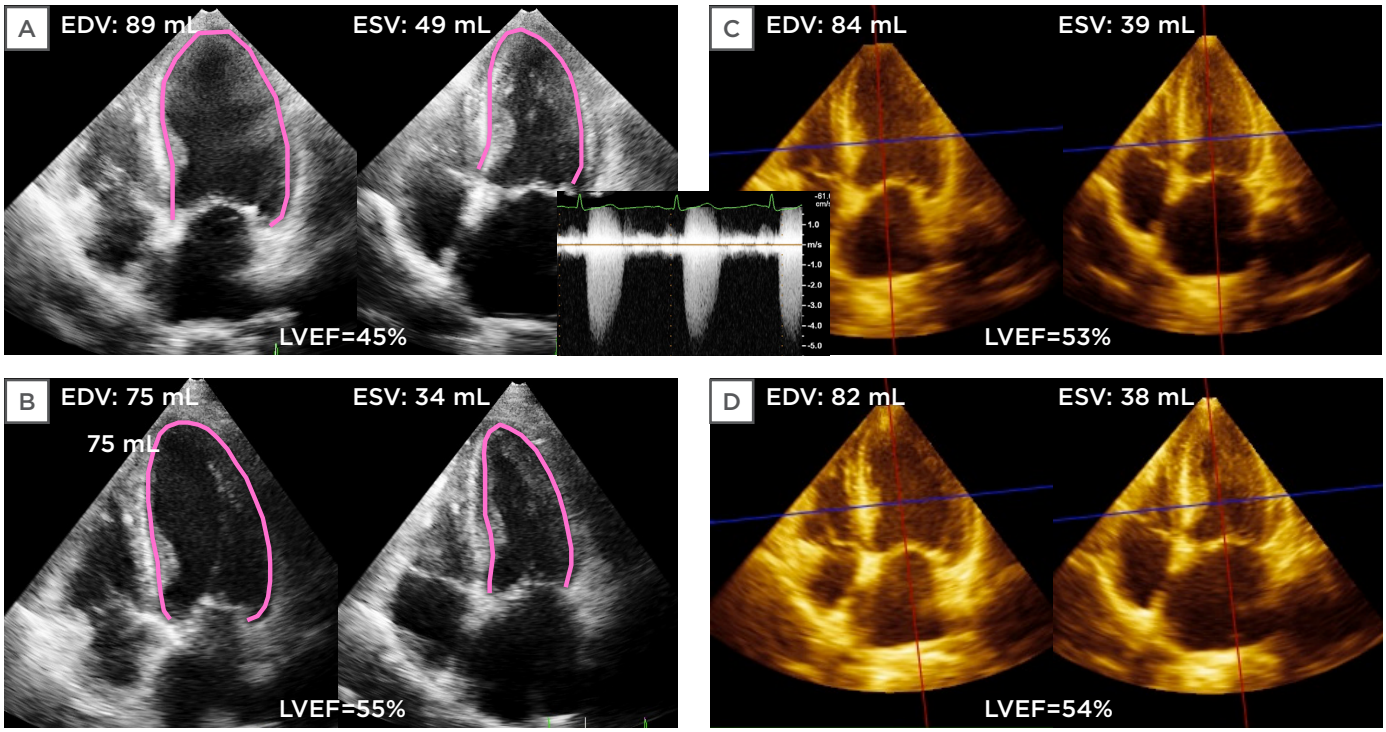


Figure 1: An asymptomatic severe aortic stenosis patient whose left ventricular ejection fraction decreased 10% during serial echocardiography studies.

A) 2D apical 4-chamber view at end-diastole and end-systole in an 80-year-old woman with asymptomatic severe aortic stenosis. The EDV, ESV, and LVEF were 89 mL, 49 mL, and 45%, respectively, measured by the biplane Simpson method. B) Corresponding apical 4-chamber view at 6 months ago showing her EDV, ESV, and LVEF were 75 mL, 34 mL, and 55%, respectively. C) Apical 4-chamber view extracted from 3D full volume dataset at current examination. EDV, ESV, and LVEF were 84 mL, 39 mL, and 53%, respectively, measured by 3DE guided 2DE biplane Simpson method. D) Corresponding apical 4-chamber view extracted from 3DE datasets at 6 months ago showing her EDV, ESV, and LVEF were 82 mL, 38 mL, and 54%, respectively. This case illustrates that interobserver variability resulted in differences in measurement without identifiable interval changes in LV geometry.

EDV: end-diastolic volume; ESV: end-systolic volume; LVEF: left ventricular ejection fraction; 3DE: 3D echocardiography.

The correlation of LV parameters against CMR is excellent (r=0.90–0.98). Despite an under-estimation of LV volumes and LVEF (ΔLVEDV, -18 mL, ΔLVESV, -10 mL, and ΔLVEF, -0.3%; 95% LOA: ±53 mL, ±36 mL, and ±5%, respectively), they also found that in the subgroup of patients with reduced LVEF (<50%), the accuracy of LV parameters reduced when compared to those with preserved LVEF (≥50%). The differences were -26 mL, -16 mL, and -0.2% for LVEDV, LVESV, and LVEF in patients with LVEF <50% and -11 mL, -4 mL, and -0.5% in those with LVEF >50%. Interestingly, Tsang et al.[8] demonstrated similarly in their study that patients with impaired LVEF (<50%) had diminished accuracy for LV volumes and LVEF against CMR. The authors used another fully automated software (HeartModel^{AI}, Philips) for LV quantification in 65 patients (60% with LVEF <50%). The correlation of LV parameters against CMR is good-to-excellent (r=0.85–0.93). In those with LVEF <50%, the differences between 3DE and CMR were -27 mL, -24 mL, and 2% for LVEDV, LVESV, and LVEF, whereas in those with LVEF >50%, the corresponding differences were smaller (-18 mL, 6 mL, and -9%, respectively). In the whole patient group, underestimation of LV volumes and LVEF against CMR was expected (-24 mL, -13 mL, and -2% for LVEDV, LVESV, and LVEF; LOA: ±50 mL, ±58 mL, and ±18%). The findings that the fully automated software did not work as well in patients with poor LV function may be due to the fact that reduced LVEF is usually associated with dilated left ventricle. In this situation, a 1 mm difference in tracing the border may lead to a larger volume error compared

to a small or normal-sized left ventricle. Although 3DE fully automated software still underestimated LV volumes with a range between 18 mL and 41 mL of LVEDV and from 7–13 mL of LVESV compared to CMR, the bias was still smaller than the corresponding bias with use of the 3DE manual tracing method employed in the previous multicentre study (mean bias for LVEDV: 67 mL; LVESV: 41 mL).[9] Most importantly, the observed bias between 3DE manual method and CMR differed significantly among four different institutions, probably due to differences between the behaviour of endocardial tracers.[9]

Another potential of this software is its high reproducibility. Intra and interobserver variability in LV volumes and LVEF was 0% when the fully automated software worked without any contour adjustment. Even though manual contour adjustment was required, the values were still <10% in contrast to 15–21% with the 3DE manual tracing method in the same 3DE datasets.[8]

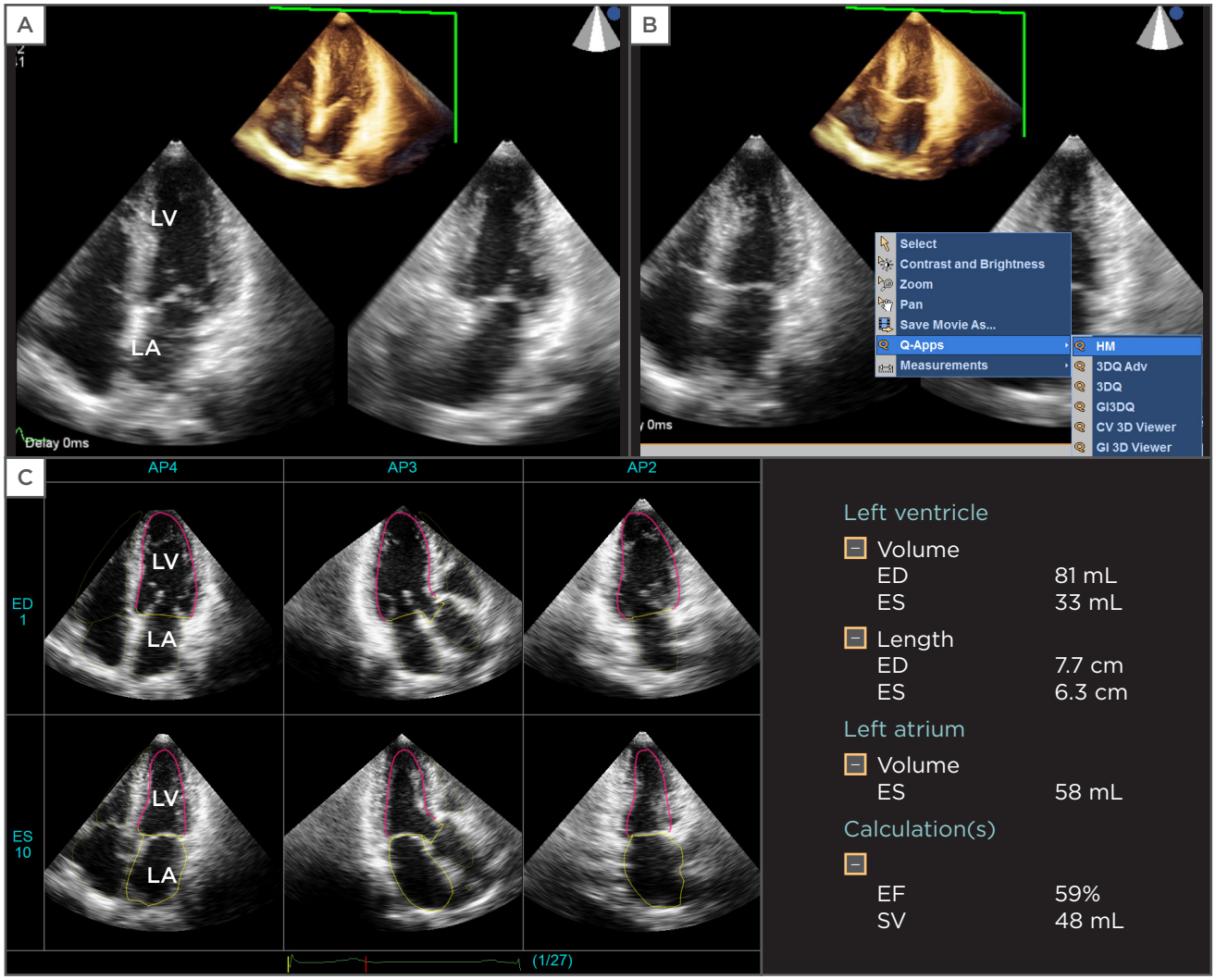


Figure 2: An example of the application of 3DE fully automated software.
A) Cropped one-beat 3DE full-volume image and two orthogonal 2DE cut images extracted from 3DE datasets. B) For the initiation of 3DE fully automated software, the examiner clicks the icon 'Q-Apps', and then selects 'HM'. The software automatically runs for LV and LA border determination at end-diastole and end-systole. C) The final result is obtained within 30 seconds. The display shows three apical long axis views extracted from the 3DE datasets at end-diastolic and end-systolic frames. The pink line denotes the LV endocardial border, and the yellow line, the LA wall. The software provides LVEDV, ESV, and LVEF. It also measures LA volume at end-systole.
3DE: three-dimensional echocardiography; 2DE: two-dimensional echocardiography; LV: left ventricle; LA: left atrial; LVEDV: left ventricular end-diastolic volume; ESV: end-systolic volume; LVEF: left ventricular ejection fraction.

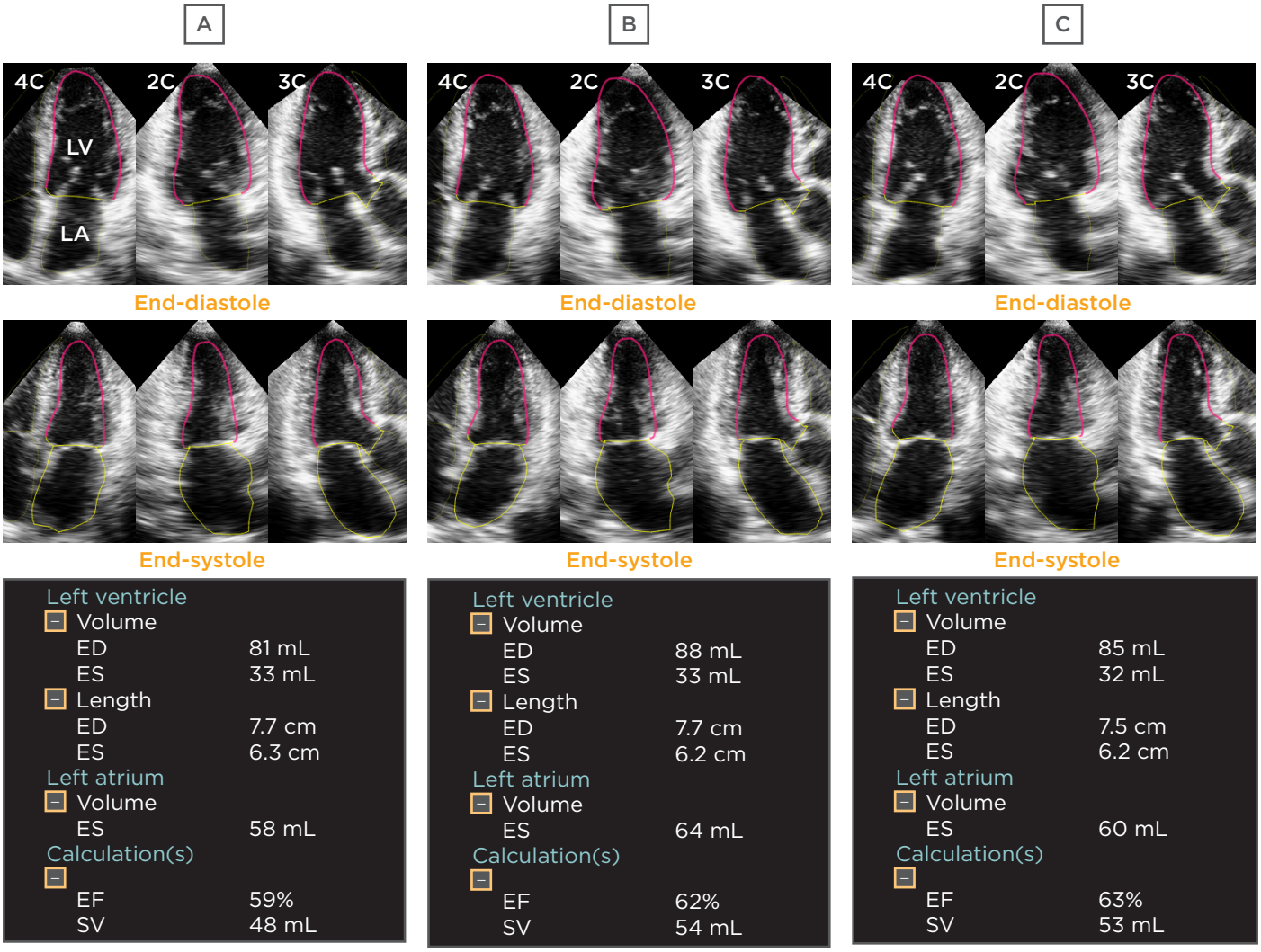


Figure 3: Test-retest variability.

Panel A to C indicates the final results of the fully automated software using different 3DE datasets acquired from the same patient. The software provided small but obviously different values of LV volumes and LVEF between three examinations.

3DE: three-dimensional echocardiography; LV: left ventricle; LVEF: left ventricular ejection fraction; ED: end-diastole; ES: end-systole; EF: ejection fraction; SV: systolic volume.

As mentioned earlier, test-retest variability is the most important factor to evaluate serial changes in LV function. Although test-retest variability of the automated 3DE program did not reach 0%, the values showed a clinically acceptable range (6–8%) (Figure 3).

Advantages

From the same 3DE datasets, 3DE fully automated software provides equivalent LV volumes and LVEF among different observers regardless of their technical skill and expertise. Also, the time required for the analysis is much shorter (with or without contour adjustment, 76±6 and 26±2 seconds, respectively)[8] than the traditional 3DE manual tracing method used by experts (144±32 seconds).[9] Of note, in patients with LV aneurysms, traditional manual tracing may require an additional 5 minutes for analysis because the deformable shell does not work as well.[10] In less experienced echocardiography labs, this fully automated software serves as an ideal option to obtain consistent and reliable LV measurements.

For patients who underwent 3DE, traditionally full-volume datasets for ≥4 cardiac cycles are acquired to ensure optimal spatial resolution with sufficient volume rate. For patients who cannot hold their breath adequately, or whose rhythm is irregular, multibeat data acquisition produces stitching artefacts resulting in unreliable assessment

of LV function.[7] To overcome this problem and widen the clinical adoption of 3DE imaging, acquisition of one-beat full-volume datasets with a relatively high-volume rate is now feasible. It is shown that the LVEF, EDV, and ESV obtained by manual tracing from one-beat acquisition are similar to that from four-beat acquisition with a high correlation.[11] As the fully automated software only operates the one-beat 3DE full-volume dataset, its efficiency in data acquisition, and its accuracy and reproducibility is expected to be better than the manual tracing method.

With the introduction of innovative catheter-based technologies (PAVR, MitraClip, Abbot Laboratories, Lake Bluff, Illinois, USA), the treatment landscape for patients with severe AS and MR has been altered rapidly. In the geriatric population, physicians frequently need to deal with the clinical decision of when to refer non-operable or high-risk severe AS or MR patients for transcatheter intervention. Implantable cardioverter defibrillator and cardiac resynchronisation therapy and defibrillator rely on accurate LV function evaluation.[12] With rising medical costs,[13] it is essential to establish LV function unequivocally during close follow-up of such patients in order to allocate health resources wisely.

LV function analysis by 3DE eliminates the need for geometric assumptions, particularly in a deformed LV, and avoids measurement errors from a foreshortened left ventricle.[14] The emergence of fully automated software for LV analysis might serve as a promising tool and solve previous problems with respect to reliability and reproducibility in 3DE analysis. Furthermore, it works rapidly and is no longer a researchers' 'toy' but a useful tool for LV quantification in a busy clinical setting. This information can be incorporated into echocardiography reports and would serve as a reliable reference for interventional cardiologists in decision-making.

Clinical Application

It is common to find atrial fibrillation in patients with severe AS/MR and those on the waiting lists for implantable cardioverter defibrillator/ cardiac resynchronisation therapy and defibrillator. Accurate determination of correct LV function is paramount in this group. However, beat-to-beat variability of LV volumes and function results in inaccurate LV measurement in one single beat and thus, 4–17 beats analysis is usually recommended in LV analysis.[15] Therefore, manual tracing in 3DE LV quantification could take ≤40 minutes, even for experts.[8] In a recently published study utilising this fully automated software in patients with atrial fibrillation, the time spent for analysis in 10 consecutive cardiac cycles was 5 minutes versus 27 minutes by the manual tracing method. A comparison of LV mechanical parameters (LVEF, EDV, ESV) between fully automated software and the manual method showed a good correlation and minimal differences.[16] Interestingly, the authors found that average values of LVEF, EDV, and ESV closely correlate to those obtained from the index beat with only a small bias. Since the index beat can be determined by calculating the preceding (RR1) and pre-preceding (RR2) R-R interval with the RR1/RR2 closest to 1.0, by using the fully automated software in an index beat, one can confidently infer that LV quantification will be accurate and representative.

CONCLUSION

With increased life expectancy, the number of non-operable and high-risk patients with severe valvular heart disease or those with heart failure is expected to grow. The advent of catheter-based technology has widened the treatment landscape. However, cost concerns highlight the importance of judicious implementation of expensive devices. LV quantification by echocardiography has an important role in the serial follow-up of patients and in clinical decision-making. Advances in ultrasound technology have helped to bring 3DE from bench-to-bedside, including improvements in high volume-rate one-beat full-volume acquisition and fully automated 3DE quantification software. Physicians or sonographers now have opportunities to produce TTE reports with reliable, reproducible, and rapid 3DE LV measurements not only in sinus rhythm, but also in those with an irregular rhythm. This fully automated quantification software for determining LV function also allows elucidation of the measurement differences of the sonographers in the decision making of the therapeutic management. This state-of-the-art technique, though still not perfect, will certainly be a valuable clinical tool for interventional cardiologists. Future prognostic studies incorporating measurements using this fully automated software are awaited.

REFERENCES

1. Nishimura RA et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):2438-88. Erratum in: J Am Coll Cardiol. 2014;63(22):2489.

2. Lang R et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14.

3. Jenkins C et al. Comparison of two- and three-dimensional echocardiography with sequential magnetic resonance imaging for evaluating left ventricular volume and ejection fraction over time in patients with healed myocardial infarction. Am J Cardiol. 2007;99(3):300-6.

4. Otterstad JE et al. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. Eur Heart J. 1997;18(3):507-13.

5. Chang SA et al. Feasibility of single-beat full-volume capture real-time three-dimensional echocardiography and auto-contouring algorithm for quantification of left ventricular volume: validation with cardiac magnetic resonance imaging. J Am Soc Echocardiogr. 2011;24(8):853-9.

6. Zhang QB et al. Novel single-beat full-volume capture real-time three-dimensional echocardiography and auto-contouring algorithm for quantification of left ventricular volume: Validation with cardiac magnetic resonance imaging. Int J Cardiol. 2013;168(3):2946-8.

7. Thavendiranathan P et al. Feasibility, accuracy, and reproducibility of real-time full-volume 3D transthoracic echocardiography to measure LV volumes and systolic function: a fully automated endocardial contouring algorithm in sinus rhythm and atrial fibrillation. JACC Cardiovasc Imaging. 2012;5(3):239-51.

8. Tsang W et al. Transthoracic 3D echocardiographic left heart chamber quantification using an automated adaptive analytics algorithm. JACC Cardiovasc Imaging. 2016;9(7):769-82.

9. Mor-Avi V et al. Real-time 3-dimensional echocardiographic quantification of left ventricular volumes: multicenter study for validation with magnetic resonance imaging and investigation of sources of error. JACC Cardiovasc Imaging. 2008;1(4):413-23.

10. Jacobs LD et al. Rapid online quantification of left ventricular volume from real-time three-dimensional echocardiographic data. Eur Heart J. 2006;27(4):460-8.

11. Yang LT et al. Feasibility of One-Beat Real-Time Full-Volume Three-Dimensional Echocardiography for Assessing Left Ventricular Volumes and Deformation Parameters. J Am Soc Echocardiogr. 2016;29(9):853-60.e2.

12. Brignole M et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013;34(29):2281-329.

13. Gadey G, Reynolds MR. Cost-effectiveness considerations in transcatheter management of valvular heart disease. Can J Cardiol. 2014;30(9):1058-63.

14. Mor-Avi V et al. Real-time 3-dimensional echocardiography: an integral component of the routine echocardiographic examination in adult patients? Circulation. 2009;119(2):314-29.

15. Dubrey SW, Falk RH. Optimal number of beats for the Doppler measurement of cardiac output in atrial fibrillation. J Am Soc Echocardiogr. 1997;10(1):67-71.

16. Otani K et al. Three-Dimensional Echocardiographic Assessment of Left Heart Chamber Size and Function with Fully Automated Quantification Software in Patients with Atrial Fibrillation. J Am Soc Echocardiogr. 2016;29(10):955-65.

STENT OR SCAFFOLD THROMBOSIS: PAST, CURRENT, AND FUTURE PERSPECTIVES

Hideki Wada,[1] Peter C. Mattson,[2] *Hiroshi Iwata[1]

1. Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan
2. Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA
**Correspondence to hiroiwata-circ@umin.ac.jp*

Disclosure: The authors have declared no conflicts of interest.
Received: 13.03.17 **Accepted:** 15.08.17
Citation: EMJ Int Cardiol. 2017;5[1]:55-61.

ABSTRACT

Stent thrombosis (ST) is uncommon yet constitutes the most feared complication following percutaneous coronary intervention. Although its incidence is now <1% within a year after stenting in patients receiving second or later-generation drug-eluting stents (DES), compared to those in the first-generation DES-era, the clinical impact of ST is still high, because the majority of cases with ST are complicated by critical consequences, including myocardial infarction and even sudden cardiac death. Moreover, the pathophysiology and risk factors leading to ST were recently re-recognised, as bioresorbable scaffolds (or biodegradable vascular scaffolds) have now been developed, and concerns have arisen regarding scaffold thrombosis, which serves as another 'ST'. Accumulating evidence through the bare-metal stent and DES-era has identified clinical factors associated with increased risk of ST, such as patient-related, lesion-related, procedure-related, and post-procedure-related risk factors. Therefore, this short review describes updated pathophysiology and contributing risk factors for stent (or scaffold) thrombosis, which are useful for risk stratification in patients with coronary artery disease in the late metallic DES-era or at the beginning of the bioresorbable scaffolds era.

Keywords: Stent thrombosis (ST), percutaneous coronary intervention (PCI), drug-eluting stent (DES), bioresorbable scaffold (BRS).

INTRODUCTION

The development and clinical introduction of metallic coronary stents in the late 1980s greatly reduced the risk of early adverse events, such as abrupt vessel closure, and in turn dramatically improved outcomes of patients who underwent percutaneous coronary intervention (PCI), compared to balloon angioplasty alone.[1] Nevertheless, deployed intracoronary stents still led to substantial concerns regarding early and remote complications. Two major causes of coronary stent failure following PCI include in-stent restenosis (ISR) and stent thrombosis (ST). In the bare-metal stent (BMS) era, the angiographic restenosis rate was high, ≤15–30%,[2] while the incidence of ST ≤1 year after stenting in patients with BMS and first-generation drug-eluting stents (DES) ranged from 0.6–3.5%.[3,4] However, the recent incidence of both ST and ISR has been markedly reduced, mainly due to widespread use of post-second-generation DES combined with an optimised cocktail of antiplatelets for optimal duration. Recent large-scale registries and randomised trials demonstrate that ST occurs ~1% through 1-year post-stenting and has a <0.5% annual incidence rate afterwards.[5,6] With respect to mechanisms of early and late stent failure, high-resolution intravascular imaging, called optical coherence tomography (OCT), showed that neoatherosclerosis, defined as lipid-rich and calcified fibroatheroma, or fibrocalcific plaque within stented segments,[7] is an important histopathological change for both ISR and ST.[8] While ISR rarely leads to critically clinical consequences, such as cardiac death, ST is a serious, potentially life-threatening clinical event typically resulting in ST-elevation myocardial infarction, including a substantially high mortality rate ≤25% within 30 days.[9,10] In recently developed strategies, other than implantation of metallic stents in the coronary artery for life,

including drug-coated balloons or bioresorbable vascular scaffolds (BRS), PCI-related thrombosis is growing increasingly clinically important.[11]

In order to standardise the nomenclature on ST from a wide range of clinical trials, registries, and meta-analyses of coronary stents, a group of experts known as the Academic Research Consortium (ARC) proposed universal definitions in 2006 that are now widely accepted.[12] This definition classified evidence of ST in accordance with certainty of clinical findings of ST as definite, probable, or possible, as well as timing after the indexed stent implantation, as early (≤30 days), late (31 days–1 year) or very late (later than a year), which may have distinct pathophysiologies. Moreover, early ST is further divided into two categories, including acute ST (≤24 hours) and subacute ST (>24 hours–30 days).

STENT THROMBOSIS IN THE BARE-METAL STENT ERA AND DEVELOPMENT OF DUAL-ANTIPLATELET THERAPY

The limitations of balloon angioplasty when it was introduced in 1977[13] included acute adverse events (induced by early abrupt vessel closure due to vascular injury without adequate acute gain), high rates of restenosis (due to the excessive healing process by activated smooth muscle cells), and accumulation of inflammatory cells against balloon-induced vascular injury with or without negative vascular remodelling.[14] Since 1986, implantation of a metallic stent in the treated coronary arteries[15] was a strategy for reducing acute complications of balloon angioplasty. However, at the beginning of the coronary stent era, a significant number of cases still continued to be complicated by ST. In short, after the introduction of stents to clinical practice, complete occlusion of stents occurred in >20% of cases, mostly within 14 days.[16] However, procedures were performed with intensive use of anticoagulants, which resulted in critical haemorrhagic complications (major bleeding occurred in 9% of patients).[17] Therefore, the most important and evolutional pharmacological development in PCI therapy was dual antiplatelet therapy (DAPT), the combination of aspirin and an adenosine diphosphate (ADP)-receptor (P2Y12) inhibitor, which dramatically reduced both early ST and bleeding complications. Accordingly, many randomised clinical trials demonstrated that DAPT was conclusively superior to anti-coagulation for the prevention of early complications after stent deployment.[18] In combination with accumulating technical and procedural optimisations, such as high-pressure inflation following stent deployment and complete coverage of the plaque without edge dissection, these intensive antiplatelet therapies successfully facilitated the further widespread indication of PCI for the treatment of a broader range of coronary artery diseases when compared to balloon angioplasty.[18]

STENT THROMBOSIS IN THE DRUG-ELUTING STENT ERA

Despite the importance of radial force powered by metallic stents for avoiding early and late constrictive vascular mechanical forces, its deployment procedure using high pressure balloon induced acute vessel injury, which enhances the vascular healing process and in turn leads to significant neointimal hyperplasia via smooth muscle cell proliferation. ISR was the main issue that motivated research interest in the development of a novel type of metallic stent. DES, which slowly and locally release anti-proliferative agents including sirolimus, paclitaxel, biolimus, and everolimus, suppress in-stent neointima hyperplasia via the inhibition of smooth muscle activation and proliferation. They have been clinically proven to be dramatically effective in reducing the incidence of ISR, which presents as target lesion/vessel revascularisation in many clinical trials, and have enabled the expansion of PCI indications to treat the lesions of even high-risk patients, such as patients with relatively long and small diseased coronary vessels, multi-vessel disease, and lesions in the left-main coronary artery that used to be encouraged for coronary artery bypass grafting rather than PCI.

In spite of the obvious superiority of DES in preventing ISR and the need for repeat revascularisation,[19] concerns regarding mainly late or very late ST have emerged due to the nature of DES, such as delayed endothelial cell proliferation and polymer-induced prolonged vessel wall inflammation followed by positive vascular remodelling, as well as late stent malaposition.[20] To minimise these concerns, second-generation DES were developed by the use of technologies such as new biocompatible polymer coatings and thinner cobalt-chromium metal struts, and they showed significant superiority in comparison with first-generation DES, decreasing the risk of ST

and ISR. The everolimus-eluting stent has been found to be safer and more effective than first-generation DES.[21,22]

PATHOPHYSIOLOGY AND MECHANISMS OF STENT THROMBOSIS

Recent large-scale registries show that, with contemporary antithrombotic therapies and modern-generation DES, the rate of early ST is relatively low, at <1%.[23] Similarly, a systematic review of randomised trials with DES reporting results at 12 months after implantation showed a median incidence of definite ST of 0.61%.[5,6] However, in spite of such a low incidence of ST in <1% of patients receiving stents, ST should not be underestimated, as critical consequences are highly likely once it occurs. Thrombus aspiration (thrombectomy) and balloon angioplasty are frequently performed in combination with repeat stenting in 30–50% of cases, as treatment of ST.[24]

It is widely known that ST occurs more frequently in complex patients and lesions, such as those with acute coronary syndromes, diabetes mellitus, chronic kidney disease and diffuse disease, small vessels, and bifurcation lesions requiring multiple stents. Even multifactorial, accumulating evidence indicates that mechanisms and pathophysiology leading to ST can be classified into four major categories: i) patient-related, ii) lesion-related, iii) procedure-related, and iv) medication (post-stenting)-related (Figure 1). As part of the patient-related factor, so-called complex patients are generally at high risk of ST, including those with smoking habits, diabetes, chronic kidney disease, and acute coronary syndromes with a large thrombotic burden. Additionally, this includes patients with thrombocytosis and with high platelet activity against antiplatelets.[25] Understanding the risk of ST according to these patient-related factors facilitates the use of procedural strategies to minimise the risk of ST, and careful patient selection, lesion selection, device selection, and planning strategy of the procedure is the first critical step. Similar to patient-related risk factors, complex lesions are also at high risk for ST, including diffuse and long lesions, which require long stenting, small vessels, bifurcations, and lesions with thrombotic burden. Furthermore, recent significant OCT studies revealed various contributing lesion-related mechanisms of ST. While stent underexpansion and dissection at stent edges were associated with early ST,[26] detailed analysis from an OCT registry revealed that findings of stent malapposition causing shear flow disturbance, neoatherosclerosis, and uncovered stent struts were risk factors for very late ST.[27] Therefore, to reduce the risk of ST, final adequate lumen area in combination with good apposition of stent to arterial wall by high-pressure balloon is particularly essential. For that purpose, intravascular imaging using intravascular ultrasound or OCT is helpful, as they can provide significant insight regarding lesion preparation and selection of stents with appropriate sizing. Additionally, residual dissection in the stent edge is also a strong predictor for ST, especially when it limits coronary flow.

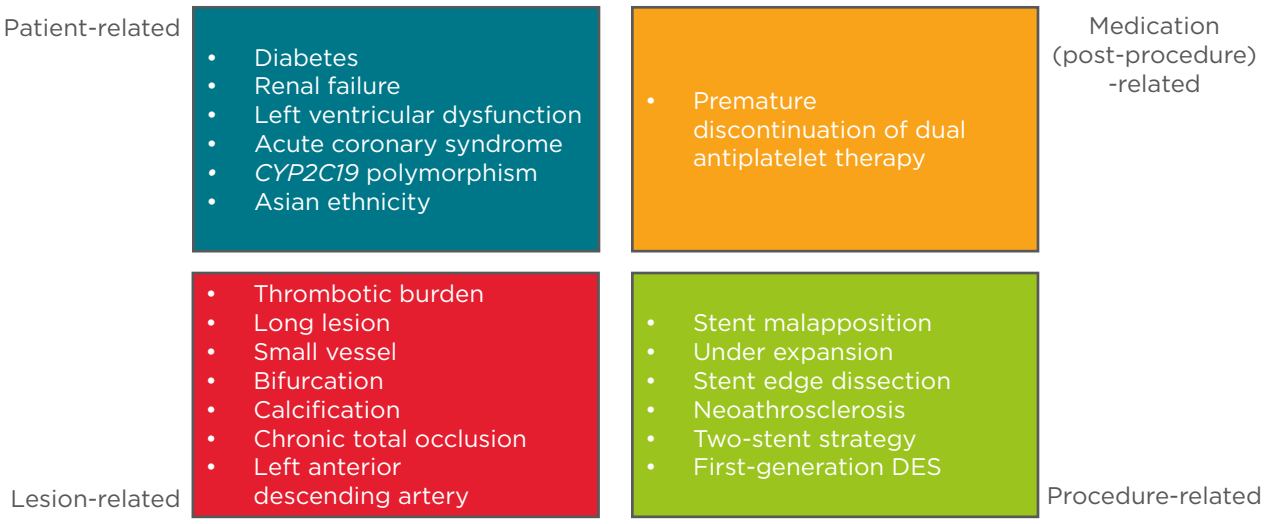


Figure 1: Risk factors associated with stent/scaffold thrombosis.
DES: drug-eluting stent.

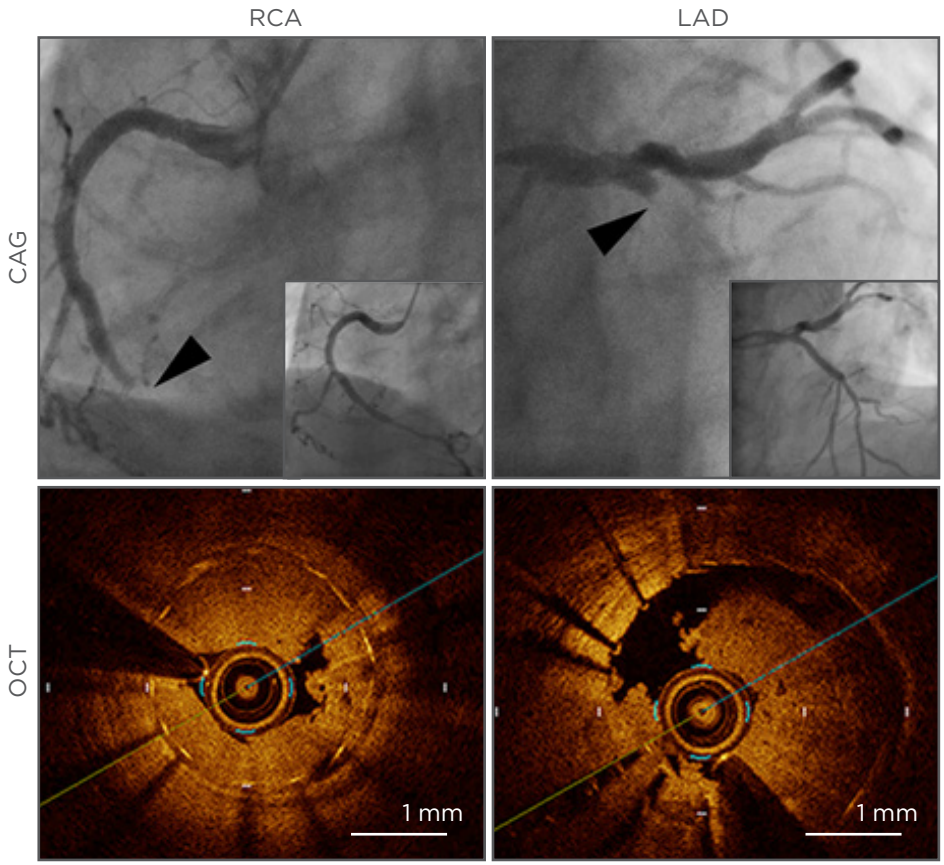


Figure 2: A case with simultaneous stent thrombosis in the right coronary artery and left anterior descending artery.

Upper: CAG at stent thrombosis (main figures) and after revascularisation with aspiration thrombectomy and balloon angioplasty (figures in right bottom corner); Lower: stent thrombosis in RCA and LAD revealed by OCT. Arrowheads indicate lesions of stent thrombosis.

RCA: right coronary artery; LAD: left anterior descending artery; CAG: coronary angiography; OCT: optical coherence tomography.

Adapted from Chikata et al.[43]

EARLY STENT THROMBOSIS (≤30 DAYS)

Clinically and pathologically, ST can be classified into two major categories according to the timeline: early ST is within the first 30 days and late ST is beyond 30 days after index procedure. Early ST is further divided into acute (≤24 hours) and subacute (>24 hours–30 days). Early ST is more common than late ST, accounting for 70% of all ST cases.[28] For early ST, lesion and procedure-related risk factors are relatively more important. Stent undersizing with incomplete stent apposition; presence of residual dissection; lesions with thrombotic burden, typically in settings of acute coronary syndromes; impaired coronary flow; and residual disease are all significant predictors of early ST.[29,30] Other than these factors, premature discontinuation of DAPT in the initial 30 days after stenting is obviously the most critical predictor of early ST.[31]

LATE STENT THROMBOSIS (>30 DAYS)

Although procedural issues in stenting will more likely lead to early ST, these factors can also play essential roles in late ST, where mechanical issues of implanted stents, such as stent under-expansion with incomplete apposition and edge dissection, remain critical for ST even after the time point of DAPT discontinuation.[29] Among these factors, incomplete stent apposition is frequently observed on intravascular imaging using OCT, rather than intravascular ultrasound, in patients with either early or late ST.[32] Moreover, a number of meta-analyses showed evidence of a significant increase in the risk of ST with both first-generation sirolimus and paclitaxel-eluting stents, compared to newer-generation DES.[3,33] In first-generation DES, delayed endothelial cell coverage of implanted stent struts induced a broad spectrum of pathological entities

including not only ST but also delayed late luminal loss contributing to late restenosis, known as the 'late catch-up phenomenon',[34] persistent vasomotor dysfunction,[35] and *de novo* in-stent atherosclerosis.[36] Induction of persistent inflammatory and thrombogenic reactions of stented vascular wall by biocompatible polymer coating of DES may cause adverse complications following DES deployment.[37] Meanwhile, newer-generation DES seem to have substantially addressed this issue by incorporating thinner stent struts, biocompatible polymer coatings whether non-erodible or biodegradable, and lower dosages of sirolimus.[5]

CYP2C19 POLYMORPHISM AND STENT THROMBOSIS

Considerable interest has focussed on predicting ST risk based on response to ADP receptor (P2Y12) antagonists. Clopidogrel, a selective inhibitor of the platelet P2Y12 receptor, has been a standard antiplatelet treatment dominantly added to aspirin following PCI, and it is an inactive pro-drug that requires hepatic metabolism by cytochrome P450 2C19 (*CYP2C19*) into its active form. However, substantial subpopulations have been recognised to have an inadequate response to clopidogrel, which leads to insufficient antiplatelet effects and, ultimately, ST. Individuals carrying at least one loss-of-function allele (either *2 or *3) of the *CYP2C19* gene demonstrate reduced active clopidogrel metabolites and suppressed antiplatelet activity.[38] The frequency for the most common loss-of-function variant *CYP2C19*2* is <15% in Caucasians and Africans, while affecting ≤35% of those of Asian descent. Accordingly, among East Asian populations in particular, the number of patients defined as a 'poor clopidogrel metaboliser' carrying the *CYP2C19*2/*2* or *2/*3 polymorphisms may be higher than previously postulated. Platelet function monitoring can measure the platelet reactivity of individual patients and may be able to adjust antiplatelet therapy for better clinical outcomes. However, no randomised clinical trial has demonstrated benefits based on platelet reactivity.[39-41] As an impaired response to P2Y12 antagonism also confers increased risk of ST,[42] alternative P2Y12 inhibitors, such as prasugrel and ticagrelor, that are less influenced by polymorphisms of the CYP2C19 gene, may be encouraged for use primarily in patients planning PCI with high-risk lesions for critical consequences once ST occurs, such as patients requiring multi-vessel or left main coronary stenting, especially in East Asians (Figure 2).[43] However, although the effects of P2Y12 inhibitors are potentially limited in East Asians, the total incidence of thrombotic complications after PCI is similar or even lower than Caucasians.[44]

BIORESORBABLE SCAFFOLDS AND THROMBOSIS

As a new-generation device to treat coronary artery disease next to DES, BRS are an important technological innovation that will be a potential breakthrough for improving outcomes of patients with coronary artery disease, and may radically change future PCI strategies. Theoretically, once the implanted scaffold is fully degraded, the stented coronary segment/artery will be free of concerns regarding future stent failure, ST, and restenosis with complete restoration of normal vasomotor function. In clinical trials to assess efficacy of BRS, which compared everolimus-eluting BRS (Absorb, Abbott Laboratories, Chicago, Illinois, USA) to a metallic everolimus-eluting cobalt chrome stent (Xience, Abbott Laboratories) that is widely used as second-generation DES, the overall performance of BRS did not seem unsatisfactory for relatively short-term follow-up, consisting of 1 year in Europe and Asia (ABSORB III and ABSORB Japan trials).[45,46] However, these trials did not seem to have enough power to detect the risk of scaffold thrombosis (scT) in patients receiving BRS. Moreover, 3-year outcomes from the ABSORB II trial, a prospective randomised trial that included 501 patients with one or two *de novo* coronary lesions, showed that treatment with BRS was associated with a two-fold increased risk of device-oriented clinical events, specifically an increased risk of target-vessel myocardial infarction, as well as an increased risk of late scT. There were six incidents of definite scT occurring beyond a year among patients who received the BRS, compared with no reported cases of definite or probable ST for patients who received the metallic DES. Additionally, vasomotor functions at 3 years were similar in both groups.[45] A meta-analysis of six trials addressing the efficacy and safety of Absorb versus Xience showed a significantly higher incidence of ST, especially within the initial 30 days after deployment.[47] Two-year results from the Amsterdam Investigator-Initiated Absorb Strategy All-Comers (AIDA) trial showed that use of BRS was associated with increased risk of scT, and of target-vessel myocardial infarction, compared to those receiving DES.[48] The US Food and Drug Administration (FDA) recently announced increased

incidence of major adverse cardiac, as well as thrombotic events in patients receiving BRS, compared to those with metallic DES based on results from the 2-year follow-up of the ABSORB III trial. The FDA recommends appropriate selection of target vessel/lesion and optimal device. Accordingly, optimal BRS implantation strategy has recently been referred to as 'PSP', referring to: Prepare the lesion, appropriate Sizing, and Post-dilatation. These findings suggest that ST after BRS implantation is more likely related to procedures, which the expertise of operators may largely affect, as implantation procedures are not very different to those in current metallic DES. Therefore, in the case of using the current version of BRS, careful patient selection and lesions in combination with efficient lesion preparation by balloon pre-dilatation, and appropriate scaffold deployment followed by sufficient post-dilatation aiming at good scaffold apposition, are critical. Moreover, for these purposes, detailed intravascular imaging, especially OCT, for optimisation of scaffold deployment, is strongly encouraged for avoiding scT. Thus, in addition to accumulation of procedural and technical tips for the delivery, further technological evolution developing thinner strut of the scaffold, strengthening radial force, and further effective delivery of antiproliferative drugs will likely be required before widespread clinical indication of BRS for more complex patients with complex lesions.

CONCLUSIONS

ST has aroused significant clinical attention along with the change of coronary metallic stents over time. Despite recent relatively low incidence, the clinical importance of ST has been recently reaffirmed, mainly due to a new era of treating coronary artery disease with BRS. For avoiding this most critical complication of PCI, establishment of careful and optimal revascularisation strategies in accordance with the complexity of patients and lesions, adequate lesion preparation and post-dilatation for good stent apposition without edge dissection, and, most importantly, selection of appropriate antiplatelet agents for appropriate duration even in consideration of genetic background is essential.

REFERENCES

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

2. Cassese S et al. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. Heart. 2014;100(2):153-9.

3. Stone GW et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med. 2007;356(10): 998-1008.

4. Kedhi E et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet. 2010;375(9710): 201-9.

5. Tada T et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. JACC Cardiovasc Interv. 2013;6(12):1267-74.

6. Byrne RA et al. Report of a European Society of Cardiology-European Association of Percutaneous Cardiovascular Interventions task force on the evaluation of coronary stents in Europe: executive summary. Eur Heart J. 2015;36(38):2608-20.

7. Tearney GJ et al; International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT). Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol. 2012;59(12): 1058-72.

8. Kang SJ et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. Circulation. 2011; 123(5):2954-63.

9. Schulz S et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. Eur Heart J. 2009;30(22):2714-21.

10. Burzotta F et al. Angiographic and clinical outcome of invasively managed patients with thrombosed coronary bare metal or drug-eluting stents: the OPTIMIST study. Eur Heart J. 2008; 29(24):3011-21.

11. Serruys PW et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. Lancet. 2016;388(10059):2479-91.

12. Cutlip DE et al.; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115(17): 2344-51.

13. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet. 1978; 1(8058):263.

14. Owens GK et al. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol Rev. 2004;84(3):767-801.

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

16. Serruys PW et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med. 1991; 324(1):13-7.

17. Schömig A et al. Four-year experience with Palmaz-Schatz stenting in coronary angioplasty complicated by dissection with threatened or present vessel closure. Circulation. 1994;90(6):2716-24.

18. Leon MB et al.; Stent Anticoagulation Restenosis Study Investigators. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med. 1998;339(23):1665-71.

19. Greenhalgh J et al. Drug-eluting stents versus bare metal stents for angina or acute coronary syndromes. Cochrane Database Syst Rev. 2010;(5):CD004587.

20. Cheneau E et al. Asymptomatic late stent thrombosis after sirolimus stent implantation. Cardiovasc Radiat Med. 2004;5(1):57-8.

21. Palmerini T et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet. 2012; 379(9824):1393-402.

22. Navarese EP et al. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. BMJ. 2013;347:f6530.

23. Räber L et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation. 2012;125(9):1110-21.

24. Armstrong EJ et al. Clinical presentation, management, and outcomes of angiographically documented early, late, and very late stent thrombosis. JACC Cardiovasc Interv. 2012;5(2):131-40.

25. Ozbek MR et al. Contour restoration in posttraumatic hemifacial asymmetry with microvascular omental free flap. A case report. Handchir Mikrochir Plast Chir. 1991;23(4):189-92.

26. Prati F et al. Suboptimal stent deployment is associated with subacute stent thrombosis: optical coherence tomography insights from a multicenter matched study. From the CLI Foundation investigators: the CLI-THRO study. Am Heart J. 2015;169(2):249-56.

27. Taniwaki M et al. Mechanisms of Very Late Drug-Eluting Stent Thrombosis Assessed by Optical Coherence Tomography. Circulation. 2016;133(7): 650-60.

28. Kimura T et al; RESTART Investigators. Comparisons of baseline demographics, clinical presentation, and long-term outcome among patients with early, late, and very late stent thrombosis of sirolimus-eluting stents: Observations from the Registry of Stent Thrombosis for Review and Reevaluation (RESTART). Circulation. 2010;122(1):52-61.

29. van Werkum JW et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol. 2009;53:1399-409.

30. Cayla G et al. Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis. JAMA. 2011; 306(16):1765-74.

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

32. Attizzani GF et al. Mechanisms, pathophysiology, and clinical aspects of incomplete stent apposition. J Am Coll Cardiol. 2014;63(14):1355-67.

33. Kastrati A et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007; 356(10):1030-9.

34. Byrne RA et al. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. JACC Cardiovasc Interv. 2009; 2(4):291-9.

35. Togni M et al. Local vascular dysfunction after coronary paclitaxel-eluting stent implantation. Int J Cardiol. 2007;120(2):212-20.

36. Otsuka F et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. Eur Heart J. 2015;36(32): 2147-59.

37. Rizas KD, Mehilli J. Stent Polymers: Do They Make a Difference? Circ Cardiovasc Interv. 2016;9(6). pii: e002943.

38. Hulot JS et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood. 2006;108(7):2244-7.

39. Price MJ et al.; GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA. 2011; 305(11):1097-105.

40. Montalescot G et al.; ARCTIC Investigators. High on-treatment platelet reactivity as a risk factor for secondary prevention after coronary stent revascularization: A landmark analysis of the ARCTIC study. Circulation. 2014;129(21):2136-43.

41. Cayla G et al; ARCTIC investigators. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet. 2016; 388(10055):2015-22.

42. Mega JL et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA. 2010;304(16): 1821-30.

43. Chikata Y et al. Simultaneous subacute coronary artery stent thrombosis in a carrier of two CYP2C19 loss-of function polymorphisms (*2/*3). Int J Cardiol. 2016; 212:148-50.

44. Jeong YH. "East asian paradox": challenge for the current antiplatelet strategy of "one-guideline-fits-all races" in acute coronary syndrome. Curr Cardiol Rep. 2014;16(5):485.

45. Serruys PW et al. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. Lancet. 2015;385(9962):43-54.

46. Kimura T et al.; ABSORB Japan Investigators. A randomized trial evaluating everolimus-eluting Absorb bioresorbable scaffolds vs. everolimus-eluting metallic stents in patients with coronary artery disease: ABSORB Japan. Eur Heart J. 2015;36(47):3332-42.

47. Ellis SG et al.; ABSORB III Investigators. Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease. N Engl J Med. 2015;373(20):1905-15.

48. Wykrzykowska JJ et al; ARCTIC Investigators. Bioresorbable Scaffolds versus Metallic Stents in Routine PCI. N Engl J Med. 2017. [Epub ahead of print].

REPAIR OF CONGENITAL HEART DEFECTS: ESSENTIALS FOR THE ADULT CARDIOLOGIST

Andrew H. Constantine,[1] Ee Ling Heng,[2] *Syed M. Afzal Sohaib[1]

1. Department of Cardiology, Imperial College Healthcare, London, UK
2. Royal Brompton & Harefield NHS Foundation Trust, London, UK
**Correspondence to s.sohaib@imperial.ac.uk*

Disclosure: The authors have declared no conflicts of interest.
Received: 17.05.16 **Accepted:** 12.05.17
Citation: EMJ Int Cardiol. 2017;5[1]:62-70.

ABSTRACT

Congenital heart disease represents the most prevalent birth defect, and surgical and interventional advances have translated to a burgeoning adult population of patients. Timely, tailored, and lesion-specific interventions are necessary to optimise long-term outcomes for this complex, heterogeneous patient cohort. We present a review of the most common defects which may be encountered in general adult cardiology. Particular focus is paid to the recommended interventional options and associated complications for each condition in line with European and American guidelines.

Keywords: Adult congenital heart disease, atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), coarctation of the aorta (CoA), pulmonary stenosis (PS).

INTRODUCTION

Congenital heart defects are the most frequently occurring birth anomaly, affecting around 8 in every 1,000 live births.[1] This corresponds to 1.35 million live births with congenital heart disease (CHD) worldwide annually,[2] representing a significant global health burden. With advances in cardiac surgery and perioperative and medical care, over 85% of children with CHD survive into adulthood.[3] This has expanded the population of adults with CHD to an estimated 13 million worldwide.[4] Excluding spontaneously healed defects and bicuspid aortic valve disease, the prevalence of adult CHD is 3.5 per 1,000 adults.[5]

Since Alfred Blalock and Helen Taussig[6] pioneered the first subclavian to pulmonary artery (PA) shunt, which "turned a blue baby pink" in 1944, congenital heart interventions have been developed for even the most complex lesions. The advent and application of cardiopulmonary bypass for CHD surgery was a major milestone in the mid-1950s. Catheter interventions in CHD began with William Rashkind and William Miller's[7] development in 1966 of balloon atrial septostomy for palliation of neonates with transposition of the great arteries. Thereafter, since the 1980s, there has been an explosion in the number and breadth of minimally invasive catheter-driven procedures, which has transformed the field of CHD.

Advances in surgical techniques and improvements in perioperative care have reduced surgical mortality to the single digits for most operations. Technological advances in imaging techniques have facilitated even antenatal diagnoses and therapies. Guidelines summarising and evaluating recent evidence have been developed to guide management strategies for individual conditions, including the timing and indications for repair and follow-up.[8,9] However, the heterogeneity of disease processes and small patient numbers along with the speciality's relative youth, has meant a lack of robust evidence. All of the recommendations stated in this review are based on expert consensus (Level C evidence), unless stated otherwise.

This review aims to introduce the non-specialist to repair of the five most common congenital heart defects seen in adults: atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), coarctation of the aorta (CoA) and pulmonary stenosis (PS). Tackling the more complex lesions is beyond the scope of this manuscript.

ATRIAL SEPTAL DEFECT

ASD is the second most common type of CHD worldwide,[10] affecting 1.3 per 1,000 live births,[11] and, as such, is frequently encountered by the general cardiologist. The term encompasses four distinct structural entities, with only the first two affecting the true atrial septum: secundum ASD (80% of ASDs), primum ASD (15%), sinus venosus defect (5%), and unroofed coronary sinus (<1%). ASDs often present incidentally in children, but advancing age harbours increasing rates of exercise intolerance, atrial tachyarrhythmias, right heart enlargement and dysfunction, and pulmonary hypertension (PH). Consequently, adults with uncorrected defects have shortened life expectancies.[12]

Table 1a: Indications for intervention in ASD.

Indications for ASD closure (class of recommendation)	
ESC 2010	**ACC/AHA 2008**
Significant shunt (signs of RV volume overload) and PVR <5 WU +/- symptoms (Class 1)	ASD with RA or RV enlargement +/- symptoms (Class 1)
Suspicion of paradoxical embolism where other causes have been excluded* (Class IIa)	Presence of paradoxical embolism or documented orthodeoxia-platypnoea* (Class IIa)
Pulmonary hypertension where PVR ≥5 WU, but <2/3 of SVR (baseline or when challenged with vasodilators e.g. nitric oxide, or after targeted PAH therapy) (Class IIb)	Net left-to-right shunting, with a PAP <2/3 of systemic pressure, PVR <2/3 of SVR, or when responsive to pulmonary vasodilator therapy or test occlusion of the defect (Class IIb)

*This is an indication for intervention in an ASD of any size.
PAP: pulmonary artery pressure; ESC: European Society of Cardiology; ACC/AHA: American College of Cardiology/American Heart Association; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; Qp/Qs: pulmonary flow/systemic flow; RA: right atrium; RV: right ventricle; SVR: systemic vascular resistance; WU: wood units; ASD: atrial septal defect.
Adapted from the 2010 ESC guidelines[8] and the 2008 ACC/AHA guidelines.[9]

Table 1b: Indications for intervention in ventricular septal defect.

Indications for VSD closure (class of recommendation)	
ESC 2010	**ACC/AHA 2008**
Symptoms attributable to left-to-right shunting through the VSD without severe pulmonary vascular disease (Class 1)	Net left-to-right shunt (Qp/Qs >2.0) and clinical evidence of LV volume overload (Class 1)
Asymptomatic patients with evidence of LV volume overload attributable to the VSD (Class 1)	Personal history of infective endocarditis (Class 1)
Pulmonary hypertension, when there is still a net left-to-right shunt (Qp/Qs >1.5) present and PAP or PVR are <2/3 of systemic values* (Class IIa)	Net left-to-right shunting (Qp/Qs >1.5) present and PAP and PVR are <2/3 of systemic values (Class IIa)
Personal history of infective endocarditis (Class IIa)	Net left-to-right shunting (Qp/Qs >1.5) present in the presence of LV systolic or diastolic failure (Class IIa)
VSD-associated prolapse of an aortic valve cusp causing progressive aortic regurgitation (Class IIa)	

*Measurements at baseline or after vasoreactivity testing or a period of pulmonary hypertension therapy.
LV: left ventricle; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; Qp/Qs: pulmonary flow/systemic flow; SVR: systemic vascular resistance; VSD: ventricular septal defect; ACC/AHA: American College of Cardiology/American Heart Association; ESC: European Society of Cardiology.
Adapted from the 2010 ESC guidelines[8] and the 2008 ACC/AHA guidelines.[9]

Internationally recognised indications for ASD closure are summarised in Table 1a.[8,9] Patients with ASDs not fulfilling these criteria should have ongoing follow-up, as shunt size can increase with age.[13] Pulmonary vascular resistance >8 WU or shunt reversal with Eisenmenger physiology are contra-indications to closure (Class III).

ASD closure may take the form of surgical repair or transcatheter device closure. Percutaneous closure is first-line in secundum ASDs with a stretched diameter <36–40 mm and a sufficient rim of tissue to anchor the device. In this population, catheter intervention has a successful closure rate of >98% with an acceptable procedural safety profile. The major complication rate is quoted at 1.6%[14] and includes erosion into surrounding structures, device thrombosis with systemic thrombo-embolism, device embolisation requiring surgery, pericardial tamponade, and death. Minor complications (1–5%) include atrial tachyarrhythmias, transient heart block, and vascular complications. Delayed complications following percutaneous closure include device endocarditis, nickel hypersensitivity, migraine, and conduction abnormalities.[15] Aspirin is recommended for 6 months following device closure, with institution specific decisions regarding extended antiplatelet therapy beyond this period.[16]

Surgical closure is required in ASDs (both secundum and non-secundum) where the anatomy precludes device closure. Modern surgical techniques involve open suture or patch closure on cardiopulmonary bypass or minimally invasive, video-assisted thoracoscopic surgery. Operative mortality is low (<1%), although advancing age and comorbidities increase morbidity, including congestive cardiac failure and longer intensive therapy unit stays.[12]

Repair normalises life expectancy when performed before the age of 25 years, and may improve exercise tolerance and right heart function when performed at any age.[17,18] Very long-term follow-up continues to provide insights into the effects of early repair, with a single-centre study of surgical ASD closure patients over four decades reporting right ventricular (RV) dysfunction in a third of patients, albeit with preserved functional status.[19] Regular follow-up should be routine in patients repaired in adulthood, with residual shunts, elevated PA pressures, or arrhythmias. The risk of arrhythmia, especially atrial fibrillation and flutter, persists following defect closure. However, pre-existing atrial arrhythmias are less prevalent following repair.[20]

VENTRICULAR SEPTAL DEFECT

Discounting bicuspid aortic valve disease, VSD is the most common CHD, affecting 4.1 per 1,000 live births[11] and accounting for 35–40% of CHD worldwide.[10] VSDs are usually subdivided into their anatomical location and can be classified as perimembranous, muscular, or subarterial. Most small (usually muscular) VSDs close spontaneously in infancy and early childhood.[21] Of the remainder, most are diagnosed and repaired during childhood. As a result, congenital VSDs of haemodynamic significance are rare in adults, with a prevalence of 0.3 per 1,000 population.[22]

VSDs repaired in childhood without evidence of a residual defect will not need further surgical intervention. Similarly, small VSDs with insignificant effects on the left ventricle (LV) or the pulmonary vasculature usually remain asymptomatic and do not require surgery.[23] However, closure is recommended in VSDs with clinical or haemodynamic consequences (Table 1b).

An Eisenmenger VSD, the classical Eisenmenger's complex, represents a large defect associated with severe PH, shunt reversal (right-to-left), and cyanosis, and is a contra-indication to closure. In such patients, pharmacotherapy used to treat consequential PH may be beneficial.[24-26] A modest amount of randomised controlled trial evidence supports a positive effect on pulmonary haemodynamics, 6-minute walk test distance, and quality of life.[27] The effect on survival and the role of combination therapy are unclear.[27,28]

Surgical techniques for VSD repair have been practiced since the 1950s.[29] Surgical closure remains the treatment of choice for most defects.[23-35] Surgery is performed through a sternotomy on cardiopulmonary bypass and with transvalvular access to the defect. The closure rate is excellent at ~97–100%.[31,34] Technical problems arise where defects cannot be easily accessed, as well as in apical defects and multiple muscular defects. Mortality and major complication rates are low (1–2%), except when elevated PA pressures and RV dysfunction are present.

Catheter-device closure can be used as an alternative to surgery in centrally located muscular VSDs and perimembranous defects.[36] It is especially useful in patients with a high-operative-risk, in those with previous attempts at surgical closure, and in restrictive VSD closure. Device closure

has a high implantation success rate (96.6%) with relatively few complications. These include a residual shunt (3.1%) and cardiac dysrhythmias (10.6%).[37] Complete heart block following percutaneous closure of peri-membranous VSDs occurs in 1% of cases,[38,39] and may develop years after repair. Complications are more common in children weighing <5 kg.[40]

Follow-up is recommended in all patients with a VSD, with shorter interval and tertiary centre follow-up for patients with LV dysfunction, residual shunt, PH, aortic regurgitation, outflow tract obstruction, and evidence of dysrhythmia.[8] Adults with small, unrepaired defects require follow-up due to the risk of an increase in shunt size, LV volume overload, and other complications, which may necessitate late repair.[41,42] Transthoracic echocardiography is usually sufficient in the surveillance of these patients. Following spontaneous closure of a VSD, or where surgical repair has been successful without a residual defect or associated lesions and with normal PA pressures, routine follow-up in a specialist centre is not required.

Patients with VSDs are at increased risk of endocarditis. Meticulous dental hygeine and regular dental review are strongly encouraged. Antibiotic prophylaxis for prevention of procedure-associated infection is not routinely recommended for uncomplicated VSDs.[43] However, the American Heart Association (AHA) recommends antibiotic prophylaxis for dental procedures in certain situations, such as in the 6 months following complete VSD closure and indefinitely in the presence of a residual VSD in relation to patch material.[44]

PATENT DUCTUS ARTERIOSUS

The ductus arteriosus is a vital structure in the fetus, connecting the proximal left PA and the descending aorta distal to the left subclavian artery. It allows shunting of blood across the non-functioning pulmonary circulation. Its persistence beyond a few weeks after birth is termed PDA. Its prevalence is 2.9 per 10,000 live births,[11] representing 10–15% of all adult CHD. PDA usually presents as an isolated lesion in adults, unlike in young children where concurrent complex defects are often present.

The initial pathophysiology is that of left-to-right shunting, the magnitude of which depends on the ductal resistance. This resistance varies with the defect length, narrowest diameter, and shape. The sequelae of LV volume overload and PH depends on the shunt size.

Patients with small ducts without an audible murmur or signs of LV volume overload and with normal PA pressures generally remain asymptomatic. They have a normal life expectancy and do not require repair. The presence of a continuous murmur in a small defect without signs of LV overload should be considered for closure (Class IIa).[8]

Moderate or large defects may be asymptomatic in childhood, or may present with fatigue and exertional dyspnoea. LV volume overload or PH may predominate and are both indications for closure (Class I). Patients with PH should be considered for closure, even when pulmonary vascular resistance is very high, as long as there is evidence of a net left-to-right shunt or pulmonary vascular reactivity at catheterisation (Class IIa). Adults with large defects may present with Eisenmenger's syndrome. Here, closure must be avoided (Class III).[8,9] The management and outcomes are similar to Eisenmenger VSD.

Where the anatomy permits, transcatheter device closure is the preferred mode of treatment, even when cardiac surgery is indicated for correction of concomitant cardiac lesions. The most frequent method used, transcatheter coil occlusion, was developed in 1992 by Cambier et al.[45] Currently, a number of occluder devices exist for different defect morphologies, achieving complete closure rates of 85–100%.[46] Serious complications are rare, including device embolisation, flow disturbance from device protrusion, access site thrombosis, and infection.

Surgical repair has been practiced since the first reported successful PDA ligation by Gross and Hubbard[47] in 1939. Surgical ligation or division are both effective. In adults, however, aortic and PDA calcification, as well as tissue friability around the aortic isthmus and PA, increase the complication rate, including PDA rupture.[48] In older adults, aortic calcification is routinely seen and transcatheter closure is therefore the preferred approach. Consequently, surgery is generally reserved for patients with very large ducts, unfavourable duct morphology for transcatheter closure,[49,50] or in accompanying PDA aneurysms (8% of pre-natal cases,[51] but rare in adults).

Follow-up is not required beyond 6 months following PDA closure in the absence of a residual shunt, LV dysfunction, or high PA pressures.

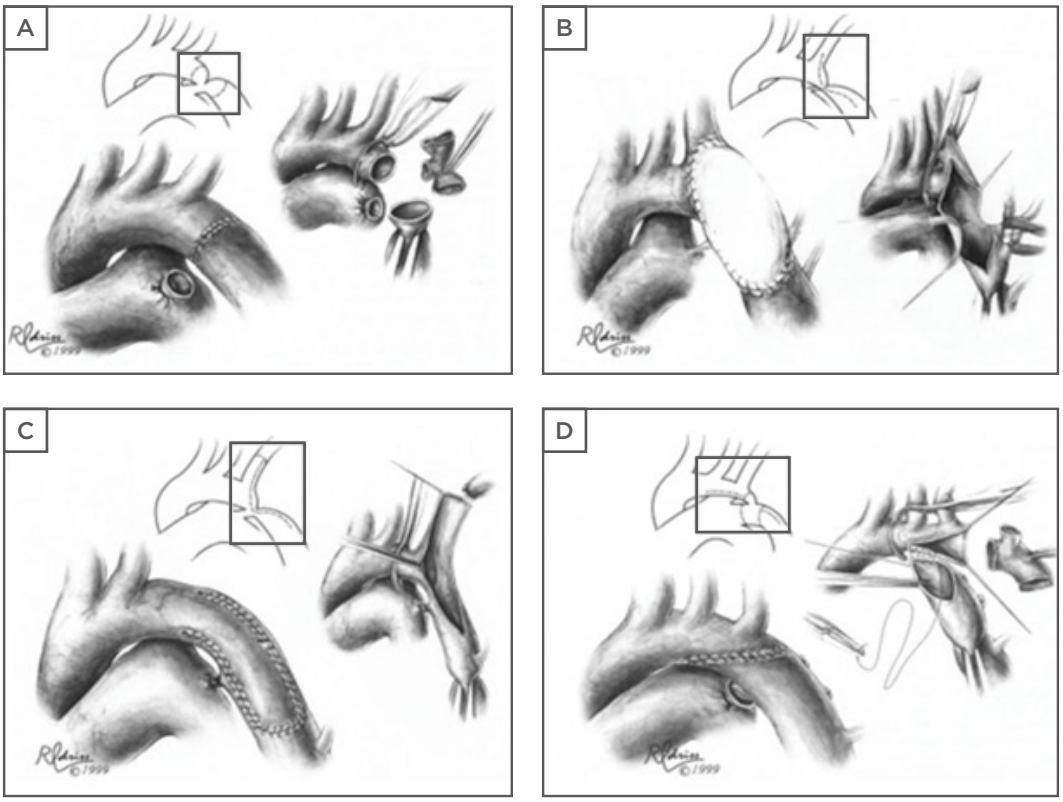


Figure 1: Surgical techniques in coarctation of the aorta repair.
A) Resection and direct end-to-end anastomosis; B) Patch aortoplasty; C) Subclavian flap aortoplasty; D) Resection with extended end-to-end anastomosis. Regardless of the surgical technique applied, late onset complications of re-coarctation and aneurysm formation (particularly following patch angioplasty) should be actively monitored for.
Figures reprinted with permission.[54]

The presence of a residual shunt, LV dysfunction, or PH necessitates follow-up in a specialist centre at 1–3 yearly intervals.

COARCTATION OF THE AORTA

CoA accounts for 5–8% of all CHD with a prevalence of 4.4 per 10,000 live births.[2,11] It is a generalised aortopathy rather than a localised pathology and represents a broad anatomical spectrum of disease; from a mild, discrete narrowing to a long, hypoplastic segment of the aorta. This clinical entity should be distinguished from pseudocoarctation, which is characterised by a kinked, elongated aortic segment without significant obstruction to blood flow (≤20 mmHg at cardiac catheterisation). Bicuspid aortic valve is the most frequent associated lesion, present in 85% of cases.

CoA is classified by its anatomical relationship with the PDA or ligamentum arteriosus and the aortic arch. A pre-ductal CoA is seen in the setting of an infant with a large PDA, where systemic blood flow is dependent on the right-to-left shunting of blood to the descending aorta. This ductal-dependent circulation requires prostaglandins to maintain duct patency until emergency repair is performed. Post-ductal CoA presents depending on the severity of the stenosis, presence of concomitant intra-cardiac lesions, and the presence of collateral vessels. Adults with CoA have usually been repaired in childhood, unless diagnosed in adulthood when investigating early-onset or resistant hypertension. Indeed, the 2008 American College of Cardiology (ACC)/AHA guidelines for adult CHD recommend that all patients with systemic arterial hypertension should be examined for brachial-femoral delay, together with performing supine bilateral arm blood pressures and prone right or left leg popliteal artery blood pressures, looking for differential pressures.[9]

Timing of repair varies according to severity. In the absence of pre-ductal CoA, early repair of childhood CoA is recommended between 2 and 5 years of age. Indications for repair in adult patients depend on symptoms, examination findings,

and imaging criteria.[8] Repair is indicated in patients with a non-invasive pressure difference >20 mmHg between upper and lower limbs, with one of the following:

- Upper limb hypertension (>140/90 mmHg)
- Pathological blood pressure response during exercise
- Significant LV hypertrophy (all Class I)

Patients with hypertension and ≥50% aortic narrowing relative to the diameter of the diaphragmatic aorta by computed tomography (CT), cardiovascular magnetic resonance (CMR), or invasive angiography, should be considered for intervention (Class IIa). It is unclear whether an incidental finding of a significant narrowing in the absence of symptoms or hypertension should be repaired (Class IIb).

Surgical repair of CoA was realised in 1944, when Clarence Crafoord[52] performed the first successful resection with end-to-end anastomosis in humans, and replicated by Robert Gross in 1945.[53] The main types of CoA repair are summarised in Figure 1. Surgery has a low mortality (<1%) in children, but this increases significantly over the age of 30.

Percutaneous balloon angioplasty was developed as an alternative to surgical repair in the late 1970s.[55] For lasting results, the technique generally involves overstretching of the vessel and a therapeutic tear of the intima with variable extension to the adventitia.[56] This predisposes to complications, such as dissection, false aneurysm, and rupture, with a relatively high rate of aneurysm formation (2–20%).[57,58] The deployment of aortic stents, both covered and bare-metal, has become the treatment of choice in those with favourable anatomy. CoA stenting overcomes many of the shortcomings of balloon dilatation by scaffolding the target lesion, reducing recoil, and recurrent stenosis. Stents can be deployed without overstretching and tearing, resulting in fewer vessel wall complications. Recent experience with covered stents gives an incidence of aneurysm formation and vessel rupture of <1%.[59] In repaired adults with residual or recurring CoA, angioplasty with or without stenting may be effective,[60] although surgery remains the modality of choice for recurrent long segment disease, or where there is concurrent hypoplasia of the arch.

Regular follow-up with interval imaging of the aorta is required in all patients. CMR is the preferred imaging modality to reduce lifetime radiation dosing. Measurement of blood pressure and appropriate use of ambulatory blood pressure monitoring is imperative as hypertension is common, even in the absence of significant residual coarctation. Imaging focusses on identifying the post-repair anatomy, associated cardiac lesions, and the development of complications, mainly restenosis and aneurysm formation. Late complications and associated pathology mean that patients with repaired CoA have a shortened life expectancy, with a 20-year survival of 84%.[61]

PULMONARY STENOSIS

PS accounts for ˜8% of all CHD at birth,[10] affecting 5.5 per 10,000 live births.[11] Obstruction is most common at the valve level as an isolated defect, accounting for 80–90% of cases. RV outflow tract obstruction (RVOTO) also occurs at the subvalvular level (infundibular or sub-infundibular PS; 5%), supravalvular level (1–2%), in a branch PA (discrete, or diffuse 'hypoplasia'; 5%), or as a combination of the above.[62] Taken together, RVOTO and PS may contribute to 20% of all CHD, including as part of tetralogy of Fallot. It is the most common valve lesion that requires therapy in adults, in part due to previously repaired patients presenting with residual lesions, such as pulmonary regurgitation or restenosis.

Morphologically, the valve is dome-shaped in the majority of cases, with a narrow central opening, but mobile valve cusps. In <20% of cases, the valve is dysplastic with poorly mobile cusps. This is characteristic of PS in Noonan's syndrome, diagnosed during adulthood in 8% of cases.[63] Stenotic valves may calcify with advancing age.

Presentation and clinical history varies with the site and severity of the RVOTO. Severe PS, isolated or as part of a syndrome (such as tetralogy of Fallot, truncus arteriosus, or some types of transposition of the great arteries) will present in neonates with heart failure and may be duct-dependent. This necessitates early repair. Most other lesions lead to progressive RVOTO, either through direct valvular calcification or reactive myocardial hypertrophy, which presents with reduced exercise capacity and exertional dyspnoea. Mild valvular PS usually does not progress.[64]

According to the 2010 European Society of Cardiology (ESC) guidelines,[8] indications for repair include RVOTO at any level, regardless of symptoms, where the Doppler peak gradient is >64 mmHg (Class I). Repair should be considered in

symptomatic patients, those with RV dysfunction, double-chambered RV (from a small VSD), significant arrhythmias, or right-to-left shunting via an ASD or VSD who do not meet Doppler criteria (Class IIa). Peripheral PS should be assessed for repair if >50% diameter narrowing and RV systolic pressure >50 mmHg with or without lung perfusion abnormalities (Class IIa).

In valvular PS, transcatheter balloon valvotomy is the treatment of choice. The procedure is considered successful when the invasive transvalvular gradient falls to <30 mmHg. The procedure is relatively safe, with the rates of mortality and serious complications cited as 0.24% and 0.35%, respectively.[62] Rarely occurring complications include transient bradycardia and hypotension at the time of balloon inflation, right bundle branch block or atrio-ventricular block, PA tears, and balloon malfunction.

Surgical therapy is still necessary for significant residual PS despite repeated balloon valvotomies and for more complex lesions. Bioprosthetic valves are preferred to mechanical valves due to the increased risk of thrombosis in right-sided lesions. More complex lesions may necessitate RVOT reconstruction in the form of patch augmentation and valved conduits. A growing minority of patients requiring intervention are suitable for percutaneous pulmonary valve implantation (PPVI). Where feasible, PPVI is a safe and effective alternative to surgical valve replacement. Follow-up studies ≤7 years have shown a high procedural success rate with a low incidence of post-procedure pulmonary regurgitation and a 5-year re-intervention rate of <25%.[65]

In patients with previous pulmonary valve intervention, progressive RVOT dysfunction may occur due to several mechanisms, including pulmonary regurgitation and conduit malfunction (stenosis, calcification, and kinking).[66] This may lead to several lifetime procedures, with repeated operations being associated with increased morbidity. In this population, PPVI may avoid or postpone open-heart surgery and its associated risks.

Patients with RVOTO require life-long follow-up with interval echocardiographic imaging. Most patients will be seen annually in specialised CHD centres, although those with mild valvular or residual PS require follow-up every 5 years.

CONCLUSIONS

Early diagnosis and, where possible, repair of congenital heart defects has created a population of adults with CHD, which is projected to rise significantly over the coming decades. Repair is rarely 'curative', with patients requiring lifelong follow-up for surveillance of late complications.

Furthermore, specialist CHD services are provided by relatively few centres, each covering large geographic areas. Therefore, adults with repaired and native congenital heart defects may present to local hospitals staffed by non-specialists, either with a chief cardiovascular complaint or with a cardiac co-morbidity. Consequently, a basic understanding of the anatomy, physiology, and the potential therapeutic interventions for these conditions is necessary to be able to make an effective assessment, provide urgent treatment and communicate with the tertiary centre as needed.

In a 'hub-and-spoke' approach, local units may be supported in looking after patients with simple defects. Care of patients with moderate-to-complex lesions requires closer links and referral to specialist centres which requires effective national frameworks combined with widespread education programmes tackling the most frequently encountered congenital heart defects.

REFERENCES

1. Mason CA et al. Prevalence is the preferred measure of frequency of birth defects. Birth Defects Res A Clin Mol Teratol. 2005;73(10):690-2.

2. Hoffman JI. Incidence of congenital heart disease: I. Postnatal incidence. Pediatr Cardiol. 1995;16(3):103-13.

3. Nieminen HP et al. Late results of pediatric cardiac surgery in Finland: A population-based study with 96% follow-up. Circulation. 2001;104(5):570-5.

4. Mulder BJ. Epidemiology of adult congenital heart disease: Demographic variations worldwide. Neth Heart J. 2012; 20(12):505-8.

5. van der Bom T et al. The prevalence of adult congenital heart disease, results from a systematic review and evidence based calculation. Am Heart J. 2012; 164(4):568-75.

6. Blalock A, Taussig H. The surgical treatment of malformations of the heart: In which there is pulmonary stenosis or pulmonary atresia. JAMA. 1945;128(3): 189-202.

7. Rashkind WJ, Miller WW. Creation of an atrial septal defect without thoracotomy. A palliative approach to complete transposition of the great arteries. JAMA. 1966;196(11):991-2.

8. Baumgartner H et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur

Heart J. 2010;31(23):2915-57.

9. Warnes CA et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008;118(23):e714-e833.

10. van der Linde D et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58(21):2241-7.

11. Reller MD et al. Prevalence of congenital heart defects in metropolitan Atlanta, 1998 – 2005. J Pediatr. 2008;153(6): 807-13.

12. Murphy JG et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. N Engl J Med. 1990;323(24):1645-50.

13. McMahon CJ et al. Natural history of growth of secundum atrial septal defects and implications for transcatheter closure. Heart. 2002;87(3):256-9.

14. Abaci A et al. Short and long term complications of device closure of atrial septal defect and patent foramen ovale: Meta-analysis of 28,142 patients from 203 studies. Catheter Cardiovasc Interv. 2013;82(7):1123-38.

15. Jalal Z et al. Long-term complications after transcatheter atrial septal defect closure: A review of the medical literature. Can J Cardiol. 2016;32(11):1315.e11-1315.e18.

16. The Amplatzer septal occluder and delivery system instructions for use. FDA IFU. September 2001. Available at: https://www.fda.gov/ohrms/dockets/ac/01/briefing/3790b1_01_sponsor.doc. Last accessed: 30 May 2017.

17. Humenberger M et al. Benefit of atrial septal defect closure in adults: Impact of age. Eur Heart J. 2011;32(5):553-60.

18. Attie F et al. Surgical treatment for secundum atrial septal defects in patients >40 years old. A randomized clinical trial. J Am Coll Cardiol. 2001;38(7):2035-42.

19. Cuypers JA et al. The unnatural history of an atrial septal defect: Longitudinal 35 year follow up after surgical closure at young age. Heart. 2013;99(18):1346-52.

20. Vecht JA et al. Atrial septal defect closure is associated with a reduced prevalence of atrial tachyarrhythmia in the short to medium term: A systematic review and meta-analysis. Heart. 2010; 96(22):1789-97.

21. Erol O et al. Natural history of prenatal isolated muscular ventricular septal defects. J Turkish Ger Gynecol Assoc. 2014; 15(2):96-9.

22. Warnes CA et al. Task force 1: The changing profile of congenital heart disease in adult life. J Am Coll Cardiol. 2001;37(5):1170-5.

23. Gabriel HM et al. Long-term outcome of patients with ventricular septal defect considered not to require surgical closure during childhood. J Am Coll Cardiol. 2002; 39(6):1066-71.

24. Manes A et al. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: A comparison between clinical subgroups. Eur Heart J. 2014; 35(11):716-24.

25. Zuckerman WA et al. Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. Am J Cardiol. 2011;107(9):1381-5.

26. Mukhopadhyay S et al. Phosphodiesterase-5 inhibitor in Eisenmenger syndrome: A preliminary observational study. Circulation. 2006; 114(17):1807-10.

27. Galiè N et al. Bosentan therapy in patients with Eisenmenger syndrome: A multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114(1):48-54.

28. Iversen K et al. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: A randomized, placebo-controlled, double-blinded trial. Eur Heart J. 2010;31(9):1124-31.

29. Cooley DA et al. Surgical considerations in repair of ventricular and atrial septal defects utilizing cardiopulmonary bypass; experience with 104 cases. Surgery. 1958; 43(2):214-25.

30. Kidd L et al. Second natural history study of congenital heart defects. Results of treatment of patients with ventricular septal defects. Circulation. 1993; 87(2 Suppl):I38-51.

31. Anderson BR et al. Contemporary outcomes of surgical ventricular septal defect closure. J Thorac Cardiovasc Surg. 2013;145(3):641-7.

32. Aydemir NA et al. Results for surgical closure of isolated ventricular septal defects in patients under one year of age. J Card Surg. 2013;28(2):174-9.

33. Wang Q et al. Ventricular septal defects closure using a minimal right vertical infraaxillary thoracotomy: Seven-year experience in 274 patients. Ann Thorac Surg. 2010;89(2):552-5.

34. Xunmin C et al. Comparison of results and complications of surgical and Amplatzer device closure of perimembranous ventricular septal defects. Int J Cardiol. 2007;120(1):28-31.

35. Saleem K et al. Outcome of ventricular septal defect closure. J Coll Physicians Surg Pak. 2004;14(6):351-4.

36. Yang J et al. Transcatheter versus surgical closure of perimembranous ventricular septal defects in children: A randomized controlled trial. J Am Coll Cardiol. 2014;63(12):1159-68.

37. Arora R et al. Transcatheter closure of congenital ventricular septal defects: Experience with various devices. J Int Cardiol. 2003;16(1):83-91.

38. Masura J et al. Percutaneous closure of perimembranous ventricular septal defects with the eccentric Amplatzer device: Multicenter follow-up study. Pediatric Cardiol. 2005;26(3):216-9.

39. Yang L et al. A systematic review on the efficacy and safety of transcatheter device closure of ventricular septal defects (VSD). J Interv Cardiol. 2014;27(3): 260-72.

40. Holzer R et al. Device closure of muscular ventricular septal defects using the Amplatzer muscular ventricular septal defect occluder: Immediate and mid-term results of a U.S. registry. J Am Coll Cardiol. 2004;43(7):1257-63.

41. Soufflet V et al. Behavior of unrepaired perimembranous ventricular septal defect in young adults. Am J Cardiol. 2010;105(3):404-7.

42. Neumayer U et al. Small ventricular septal defects in adults. Eur Heart J. 1998;19(10):1573-82.

43. National Institute for Health and Clinical Excellence. Prophylaxis against infective endocarditis: Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures. 2008. London: National Institute for Health and Clinical Excellence.

44. Wilson W et al.; American Heart Association. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116(15):1736-54.

45. Cambier PA et al. Percutaneous closure of the small (less than 2.5 mm) patent ductus arteriosus using coil embolization. Am J Cardiol. 1992;69(8):815-6.

46. Gamboa R et al. Percutaneous closure of patent ductus arteriosus in adults using different devices. Rev Esp Cardiol. 2010;63(6):726-9.

47. Gross RE, Hubbard JP. Surgical ligation of a patent ductus arteriosus: Report of first successful case. JAMA. 1939;

112(8):729-31.

48. Ng AS et al. Patent ductus arteriosus in patients more than 50 years old. Int J Cardiol. 1986;11(3):277-85.

49. Fisher RG et al. Patent ductus arteriosus in adults--long-term follow-up: Nonsurgical versus surgical treatment. J Am Coll Cardiol. 1986;8(2):280-4.

50. John S et al. The adult ductus: Review of surgical experience with 131 patients. J Thorac Cardiovasc Surg. 1981;82(2):314-9.

51. Jan SL et al. Isolated neonatal ductus arteriosus aneurysm. J Am Coll Cardiol. 2002;39(2):342-7.

52. Crafoord C. Congenital coarctation of the aorta and its surgical treatment. J Thorac Surg. 1945;14(5):347-61.

53. Gross RE. Surgical correction for coarctation of the aorta. Surgery. 1945; 18(6):673-8.

54. Dodge-Khatami A et al. Risk factors for recoarctation and results of reoperation: A 40-year review. J Card Surg. 2000;15(6):369-77.

55. Singer MI et al. Transluminal aortic balloon angioplasty for coarctation of the aorta in the newborn. Am Heart J. 1982;103(1):131-2.

56. Ino T et al. Dilatation mechanism of balloon angioplasty in children: Assessment by angiography and intravascular ultrasound. Cardiovasc Intervent Radiol. 1998;21(2):102-8.

57. Fletcher SE et al. Balloon angioplasty of native coarctation of the aorta: Midterm follow-up and prognostic factors. J Am Coll Cardiol. 1995;25(3):730-4.

58. Rao PS et al. Five- to nine-year follow-up results of balloon angioplasty of native aortic coarctation in infants and children. J Am Coll Cardiol. 1996;27(2):462-70.

59. Qureshi SA et al. Use of covered Cheatham-Platinum stents in aortic coarctation and recoarctation. Cardiol Young. 2004;14(1):50-4.

60. Shah L et al. Use of endovascular stents for the treatment of coarctation of the aorta in children and adults: Immediate and midterm results. J Invasive Cardiol. 2005;17(11):614-8.

61. Cohen M et al. Coarctation of the aorta: Long-term follow-up and prediction of outcome after surgical correction. Circulation. 1989;80(4):840-5.

62. Cuypers JA et al. Pulmonary stenosis: update on diagnosis and therapeutic options. Heart. 2013;99(5):339-47.

63. Colquitt JL, Noonan JA. Cardiac findings in Noonan syndrome on long-term follow-up. Congenit Heart Dis. 2014; 9(2):144-50.

64. Hayes CJ et al. Second natural history study of congenital heart defects. Results of treatment of patients with pulmonary valvar stenosis. Circulation. 1993; 87(2 Suppl):I28-37.

65. Cheatham JP et al. Clinical and hemodynamic outcomes up to 7 years after transcatheter pulmonary valve replacement in the US melody valve investigational device exemption trial. Circulation. 2015;131(22):1960-70.

66. Wells WJ et al. Homograft conduit failure in infants is not due to somatic outgrowth. J Thorac Cardiovasc Surg. 2002;124(1):88-96.

IS THERE AN OPTIMAL DURATION OF DUAL ANTIPLATELET THERAPY AFTER DRUG-ELUTING STENT IMPLANTATION?

***Bernard Cheung,[1-3] Yue Fei,[1] Man-Fung Tsoi,[1] Tommy Tsang Cheung[1]**

1. Division of Clinical Pharmacology and Therapeutics, Department of Medicine, The University of Hong Kong, Pokfulam, Hong Kong
2. State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Pokfulam, Hong Kong
3. Institute of Cardiovascular Science and Medicine, The University of Hong Kong, Pokfulam, Hong Kong
**Correspondence to mycheung@hku.hk*

Disclosure: The authors have declared no conflicts of interest.
Received: 06.01.17 **Accepted:** 28.03.17
Citation: EMJ Int Cardiol. 2017;5[1]:71-79.

ABSTRACT

Early discontinuation of dual antiplatelet therapy (DAPT) has been identified as a risk factor for late stent thrombosis after the implantation of drug-eluting stents (DES). Different durations of DAPT have been evaluated in observational studies and randomised controlled trials, but the results on the risk of ischaemic and bleeding events have been variable and controversial. Although extended DAPT shows an ischaemic benefit, it is associated with increased bleeding risk, while short-term DAPT has been suggested to be safe in recent trials with the newer generation of DES. Uncertainty regarding the optimal duration of DAPT makes clinical decisions challenging. In this review, evidence from the latest clinical trials on the duration of DAPT after DES implantation and the factors that affect DAPT duration is examined to find the optimal balance between thrombotic and bleeding risks, which would be a useful guide to clinical practice.

Keywords: Drug-eluting stent (DES), dual antiplatelet therapy (DAPT), percutaneous coronary intervention (PCI), bleeding.

INTRODUCTION

Drug-eluting stents (DES) are implanted to reduce the likelihood of restenosis in percutaneous coronary intervention (PCI). Compared with bare-metal stents (BMS), DES significantly reduce the risk of restenosis and the need for target-lesion revascularisation. However, a DES is associated with increased late stent thrombosis (STH) and very late STH, which may result in life-threatening complications.[1-4] Dual antiplatelet therapy (DAPT) means using aspirin together with a platelet $P2Y_{12}$ receptor antagonist such as clopidogrel, prasugrel, and ticagrelor. This therapy reduces the frequency of STH in patients with BMS implantation effectively;[5] therefore, DAPT is thought to be effective in reducing the risk of STH, myocardial infarction (MI), and subsequent ischaemic complications at sites outside of stented segments after DES implantation.

Currently, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Society for Cardiac Angiography and Interventions (SCAI) Guideline recommends that patients with stable ischaemic heart disease should receive 6 months DAPT instead of 12 months DAPT after DES implantation.[6] The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) recommend a 6-month regimen for patients with stable coronary artery disease after receiving new-generation DES.[7] A 12-month regimen is still recommended for those with non-ST-segment elevation acute coronary syndrome (ACS) and ST-segment elevation myocardial infarction (STEMI) by both guidelines. However, the level of evidence for both recommended durations of DAPT is Grade B,[7] which means more clinical studies are required to support these guidelines. Studies have been conducted to evaluate the

safety and efficacy of different durations of DAPT recommended by different societies. Therefore, there is a need to review the currently available evidence on optimal durations of DAPT after DES implantation.

Premature cessation of DAPT has been identified as the most important risk factor of STH, which has led to recommendations for a prolonged DAPT regimen.[8] However, previous evidence has suggested that extended DAPT is associated with increased risk of bleeding as well as all-cause mortality.[9-12] With the recent advances in DES and the development of newer antiplatelet agents, determination of the optimal DAPT duration is crucial for balancing risks and benefits between ischaemic benefits and bleeding. The research question has become how to avoid premature discontinuation of DAPT and prevent increased bleeding at the same time.

CLINICAL EVIDENCE ON DURATIONS OF DUAL ANTIPLATELET THERAPY

Evidence from Observational Studies

Observational studies have shown the benefit of extended DAPT beyond 1 year in terms of lower mortality rate and the frequency of STH and MI. The characteristics of these studies are summarised in Table 1. The BASKET-LATE study reported a greater frequency of late cardiac death or MI in patients receiving DES implantation compared with those receiving BMS implantation (4.9% versus 1.3%) after the discontinuation of DAPT at 6 months.[8] The Duke Heart Center Registry found a 50% increase in the rates of all-cause mortality or MI in patients in whom DAPT was withdrawn at 6 months compared with those who received 24 months DAPT (3.1% versus 7.2%, p=0.02).[13] In the Dutch Registry, early discontinuation of DAPT after DES implantation was reported as a strong predictor of STH (30.7% of 418 DES receivers).[14] Similarly, the Melbourne Interventional Group (MIG) Registry found a lower mortality rate in patients receiving 12 months DAPT than patients receiving 6 months DAPT (2.8% versus 5.3%, p=0.012).[15] However, in the PARIS Registry, continuing DAPT beyond 12 months did not reduce thrombotic risk but was associated with a higher risk of major adverse events when compared to physician-guided cessation for stable patients, which therefore challenged the existing paradigms for extension of DAPT duration.[16] In these studies, first-generation DES were largely used. Therefore, these observations may not be applicable to newer generations of DES.

Evidence from Randomised Controlled Trials

Two randomised controlled trials compared short-term DAPT <12 months and extended DAPT for ≥12 months, while six trials compared safety and efficacy between short-term DAPT <12 months and 12 months DAPT. The characteristics of these studies are summarised in Table 2. All studies demonstrated the non-inferiority of shorter duration of DAPT (3–6 months) with comparable or even better efficacy and safety outcomes than longer duration of DAPT (≥12 months).

Table 1: Characteristics of observational studies allocating different dual antiplatelet therapy durations.

Studies	Total number (DES)	DAPT duration (months)	DES type	Primary outcomes	Number of STH
BASKET-LATE[8]	746 (545)	7–18	BMS, DES	Cardiac death or MI	16
Duke Heart Center Registry[13]	4,666 (1,501)	6–24	BMS, DES	Death, non-fatal MI and composite of death and MI	NR
Dutch Registry[14]	21,009 (11,225)	3–12	BMS, DES	STH	437
Melbourne Interventional Group Registry[15]	2,980 (1,669)	<6 versus ≥12	BMS, DES	Death, MI, target-lesion revascularisation, TVR, and composite of death, MI, and TVR	NR
Paris Registry[16]	5,018 (3,679)	1–24	BMS, DES	Death, MI, STH, TLR, bleeding, and composite of cardiac death, STH, MI, and TLR	NR

DAPT: dual antiplatelet therapy; MI: myocardial infarction; NR: not reported; STH: stent thrombosis; BMS: bare-metal stent; DES: drug-eluting stent; TVR: target-vessel revascularisation; TLR: target-lesion revascularisation.

Table 2: Randomised controlled trials comparing 1) short-term DAPT (<12 months) and 12 months DAPT; 2) short-term DAPT and extended DAPT (>12 months); 3) extended DAPT and 12 months DAPT.

Studies (ClinicalTrials.gov Identifier)	Number of participants	DAPT duration (months)	DES Type	DAPT drugs	Primary outcomes	Number of STH (shorter versus longer DAPT duration)
Short-term DAPT (<12 months) versus 12 months DAPT						
EXCELLENT[19] (NCT00698607)	1,443	6 versus 12	SES[a], EES[b]	clopidogrel + aspirin	Composite of cardiac death, MI, or ischaemia-driven TVR	6 versus 1
SECURITY[20] (NCT00944333)	1,399	6 versus 12	DES[b]	clopidogrel + aspirin	Composite of cardiac death, MI, stroke, STH, or bleeding	2 versus 3
RESET[23] (NCT01145079)	2,117	3 versus 12	SES[a], EES[b], E-ZES[b], R-ZES[b]	clopidogrel + aspirin	Composite of cardiac death, MI, STH, ischaemia-driven TVR, or bleeding	2 versus 3
OPTIMIZE[24] (NCT01113372)	3,120	3 versus 12	E-ZES	clopidogrel + aspirin	Composite of death, MI, stroke, or major bleeding	9 versus 11
ISAR-SAFE[21] (NCT00661206)	6,000	6 versus 12	BES, SES[a], EES[b], ZES[b]	clopidogrel + antiplatelet drug (not specified)	Composite of death, MI, STH, stroke, or major bleeding	5 versus 3
IVUS-XPL 2016[22] (NCT01308281)	1,400	6 versus 12	EES[b]	clopidogrel + aspirin	Composite of cardiac death, MI, stroke, or major bleeding	2 versus 2
I-LOVE-IT 2[46] (NCT01681381)	1,929	6 versus 12	BP-SES	clopidogrel + aspirin	Composite of cardiac death, target vessel MI, or clinically indicated target lesion revascularisation	11 versus 7
Short-term DAPT versus extended DAPT (>12 months)						
PRODIGY[17] (NCT00611286)	1,970	6 versus 24	BMS, PES[a], ZES[b], EES[b]	clopidogrel + aspirin	Composite of death, MI, or cerebrovascular accident	15 versus 13
ITALIC[18] (NCT01476020)	1,850	6 versus 24	EES[b]	clopidogrel, prasugrel, or ticagrelor + aspirin	Composite of death, MI, stroke, urgent TVR, stroke, or major bleeding	3 versus 0
Extended DAPT versus 12 months DAPT						
ZEST-LATE/ REAL-LATE[25] (NCT00590174/ NCT00484926)	2,701	12 versus 24	PES[a], SES[a], ZES[b]	clopidogrel + aspirin	Composite of cardiac death or MI	4 versus 5
DES-LATE[26] (NCT01186146)	5,045	12 versus 24	SES[a], PES[a]; ZES[b], EES[b]	clopidogrel + aspirin	Composite of cardiac death, MI, or stroke	11 versus 7

Table 2 continued.

Studies (ClinicalTrials.gov Identifier)	Number of participants	DAPT duration (months)	DES Type	DAPT drugs	Primary outcomes	Number of STH (shorter versus longer DAPT duration)
ARCTIC-Interruption[27] (NCT00827411)	1,259	12 versus 18	DES	thienopyridine + aspirin	Composite of death, MI, stroke or transient ischaemic attack, STH, and urgent TVR	3 versus 0
OPTIDUAL[29] (NCT00822536)	1,385	12 versus 30	SES[a], PES[a]; ZES[b], EES[b]	clopidogrel + aspirin	Composite of death, MI, stroke, or major bleeding	1 versus 3
DAPT[28] (NCT00977938)	9,961	12 versus 30	SES[a], PES[a]; ZES[b], EES[b]	clopidogrel or prasugrel + aspirin	STH, bleeding and composite of death, MI, or stroke	65 versus 19

[a]First-generation DES: PES, SES; [b]Second-generation DES: ZES, EES.
DAPT: dual antiplatelet therapy; MI: myocardial infarction; STH: stent thrombosis; TVR: target vessel revascularisation; BMS: bare-metal stent; DES: drug-eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; BP-SES: biodegradable polymer sirolimus-eluting stent; ZES: zotarolimus-eluting stent; E-ZES: endeavor zotarolimus-eluting stent; R-ZES: resolute zotarolimus-eluting stent; BES: biolimus-eluting stent.

In the PRODIGY trial, patients were randomised to either three different types of DES, or BMS, while receiving 6 or 24 months DAPT. No significant difference was observed in the primary endpoints between the two groups during the follow-up, except for patients that received zotarolimus-eluting stent implantation. However, more frequent bleeding was found in the 24-month group.[17] The ITALIC study demonstrated that the rates of bleeding and thrombotic events did not significantly differ between patients receiving these two DAPT durations after everolimus-eluting stent implantation.[18]

Both the EXCELLENT and the SECURITY trials suggested the non-inferiority of 6 months compared to 12 months DAPT regarding the incidence of cardiac death, MI, stroke, STH, and bleeding after either first-generation or second-generation DES implantation.[19,20] In the ISAR-SAFE study, there was no significant difference in the prevention of death, STH, MI, stroke, and major bleeding between 6 months and 12 months DAPT,[21] which was further confirmed in the recent IVUS-XPL trial.[22] Randomised controlled trials with shorter DAPT of <6 months have also been conducted. The RESET trial showed that 3 months therapy was non-inferior to 12 months therapy with respect to the incidence of primary endpoints, which included cardiac death, MI, STH, ischaemia-driven target vessel revascularisation (TVR), and bleeding.[23] This finding was also consistent with the OPTIMIZE study, which suggested that there were similar effects of 3 months and 12 months DAPT in reducing adverse clinical and cerebral events among patients receiving second-generation DES as no significant increase in STH risk was found in the 3-month group.[24]

There were four randomised controlled trials comparing safety and efficacy between DAPT beyond 12 months and 12 months DAPT. The characteristics of these trials are summarised in Table 2. All studies reported that extended DAPT was associated with increased frequency of major bleeds. Results from the ZEST-LATE/REAL-LATE trials showed the rates of composite events (MI, stroke, and death) and bleeds were higher in patients receiving 24 months DAPT.[25] The extended DES-LATE study confirmed these findings. There was no significant difference in the rate of composite events between 12 months and 24 months DAPT at 48-month follow-up (3.2% versus 3.8%, p=0.26), but there was a significant increase in frequency of

major bleeding with 24 months DAPT (p=0.026).[26] The ARCTIC-Interruption study reported that major bleeding was more common with extended DAPT, but there was a non-significant difference in the occurrence of the composite of death, STH, stroke, or urgent TVR.[27]

The DAPT study was a trial recruiting the largest patient populations and therefore may be more generalisable in clinical practice. The study aimed to determine the benefits and risks of 30 months versus 12 months DAPT in >20,000 patients receiving stent implantation. Unlike previous trials, the therapy and allocation were blinded with both first and second-generation DES as well as clopidogrel and prasugrel. It showed a significant reduction in STH (hazard ratio [HR]: 0.29; 95% confidence interval [CI]: 0.17–0.48) and MI (HR: 0.47; 95% CI: 0.37–0.61) but with a concurrent increase in the risk of major bleeding (HR: 1.61; 95% CI: 1.21–2.16) and non-cardiovascular mortality (HR: 2.23; 95% CI: 1.32–3.78) with extended DAPT. However, the exclusion of those patients at high risk of ischaemic events and bleeding in the first 12 months in the DAPT study may not represent real-world patients and so the generalisability is limited.[28]

The OPTIDUAL study compared patients receiving 48 months and 12 months DAPT. This study failed to demonstrate the superiority of extended DAPT in reducing all-cause mortality, MI, stroke, or major bleeding compared to 12 months DAPT after DES implantation (p=0.17). This study showed a non-significant difference in all-cause mortality as well as non-cardiovascular mortality. However, the study was limited due to early termination and a low sample size that may not have the statistical power to demonstrate the beneficial effect of extended DAPT. Excluding patients with malignancies or other coexisting conditions associated with a life expectancy of <2 years might have excluded a high-risk group.[29] There is a need for more studies to be conducted on patients without malignancies or other coexisting conditions associated with a life expectancy of <2 years.

Meta-Analyses

Meta-analyses of the above-mentioned trials[17-21,23,24,26-29] demonstrated the beneficial effect of extended DAPT beyond 12 months on reducing frequency of STH and MI. However, there was a significant increase in the frequency of major bleeds and all-cause mortality as compared with 12 months DAPT.[11,30] Extended DAPT was especially protective in reducing the risk of recurrent MI for patients with prior MI at high risk of late ischaemic events than early discontinuation of DAPT before 12 months (risk ratio: 0.70; 95% CI: 0.55–0.88, p=0.003).[31] Extended DAPT may also protect from the occurrence of atherothrombotic events outside the stented segments throughout the coronary vasculature.[32] The increase in all-cause mortality was driven by non-cardiovascular mortality,[10-12] although no significant association was found between extended DAPT and non-cardiovascular mortality in a recent study evaluating the effect of extended DAPT on mortality.[33] The inclusion criteria for this analysis, which included the trials comparing DAPT ≥6 months versus 0–6 months DAPT regardless of stent types implanted, may be responsible for this contradiction. One meta-analysis found no difference regarding the risk of all-cause and cardiac mortality. The rate of STH in short-term DAPT group could also be diminished by using safer and more effective second-generation DES.[34] On the other hand, all the meta-analyses indicated that shorter duration did not differ from 12 months DAPT with respect to efficacy or safety endpoints and actually could be protective in major bleeding.

These meta-analyses were limited by the heterogeneity in protocol designs, the inclusion and exclusion criteria of populations, the definitions of clinical events, and the lengths of follow-up. Patients and interventions in the included studies might not be representative of real clinical settings. These analyses did not include the OPTIDUAL study. The overall effect on short-term versus extended DAPT should therefore be cautiously interpreted and updated when new evidence becomes available.

FACTORS ASSOCIATED WITH DUAL ANTIPLATELET THERAPY DURATION

Diabetes Mellitus

Diabetes mellitus is a risk factor for thrombotic events after stent implantation. There was some evidence demonstrating a relationship between diabetes and DAPT duration, but it was not sufficient to suggest an optimal duration of DAPT in patients with diabetes. A study suggested that prolonged DAPT duration was associated with a decreased risk of death and MI in diabetic patients.[35] This finding was further confirmed by the subgroup analysis of the EXCELLENT trial, which found greater benefits from 12 months than 6 months DAPT in diabetic patients.[19] In addition,

this evidence was confirmed in recent reports concerning the advantage of newer-generation DES in diabetic patients.[36,37] However, these findings were not confirmed by a recent sub-study from the SECURITY trial, in which no benefit of extending DAPT beyond 6 months in the prevention of ischaemic or bleeding events was observed in diabetic patients.[38] The effect of stent type on diabetic patients will accordingly affect the decision on DAPT duration[39] and should therefore be examined in randomised controlled trials with a sufficient number of patients.

High Bleeding Risk

Extended duration of DAPT could prevent late and very late STH but at the price of increased bleeding risk. Current guidelines recommend shorter durations of DAPT with second-generation DES in patients with higher bleeding risk (e.g. advanced age, renal insufficiency, history of transient ischaemic attack, stroke).[6,7,40] One month's DAPT following BMS implantation has also been given for patients at a high bleeding risk, but this works for the BioFreedom™ (Biosensors Europe, Morges, Switzerland) DES and not BMS, as shown in the LEADERS FREE trial.[41] It is important to predict bleeding complications as well as thrombotic events. Predicted models have been developed for bleeding events.[42] However, the availability of emergency medical care, as well as clinical presentation of patients, may influence the complications of major bleeding, while clinical predictors such as ACS, diabetes, and renal insufficiency were not only reported as risk factors of STH but also of bleeding, which might make it difficult to balance thrombotic prevention and bleeding risk. More data balancing STH and bleeding risks in varied clinical settings are highly necessary.

UNRESOLVED ISSUES AND CLINICAL IMPLICATIONS

The results of current meta-analyses indicate that recommendations of DAPT duration after DES implantation should be carefully individualised by weighing up benefits and risks. The standard 12 months DAPT is a reasonable trade-off justified by the totality of the current evidence from randomised controlled trials. However, the risks of thrombosis and bleeding are different in every patient.

Newer Generation Drug Eluting Stents

An extended duration of DAPT shows advantages in preventing late and very late STH in patients with first-generation DES implantation. The adverse consequence of DAPT discontinuation on increased STH has led to the development of a newer generation of DES.[43] A significant decrease in STH with second-generation DES was observed when DAPT was ceased before 12 months, but no differences were observed between first and second-generation DES with prolonged DAPT.[44] New-generation DES have been suggested to be safer than both BMS and early-generation DES with a significantly lower risk of early, late, and very late STH in short and long-term follow-up.[45] With a more favourable healing profile and improved re-endothelialisation properties, a shorter duration of DAPT may be considered as a safe, effective, or beneficial strategy for patients undergoing PCI with newer-generation DES and modern interventional techniques, especially in those at high bleeding risk. However, there were few stent-specific studies performed. A recently published randomised sub-study of the I-LOVE-IT 2 trial has shown the non-inferiority in safety and efficacy of 6–12 month DAPT after the implantation of novel DES (biodegradable polymer sirolimus-eluting stents).[46] More DES-specific studies are required, although it is a challenge to conduct randomised controlled trials on newer-generation DES because of the lower rate of STH events.

Newer $P2Y_{12}$ Inhibitors

Newer $P2Y_{12}$ antagonists with greater suppression of platelet activity, and hence lower rates of recurrent ischaemic events, are increasingly used instead of clopidogrel.[47] However, evidence on the optimal duration of DAPT with these newer inhibitors is limited. Prasugrel and ticagrelor are recommended on equal terms with clopidogrel in patients with ACS or DES implantation in current guidelines.[6] In fact, newer $P2Y_{12}$ antagonists may result in a significant difference in the balance between ischaemic and bleeding risk. Prasugrel and ticagrelor were found to be more effective than standard or even high-dose clopidogrel in STEMI patients after implantation of either DES or BMS.[48] Further randomised controlled trials are needed to examine the effect of novel $P2Y_{12}$ inhibitors under diverse durations of DAPT.

Clinical Choice

The clinical decision on DAPT duration should be individualised according to each patient's ischaemic and bleeding profile. The protection of extended DAPT duration on STH is counterbalanced by an increased risk of bleeding and all-cause mortality.

Table 3: Risk factors for stent thrombosis and bleeding after percutaneous coronary intervention.[52]

	Stent thrombosis	Bleeding
Patient characteristics	Diabetes, ACS, malignancy, left ventricular dysfunction	Age, history of bleeding, ACS, low body weight, gastro-intestinal disease, impaired kidney function, liver disease, CVA, malignancy
Procedural factors	Stent type and size, incomplete stent expansion, overlapping stents, small vessel calibre	No vascular closure device
Pharmacological factors	Premature discontinuation of DAPT, slow metabolisers of the antiplatelet pro-drug	Prolonged DAPT, concurrent use of oral anticoagulant

ACS: acute coronary syndrome; CVA: cerebrovascular accident; DES: drug-eluting stent; DAPT: dual antiplatelet therapy.

The application of a prolonged DAPT regimen for >12 months would be reasonable in selected patient populations beyond prevention of STH. It could be contemplated for prevention of MI in patients having a high ischaemic risk but a low bleeding threat and with a good tolerance of the initially recommended DAPT duration. Patients with a history of clinically significant intracranial or gastrointestinal bleeding should be allocated short-term DAPT. Premature discontinuation of DAPT should be avoided and newer-generation DES should be applied to prevent late and very late STH events. The DAPT Score, developed from the DAPT trial, could be useful to predict the risk of bleeding and decide whether to continue DAPT beyond 12 months or not. Several risk scoring systems have been developed to predict future ischaemic and bleeding risks after PCI and identify patients who can benefit from different DAPT durations. Patients with a DAPT Score ≥2 may consider extending DAPT >12 months regardless of MI status and vice versa.[49] Patients with a PARIS Score at 0–3, 4–7, and ≥8 may have low, intermediate, and high bleeding risk, respectively. Shorter DAPT durations should be considered if a higher PARIS Score is predicted.[50] However, the predictive accuracy of these scores should be further verified in large studies with more diverse patients before we can use them to guide clinical decision-making on duration and potency of DAPT.

Future Studies

Before implementing the optimal choice of DAPT for DES receivers, the limitations of clinical trial evidence must not be overlooked. The major limitation of current meta-analyses is a lack of patient-level data, which precludes covariate-adjusted and time-to-event analysis of studies of different durations of DAPT. It is therefore necessary to conduct better-powered, larger, long-term follow-up clinical trials to shed more light on deciding the optimal duration of DAPT. Subgroup analysis can then be conducted to provide some evidence on risks and benefits in specific groups of patients. The potential effects of genetic variations on platelet responsiveness may influence the effectiveness of DAPT[51] and should therefore be added to further studies.

When new stents and antiplatelet drugs are introduced, optimal DAPT duration needs to be re-evaluated. The clinical presentations and bleeding and ischaemic risk profiles of patients are important factors to be taken into consideration as well. Any change in the clinical profile of patients may alter the risk-benefit balance or compliance with DAPT. Potential risk factors of STH and bleeding are summarised in Table 3. Therefore, physicians must carefully weigh up the potential benefit with respect to a reduced risk of ischaemic events and late STH against an increased risk of bleeding before making the therapeutic decision.

CONCLUSIONS

DAPT prevents STH in patients after DES implantation but there are bleeding complications. As the balance of risk and benefit differs among patients, physicians should balance the risk of bleeding against benefits of preventing ischaemic events in each patient carefully and explain to patients. Large randomised controlled trials with newer generations of DES and $P2Y_{12}$ antagonists should be conducted to provide evidence with sufficient statistical power.

REFERENCES

1. Bangalore S et al. Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. Circulation. 2012;125(23):2873-91.

2. Navarese EP et al. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. BMJ. 2013;347: f6530.

3. Camenzind E et al. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation. 2007;115(11):1440-55; discussion 55.

4. Palmerini T et al. Long-Term Safety of Drug-Eluting and Bare-Metal Stents Evidence From a Comprehensive Network Meta-Analysis. J Am Coll Cardiol. 2015; 65(23):2496-507.

5. Ielasi A et al. Stent thrombosis and duration of dual antiplatelet therapy. Curr Pharm Design. 2010;16(36):4052-63.

6. Levine GN et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2016. doi: 10.1161/CIR.0000000000000404.

7. Windecker S et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2014;72(12): 1253-379.

8. Pfisterer M et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006;48(12):2584-91.

9. Cassese S et al. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomised trials. Eur Heart J 2012; 33(24):3078-87.

10. Liou K et al. Optimal duration of dual antiplatelet therapy following drug-eluting stents implantation: A meta-analysis of 7 randomised controlled trials. Int J Cardiol. 2015; 201:578-80.

11. Navarese EP et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. BMJ. 2015; 350:h1618.

12. Tsoi MF et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of large randomised controlled trials. Scientific Reports. 2015;5:13204.

13. Eisenstein EL et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA. 2007;297(2):159-68.

14. van Werkum JW et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol. 2009;53(16):1399-409.

15. Butler MJ et al. The effect of intended duration of clopidogrel use on early and late mortality and major adverse cardiac events in patients with drug-eluting stents. Am Heart J. 2009;157(5):899-907.

16. Mehran R et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet. 2013; 382(9906):1714-22.

17. Valgimigli M et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012;125(16): 2015-26.17.

18. Gilard M et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. J Am Coll Cardiol. 2015;65(8):777-86.

19. Gwon HC et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation. 2012;125(3):505-13.

20. Colombo A et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol. 2014; 64(20):2086-97.

21. Schulz-Schüpke S et al. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J. 2015;36(20): 1252-63.

22. Hong SJ et al.; IVUS-XPL Investigators. 6-Month versus 12-Month dual-antiplatelet therapy following long everolimus-eluting stent implantation the IVUS-XPL randomised clinical trial. JACC Cardiovasc Interv. 2016;9(14): 1438-46.

23. Kim BK et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol. 2012;60(15):1340-8.

24. Feres F et al. Optimized duration of clopidogrel therapy following treatment with the Endeavor zotarolimus-eluting stent in real-world clinical practice (OPTIMIZE) trial: rationale and design of a large-scale, randomized, multicenter study. Am Heart J. 2012;164(6): 810-6.e3.

25. Park SJ et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. New Engl J Med. 2010;362(15):1374-82.

26. Lee CW et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized controlled trial. Circulation. 2014;129(3):304-12.

27. Collet JP et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet. 2014;384(9954):1577-85.

28. Mauri L et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. New Engl J Med. 2014; 371(23):2155-66.

29. Helft G et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. Eur Heart J. 2015; pii:ehv481.

30. Fei Y et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of randomized controlled trials. Int J Cardiol. 2016;220:895-900.

31. Udell JA et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016; 37(4):390-9.

32. Stone GW et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226-35.

33. Elmariah S et al. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. Lancet. 2015;385(9970):792-8.

34. Giustino G et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2015; 65(13):1298-310.

35. Iakovou I et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting

stents. JAMA. 2005;293(17):2126-30.

36. Vardi M et al. Long-term efficacy and safety of zotarolimus-eluting stent in patients with diabetes mellitus: pooled 5-year results from the ENDEAVOR III and IV trials. Catheter Cardiovasc Interv. 2013; 82(7):1031-8.

37. Yan P et al. Second- versus first-generation drug-eluting stents for diabetic patients: a meta-analysis. Arch Med Sci. 2014;10(2):213-21.

38. Tarantini G et al. Optimal duration of dual antiplatelet therapy after second-generation drug-eluting stent implantation in patients with diabetes: The SECURITY (Second-Generation Drug-Eluting Stent Implantation Followed By Six- Versus Twelve-Month Dual Antiplatelet Therapy)-diabetes substudy. Int J Cardiol. 2016;207:168-76.

39. Brar SS et al. Long-term outcomes by clopidogrel duration and stent type in a diabetic population with de novo coronary artery lesions. J Am Coll Cardiol. 2008;51(23):2220-7.

40. Ducrocq G et al. A history of stroke/transient ischemic attack indicates high risks of cardiovascular event and hemorrhagic stroke in patients with coronary artery disease. Circulation. 2013;127(6):730-8.

41. Urban P et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med. 2015;373(21):2038-47.

42. Garg P et al. Balancing the risks of bleeding and stent thrombosis: a decision analytic model to compare durations of dual antiplatelet therapy after drug-eluting stents. Am Heart J. 2015;169(2): 222-33.

43. Onuma Y, Serruys PW. Bioresorbable scaffold: The advent of a new era in percutaneous coronary and peripheral revascularization? Circulation. 2011;123(7): 779-97.

44. Camenzind E et al. Modifying effect of dual antiplatelet therapy on incidence of stent thrombosis according to implanted drug-eluting stent type. Eur Heart J. 2014; 35(29):1932-48.

45. Sarno G et al. Stent thrombosis in new-generation drug-eluting stents in patients with STEMI undergoing primary PCI: a report from SCAAR. J Am Coll Cardiol. 2014;64(1):16-24.

46. Yaling Han et al. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent randomized substudy of the I-LOVE-IT 2 trial. Circ Cardiovasc Interv. 2016;9(2):e003145.

47. Norgard NB, DiNicolantonio JJ. P2Y12 antagonists in non-ST-segment elevation acute coronary syndromes: latest evidence and optimal use. Ther Adv Chronic Dis. 2015;6(4):204-18.

48. Rafique AM et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: A network meta-analysis. JACC Cardiovasc Interv. 2016; 9(10):1036-46.

49. Yeh RW et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond year 1 after percutaneous coronary intervention. JAMA 2016;315(16): 1735-49.

50. Baber U et al. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. J Am Coll Cardiol. 2016;67(19):2224-34.

51. Vries MJ et al. Assessment of bleeding risk in patients with coronary artery disease on dual antiplatelet therapy. A systematic review. Thromb Haemost. 2015; 115(1):7-24.

52. Binder RK, Luscher TF. Duration of dual antiplatelet therapy after coronary artery stenting: where is the sweet spot between ischaemia and bleeding? Eur Heart J. 2015;36(20):1207-11.

DRUG-COATED BALLOONS AND CORONARY BIFURCATION LESIONS

***Alessandro Durante,[1] Pietro Leonida Laforgia[2]**

1. Ospedale Valduce, Como, Italy
2. Università degli Studi di Milano, Milan, Italy
**Correspondence to durante.alessandro@gmail.com*

Disclosure: The authors have declared no conflicts of interest.
Received: 04.03.17 **Accepted:** 23.05.17
Citation: EMJ Int Cardiol. 2017;5[1]:80-84.

ABSTRACT

Bifurcation coronary lesions still represent a challenge for interventional cardiologists. Although provisional stenting is considered the gold standard for the treatment of bifurcations, some studies report good results with two-stent techniques. In the last few years, drug-coated balloons have been used for the treatment of several kinds of coronary lesion, such as in-stent restenosis, small vessels, and bifurcations. The use of drug coated balloons for the treatment of the side branch after provisional stenting is a promising option for further improving provisional stenting results.

Keywords: Drug-eluting balloon (DEB), drug-coated balloon (DCB), coronary bifurcations, coronary artery disease.

INTRODUCTION

The treatment of coronary bifurcation lesions still represents one of the greatest challenges for interventional cardiologists, due to the technical complexity, the lower success rates compared to non-bifurcation lesions, and the lack of clear scientific data. In this review article, we will briefly describe the current treatment options for bifurcation lesions and examine more deeply the role of drug-coated balloons (DCB) in this context.

CORONARY BIFURCATION LESIONS

A coronary bifurcation lesion is defined as "coronary artery narrowing occurring adjacent to, and/or involving, the origin of a significant side branch".[1] A significant side branch (SB) is a branch that, if lost, can impact the prognosis of the patient; thus, determination of the SB as significant usually depends upon the subjective judgement of each single interventional cardiologist.

BIFURCATION CLASSIFICATION

Several different classifications of coronary bifurcation lesions have been proposed, due to the variety of possible bifurcation lesions, with different technical implications, treatment options, and prognoses. The most used, for its simplicity and reproducibility, is the Medina classification. This classification is based on the presence or absence of narrowing >50% on each of the three components of the bifurcation: the main branch proximal (MBP), the main branch distal, and the SB. A value of 0 or 1 is assigned to each of the three segments in the following order: MBP, main branch distal, and SB. For example, a bifurcation lesion involving the MBP and the SB would be defined as 1,0,1. Seven morphologies are therefore possible.[2] Despite being the most used classification, the Medina has several limitations, since it does not consider the plaque burden, branch diameter, lesion length, bifurcation angles, the presence of ostial disease, or calcification. Thus, different classifications have been proposed, such as the Movahed classification.[3,4]

CURRENT TREATMENT OF BIFURCATION LESIONS

The goal of percutaneous coronary intervention in bifurcation lesions is to maximise flow in the main branch (MB), maintain flow in the SB, prevent its occlusion, and maximise long-term patency

of both vessels. The provisional stent strategy is currently the standard approach for treatment of bifurcation lesions: it involves stenting the MB first (most commonly with a drug-eluting stent [DES]), and then evaluating whether there is a need to treat the SB (with balloon angioplasty or stenting), which would only be performed in cases of flow limitation, a large dissection, or a large myocardial territory subsiding the SB.[5,6]

When needed, stenting of the SB can be performed via a T-stenting technique, or with an overlapping technique, such as T and protrusion, culotte, or crush. At the end of the procedure, whether SB stenting has been performed or not, kissing balloon inflation (or post-dilation) can be performed, although its benefit is not clear.[7]

Despite being a valid approach, two-stent techniques are less frequently used, since the majority of studies have failed to demonstrate a benefit in choosing two-stent techniques over provisional stenting. A recent meta-analysis, including nine randomised trials comparing provisional strategy with two-stent techniques, demonstrated that a complex strategy has similar safety (death, stent thrombosis) and efficacy (restenosis, target lesion/vessel revascularisation) compared to provisional stenting, despite carrying an increased risk of early and late myocardial infarction. However, subgroup analysis suggests that two-stent techniques may be preferable in patients with true bifurcation lesions (bifurcation with a lesion both in the MB and the SB), with large SB.[8] Two-stent techniques include T-stenting (which is preferred for T-shape angulation), T and protrusion, culotte, and crush (which can be implemented with technical refinements, such as mini-crush, step-crush, or double kissing crush).[9] The description of these techniques goes beyond the purpose of this review and thus will not be addressed.

The recent EBC TWO study comparing the provisional T-stent versus culotte two-stent technique in large caliber true bifurcation lesions, concluded that there is no difference between provisional strategy and a two-stent culotte strategy in a composite endpoint of death, myocardial infarction, and target vessel revascularisation at 12 months.[10] Moreover, a recent analysis of 5-year survival from the NORDIC I and the BBC ONE studies demonstrated that 5-year mortality was lower among patients who underwent provisional stenting compared to a complex strategy (culotte, crush, and T-stenting).[11] Finally, it is likely that double-stent strategies carry a higher risk of late stent thrombosis compared to single-stenting, as suggested by a meta-analysis of 12 major studies of bifurcation percutaneous coronary intervention, for a total of 6,961 patients.[12]

Table 1: Studies of drug-coated balloons in bifurcation lesions.

Name	Year of publication	Type of study	Design of study	Patients	Restenosis rate	ST rate	TLR rate	Conclusions
PEPCAD V[28]	2011	Prospective, dual-centre, single-arm, Phase II study	DCB in the MB and the SB and subsequent BMS in the MB	28	3.8% in the MB; 7.7% in the SB (at 9 months)	2 patients (7.1%) at 6 and 8 months	1 patient (3.5%)	Feasible procedure; no increased incidence of early and late complications
DEBIUT[30]	2012	Randomised, multicentre, single-blinded 3-arm study	A) DEB in both the MB and SB and BMS in the MB; B) BMS in the MB and regular balloon angioplasty in the SB; or C) paclitaxel DES in the MB and regular balloon in the SB	117	Group A: 8 (24.2%); Group B: 10 (28.6%); Group C: 6 (15%) at 6 months	Group C: 1 (2.5%)	Group A: 6 (15%); Group B: 10 (27%); Group C: 6 (15%) at 6 months	Pretreatment of both MB and SB with DEB failed to show angiographic and clinical superiority over conventional BMS using a provisional T-stenting technique. Moreover, DES showed superior angiographic results than DEB and BMS
BABILON[31]	2014	Multicentre, randomised trial	A) DCB in the MB and SB and BMS in in the MB; B) provisional T-stenting with DES	108	Group A: 9 (17.3%); Group B: 3 (5.4%)	Group A: 1 (1.9%); Group B: 1 (1.9%)	Group A: 8 (15.4%); Group B: 2 (3.6%)	DEB pretreatment before BMS implantation in MB carried worse angiographic and clinical outcomes at 9 months, compared to DES only

Table 1 continued.

Name	Year of publication	Type of study	Design of study	Patients	Restenosis rate	ST rate	TLR rate	Conclusions
DEBSIDE[32]	2015	Multicentre, randomised trial	DES in the MB and DCB in the SB (with DANUBIO balloon)	50	3 (7.5%) at 6 months	0	1 patient (2.5%) at 6 months	Good angiographic and clinical outcomes in the SB after treatment with a DEB at 6 months post-procedure
SARPEDON[33]	2015	Single-centre, single-arm prospective registry	DCB after DES in the MB	50	2 in the MB (4%); 3 in the SB (6%); 5 (10%) overall	0	3 (5.2%) at 1 year	Good results with DCB after DES in the MB
PEPCAD-BIF[34]	2016	Multicentre, randomised trial	A) DCB after MB stenting; B) POBA after MB stenting	64	Group A: 2 (6%); Group B: 9 (26%)	0	Group A: 1 (3%); Group B: 3 (9%)	Better outcome with DCB after MB stenting than with POBA

TLR: target lesion revascularisation; ST: stent thrombosis; DCB: drug-coated balloon; MB: main branch; SB: side branch; BMS: bare-metal stent; POBA: plain old balloon angioplasty; DES: drug-eluting stent.

DRUG-COATED BALLOONS

DCB, on the other hand, have emerged as a possible alternative to DES to prevent restenosis. DCB are semi-compliant angioplasty balloons covered with an antiproliferative drug (most commonly paclitaxel, since sirolimus is not lipophilic) that is rapidly released upon contact with the vessel wall.[13] DCB are not primarily used to improve the culprit stenosis; lesions should be pretreated with standard balloon angioplasty, a non-compliant balloon, and/or scoring balloons. When a good angiographic result is achieved, DCB can be inflated for 30–90 seconds, depending on the DCB used, to allow adequate drug transfer.

DCB thus combine mechanical expansion of the vessel and reduction of neo-intimal hyperplasia without leaving a foreign body, abolishing the risk of late and very late stent thrombosis and reducing the need for dual antiplatelet treatment.[14] Currently, the use of DCB is established in the treatment of in-stent restenosis (ISR), as first described in the PACCOCATH ISR I trial.[15] Further studies have confirmed the superiority of DCB in the treatment of bare-metal stent (BMS) ISR over a paclitaxel-eluting stent, also at long-term follow-up.[16]

In regard to DES ISR, the role of drug-eluting balloons (DEB) is more controversial; DCB have proven to be superior to plain old balloon angioplasty (POBA) for the treatment of ISR occurring in a previously implanted DES in the PEPCAD-DES trial.[17] Furthermore, the ISAR-DESIRE 3 trial compared DCB with paclitaxel-eluting stents in DES ISR and showed no differences between groups in the frequency of death, myocardial infarction, or target lesion thrombosis.[18] On the other hand, DCB have not proven to be superior compared with newer DES: the RIBS V trial compared the DCB with a second-generation DES (everolimus-eluting stent) in the treatment of BMS ISR; at 9 months, the DES group had superior clinical outcomes, including reduced need for target lesion revascularisation (TLR) (8% versus 16%).[19]

However, it is important to underline that not many studies have been conducted in this context. A meta-analysis of observational and randomised data, comparing outcomes in the management of DES ISR using DES, DCB, or POBA showed that the relative risk reduction for TLR for DES was similar to DCB but without the need for an additional stent layer.[20] All being said, as depicted by European Society of Cardiology (ESC) Guidelines on myocardial revascularisation, DCB are recommended for the treatment of ISR after prior BMS or DES, with a Class I indication and level of evidence A.[21]

Another application for DCB is the treatment of small-vessel disease, when technical difficulties outweigh the benefit of placing a stent and where there is more neo-intimal hyperplasia and therefore a higher risk of restenosis.[22] Numerous studies, including the BELLO trial, described a benefit in using DEB instead of placing a stent in vessels with a diameter <2.5 mm.[23]

DRUG-COATED BALLOONS IN BIFURCATION LESIONS

As previously outlined, the treatment of bifurcation lesions is controversial and carries numerous technical difficulties. As previously reported, provisional stenting strategy is the preferred technique for bifurcations; therefore, DCB could carry a potential benefit by administrating an anti-proliferative drug to the vessel wall without stenting the SB. Deploying a stent in the SB could lead to inadequate expansion at the ostium or the protrusion of stent struts into the MB, carrying increased rates of complications without the provision of long-term benefits. As a matter of fact, the incidence of TLR ranges between 1.3% and 17.9%, depending on the population and the technique used. The incidence of stent thrombosis is between 0.4% and 3.7% at 1 year.[24] On the other hand, suboptimal SB results may carry negative prognostic implications.[25] Moreover, SB restenosis may range between 7.9% and 15.4%.[26]

Recent studies have been conducted to evaluate if DCB could be beneficial in the treatment of coronary bifurcation lesions, considering the benefit in ISR and in small vessel disease (Table 1). The PEPCAD V registry was a prospective, multicentre, single-arm trial, in which 28 patients were treated with pre-dilation using a DCB in both the MB and the SB, followed by BMS implantation on the MB only when thrombolysis in myocardial infarction flow was <2, or the MB had a stenosis >50% (14.3% of patients). In this study, the procedural success was 100%. At 9 months, the reported restenosis rate was only 3.8% in the MB and 7.7% in the SB and this was lower compared to restenosis after DES implantation in other studies (4.6–6.7% [MB] and 13.2–14.7% [SB] in the CACTUS study; 0.6–5.1% [MB] and 11.5–19.2% [SB] in the Nordic study).[27-29]

The 2012 multicentre, randomised DEBIUT trial compared three different strategies among 117 patients: DCB in both the MB and SB and BMS in the MB; BMS in the MB and POBA in the SB; paclitaxel DES in the MB and regular balloon in the SB. This study showed that angiographic outcome was similar in the group with DCB+BMS compared with BMS only, but inferior to the group with DES in the MB, suggesting that pretreatment with DCB did not carry any advantage over DES. However, binary restenosis rates at 6 months and major adverse cardiovascular event (MACE) rates were similar between the three groups at 12 months.[30] Negative results came also from the BABILON trial, in which DEB pretreatment before BMS implantation in the MB carried worse angiographic and clinical outcomes at 9 months, compared to DES only.[31]

On the other hand, the DEBSIDE trial analysed the role of DCB in the SB, using the novel DANUBIO balloon, after placement of a DES in the MB; in this group of 52 patients, the results were promising, with a very low risk of complications and of TLR (1 patient) at 6 months, with a good angiographic outcome.[32] Similar results were found in the SARPEDON study which assessed the efficacy of DCB at the SB ostium after DES implantation in the MB, with good angiographic outcome and low rate of restenosis, although a high rate of MACE (19% at 1 year).[33]

Finally, the PEPCAD-BIF multicentre trial was published in 2016, which enrolled 64 patients with a bifurcation lesion and randomised them to DCB versus POBA after MB stenting. Only 5 patients underwent stenting in the SB as a bail-out strategy. The trial showed that the use of DCB after MB stenting was superior to POBA for restenosis rate (6% versus 26% in the POBA group; p=0.045), TLR (1 patient versus 3 patients) and angiographic endpoint.[34]

CONCLUSIONS

Despite the lack of data, the use of DCB in the treatment of bifurcation lesions in addition to standard provisional stenting could be an innovative and useful strategy when SB stenting is not needed, because of the lack of additional procedural risk compared to standard treatment and because of the possible positive prognostic implications, especially by reducing the risk of progression of the disease within the SB.

In our opinion, DCB could be an option for the treatment of the SB after provisional stenting of the MB with a new-generation DES. Further studies are needed to determine whether DCB could improve the overall treatment of bifurcation lesions, since current data is not sufficient to establish the correct treatment for bifurcations lesions and for the use of DCB in this context.

REFERENCES

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

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

3. Movahed MR. Studies involving coronary bifurcation interventions should utilize the most comprehensive and technically relevant Movahed coronary bifurcation classification for better communication and accuracy. Am J Cardiol. 2010;105(8):1204-5.

4. Louvard Y, Medina A. Definitions and classifications of bifurcation lesions and treatment. EuroIntervention. 2015; 11 Suppl V:V23-6.

5. Brar SS et al. Bifurcation stenting with drug-eluting stents: a systematic review and meta-analysis of randomised trials. EuroIntervention. 2009;5(4):475-84.

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

7. Murasato Y et al. Final kissing balloon inflation: the whole story. EuroIntervention. 2015;11SupplV:V81-5.

8. Gao XF et al. Stenting strategy for coronary artery bifurcation with drug-eluting stents: a meta-analysis of nine randomised trials and systematic review. EuroIntervention. 2014;10(5):561-9.10.

9. Lassen JF et al. Percutaneous coronary intervention for coronary bifurcation disease: 11th consensus document from the European Bifurcation Club. EuroIntervention. 2016;12(1):38-46.

10. Hildick-Smith D et al. The EBC TWO Study (European Bifurcation Coronary TWO): A Randomized Comparison of Provisional T-Stenting Versus a Systematic 2 Stent Culotte Strategy in Large Caliber True Bifurcations. Circ Cardiovasc Interv. 2016;9(9):e003643.

11. Behan MW et al. Coronary bifurcation lesions treated with simple or complex stenting: 5-year survival from patient-level pooled analysis of the Nordic Bifurcation Study and the British Bifurcation Coronary Study. Eur Heart J. 2016;37(24):1923-8.

12. Zimarino M et al. Late thrombosis after double versus single drug-eluting stent in the treatment of coronary bifurcations: a meta-analysis of randomized and observational Studies. JACC Cardiovasc Interv. 2013;6(7):687-95.

13. Jackson D et al. A review of the coronary applications of the drug coated balloon. Int J Cardiol. 2017;226:77-86.

14. Richelsen RK et al. Drug-Eluting Balloons in the Treatment of Coronary De Novo Lesions: A Comprehensive Review. Cardiol Ther. 2016;5(2):133-60.

15. Scheller B et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med. 2006;355(20):2113-24.

16. Unverdorben M et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis: the three-year results of the PEPCAD II ISR study. EuroIntervention. 2015;11(8):926-34.

17. Rittger H et al. Long-Term Outcomes After Treatment With a Paclitaxel-Coated Balloon Versus Balloon Angioplasty: Insights From the PEPCAD-DES Study (Treatment of Drug-eluting Stent [DES] In-Stent Restenosis With SeQuent Please Paclitaxel-Coated Percutaneous Transluminal Coronary Angioplasty [PTCA] Catheter). JACC Cardiovasc Interv. 2015;8(13):1695-700.

18. Byrne RA et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet. 2013; 381(9865):461-7.

19. Alfonso F et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). J Am Coll Cardiol. 2014;63(14):1378-86.

20. Goel SS et al. Management of drug eluting stent in-stent restenosis: A systematic review and meta-analysis. Catheter Cardiovasc Interv. 2016;87(6): 1080-91.

21. Kolh P et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur J Cardiothorac Surg. 2014;46(4):517-92.

22. Zeymer U, Scheller B. PCI in small vessels: the case for a drug-coated balloon based intervention. EuroIntervention. 2011; 7SupplK:K57-60.

23. Latib A et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. J Am Coll Cardiol. 2012;60(24):2473-80.

24. Paraggio L et al. Update on Provisional Technique for Bifurcation Interventions. Curr Cardiol Rep. 2016;18(3):27.

25. Niccoli G et al. Coronary bifurcation lesions: to stent one branch or both? A meta-analysis of patients treated with drug eluting stents. Int J Cardiol. 2010; 139(1):80-91.

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

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

28. Mathey DG et al. Treatment of bifurcation lesions with a drug-eluting balloon: the PEPCAD V (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) trial. EuroIntervention. 2011; 7SupplK:K61-5.

29. Steigen TK et al. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. Circulation. 2006;114(18):1955-61.

30. Stella PR et al. A multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in bifurcation lesions treated with a single-stenting technique: six-month angiographic and 12-month clinical results of the drug-eluting balloon in bifurcations trial. Catheter Cardiovasc Interv. 2012;80(7):1138-46.

31. López Mínguez JR et al. A prospective randomised study of the paclitaxel-coated balloon catheter in bifurcated coronary lesions (BABILON trial): 24-month clinical and angiographic results. EuroIntervention. 2014;10(1):50-7.

32. Berland J et al. DANUBIO - a new drug-eluting balloon for the treatment of side branches in bifurcation lesions: six-month angiographic follow-up results of the DEBSIDE trial. EuroIntervention. 2015;11(8):868-76.

33. Jim MH et al. Six month angiographic result of supplementary paclitaxel-eluting balloon deployment to treat side branch ostium narrowing (SARPEDON). Int J Cardiol. 2015;187:594-7.

34. Kleber FX et al. Drug eluting balloons as stand alone procedure for coronary bifurcational lesions: results of the randomized multicenter PEPCAD-BIF trial. Clin Res Cardiol. 2016;105(7):613-21.

PERCUTANEOUS CORONARY INTERVENTION FOR CHRONIC TOTAL OCCLUSION, A REVIEW OF INDICATIONS, TECHNIQUES, AND COMPLICATIONS

***Maria-Cruz Ferrer-Gracia**

Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
**Correspondence to mcferrer10@gmail.com*

Disclosure: The author has declared no conflicts of interest.
Received: 03.02.16 **Accepted:** 28.04.16
Citation: EMJ Int Cardiol. 2017;5[1]:85-95.

ABSTRACT

Percutaneous coronary intervention for chronic total occlusion (CTO) remains a challenging prospect for many interventional cardiologists. The treatment of these lesions is heterogeneous, as is the success rate. The aim of this review is to learn about how to approach these patients and lesions and discover the latest tendencies and research in interventional approaches in this field, as well as how to perform a useful pre-procedural approach, dual injection, lesion crossing, and modification to success. Finally, complications specific to CTO percutaneous intervention should be taken into account. Current guidelines, recommendations, and references to other significant articles which detail different aspects of management in patients with these complex lesions could be a useful guide for people beginning in this area. Algorithms of treatment, step approach, and proctoring are the current tendencies for CTO.

Keywords: Chronic total occlusion (CTO), percutaneous treatment, anterograde approach, retrograde approach.

INTRODUCTION

Chronic total occlusion (CTO) is defined as the total obstruction of a coronary artery for >3 months. This duration has implications for the histopathological characteristics and the success rates associated with intervention.

Among patients diagnosed with coronary disease on angiography, CTO are seen in ~20%,[1,2] however rates as high as 50% can be found in patients who are receiving re-interventions, such as those who have previously had coronary artery bypass graft (CABG) surgery.[1,3,4] Approximately 35% of CTO are currently treated by revascularisation (either CABG or percutaneous coronary intervention [PCI]). In the Canadian multicentre CTO registry, the majority of patients with CTO underwent medical treatment (64%) or were referred for CABG surgery (26%), while only 10% were referred for CTO PCI revascularisation.[1] The referral rate of CTO PCI is between 1% and 16%, suggesting several issues:

- Patients are treated according to operator expertise (specific training) and institutional practice (high cost and resource utilisation) rather than clinical need[5]
- There are concerns regarding higher technical difficulty and perceived risk of complications compared with non-invasive treatment
- A lack of consensus regarding which patients would benefit from CTO revascularisation[6]

There are no randomised controlled data comparing recanalisation with medical therapy. The success of CTO PCI is largely dependent on the level of operator experience with different features of CTO,[7] therefore step training of the operators in order to understand varied lesion specific characteristics is important.[7-9]

The rationale for the treatment of CTO has two key clinical decision points: first, whether to revascularise; and second, by which modality. Clinical need for revascularisation includes relief of the exercise-limiting symptoms of angina or dyspnoea, and also, prognostic factors such as improving regional left ventricular function.[10] Figure 1 shows an algorithm to guide treatment decisions in these patients and lesions.

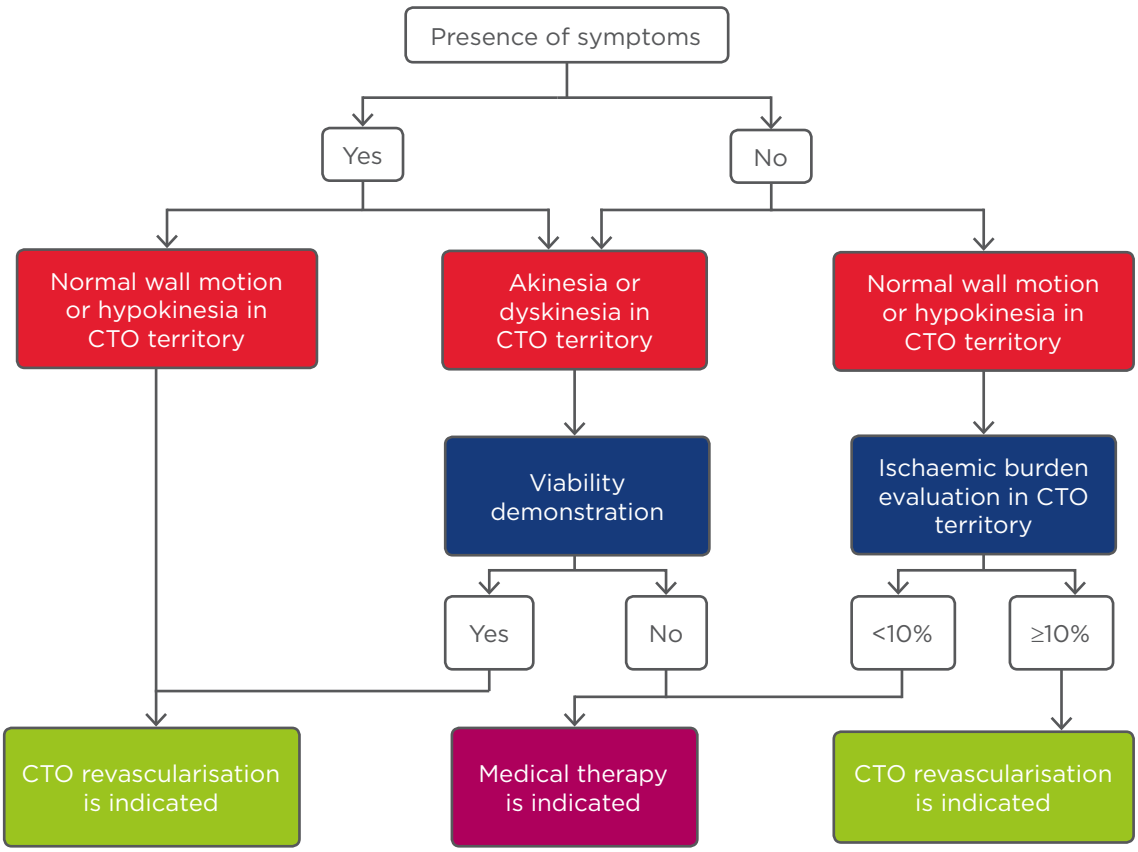


Figure 1: Algorithm of treatment in patients with chronic total occlusion.
CTO: chronic total occlusion.
Adapted from Galassi et al.[11] with permission.

Table 1: Chronic total occlusion percutaneous coronary intervention in current guidelines.[12,13]

Guidelines	Class of recommendation	Level of evidence	Recommendations
European	IIa	B	Percutaneous recanalisation of CTO should be considered in patients with expected ischaemia reduction in a corresponding myocardial territory and/or angina relief.
European	IIb	B	Retrograde recanalisation of CTO may be considered after a failed anterograde approach or as the primary approach in selected patients.
American	IIa	B	PCI of a CTO in patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise.

PCI: percutaneous coronary intervention; CTO: chronic total occlusion.

Discussions of optimal treatment are reflected in the evolution of the approach to CTO treatment in European[12] and American[13] guidelines as shown in Table 1. Since the publication of these guidelines, CTO PCI has undergone drastic improvements with success rates consistently >90% and major complication rates around 2% reported at several expert CTO sites.[14-16] Taking economic aspects into account, it is uncertain whether PCI as an initial strategy would achieve a socially acceptable cost threshold, at any level of angina severity. However, a decision-analytic model suggests that CTO PCI is cost-effective in a patient population with severe angina symptoms. Relevant quality of life metrics should be employed prior to CTO PCI.[17,18]

GENERAL ASPECTS IN CHRONIC TOTAL OCCLUSION LESIONS

Aetiology and Origin of a Chronic Total Occlusion

The development of a CTO could happen after a myocardial infarction; it has been described in 45% of patients without treatment, in 30% of patients after thrombolysis,[19,20] and in 5–10% of patients after failed primary PCI or vessel reocclusion.[21,22] However, the majority (˜60%) of patients with a CTO do not have a history of myocardial infarction.[1] This could be due to the recruitment of collateral vessels to counterbalance the gradual progression to an occluded artery, limiting myocardial damage and resulting in mild or absent clinical symptoms.[23]

Histopathology

Anatomopathological studies of patients in whom a CTO was identified at least 3 months before, showed that thrombotic occlusion progressed over time from soft to hard. Long-term CTO, particularly without previous CABG, also have a high prevalence of negative remodelling.[24] Hard intimal plaques are characterised by calcification. Although severity and extent of calcification and the collagen content of the intimal plaque increases with the duration of CTO, calcium is present in 54% of occlusions <3 months old. Within CTO lesions, microchannels are often observed and they might facilitate lesion crossing during CTO PCI. Microchannels mostly lead into the adventitia, small side branches, or vasa vasorum; however, they can also extend from the proximal to the distal lumen.[25] These differences, along with an abrupt and tapering pattern of proximal and distal lumens, are likely to affect the success rate of PCI in CTO. Furthermore, the prevalence of the tapering pattern in the distal lumen was significantly higher than that in the proximal lumen, suggesting the advantage of a retrograde approach.[24]

Coronary Collateral Circulation

Anastomotic channels represent a native system for coronary arterial bypass allowing bidirectional flow. Collaterals therefore provide an alternative source of blood supply to the myocardium jeopardised by occlusive coronary artery disease, and they can help to preserve myocardial function in the setting of a CTO.[26,27] Coronary collateral pathways are present in >70% of patients with either complete artery occlusion or coronary stenosis >90%.[28]

It is important to note that angiographically visualised collateral vessels do not always indicate myocardial viability. Thus a viability assessment should be undertaken before considering CTO recanalisation in patients with abnormal regional wall motion. In an invasive study using fractional flow reserve, <10% of collaterals provided a normal functional reserve during pharmacological stress.[29] Cardiac magnetic resonance imaging with pharmacological stress testing, perfusion, and contrast enhancement is the optimal assessment to determine whether CTO PCI is indicated in in patients without severe symptoms or ischaemia.[6,30] In patients with evidence of significant myocardial inducible perfusion defect and viability on cardiac magnetic resonance, CTO recanalisation reduces ischaemic burden, favours reverse remodelling, and ameliorates quality of life.[31,32] Positron emission tomography/computed tomography,[33] perfusion contrast echocardiography,[34] and scintigraphy[35] may be used as alternatives to magnetic resonance imaging.

From a technical standpoint, understanding the presence, quality, and location of collateral vessels is key to maximising the likelihood of CTO recanalisation procedural success. Dual injections of the CTO PCI target vessel and the donor artery or branch reveals the presence, size, and tortuosity of the collateral vessels and helps determine whether a retrograde approach is feasible.[4] The presence of collateral flow does not seem to predict later restenosis or re-occlusion of the target vessel.[36]

Clinical and Epidemiological Characteristics of Patients with Chronic Total Occlusion

Patients affected by CTO sometimes show atypical symptoms; shortness of breath and exercise limitation are more frequently observed than typical angina.[11] CTO are frequent in patients with relevant coronary artery disease (CAD), >50% have well-preserved left ventricular function, and ˜80% have no Q-waves in the CTO territory suggesting viable myocardium.[1,2,37] In patients with diagnosed CTO the mean age is 66±11 years; they also have a higher prevalence of all cardiovascular risk factors and previous myocardial infarction than patients with CAD but not CTO.[1]

There are sex differences: 80% of patients with CAD and CTO are men,[1] and women who receive a CTO PCI tend to be older, have higher rates of hypertension and diabetes mellitus, and are less likely to smoke compared with male patients. Moreover, female patients more often have a CTO located in the left anterior descending coronary artery, shorter and fewer blunt stumps and bridging collaterals than men, and are less likely to develop multivessel disease (MVD). However, after multivariable adjustment for known predictors, sex was not associated with CTO PCI failure.[38]

Indications of Treatment

There are three main reasons to recommend a CTO recanalisation:

- To relieve the exercise limiting symptoms of angina or dyspnoea, and, in moderately symptomatic patients, to resolve ischaemia detected by non-invasive stress testing
- To improve regional left ventricular function in the territory of the occluded artery
- To improve the prognosis of the patient as there is considerable risk of future progression of CAD in the remaining patent arteries[10]

CTO PCI is indicated when occlusion of an artery leads to angina, ischaemia,[11,12] left ventricular dysfunction, and electrical instability, especially when the left anterior descending coronary artery is involved.[6] Registries of patients with CTO showed that successful percutaneous revascularisation is associated with improved clinical outcomes: improvements in angina and quality of life,[39] a potential improvement in electrical myocardial stability,[32,40] a reduced need for CABG surgery,[41] enhanced tolerance of future coronary events; increased left ventricular function.[42,43] and in the context of complete coronary revascularisation, a substantial increase in survival.[41,44-48]

A rate of 10–12.5% of myocardium 'at risk' was recognised to be the cut-off point above which percutaneous treatment shows clear survival benefit for patients.[2] However, in 2011 the STICH investigators reported that after correction of other prognostic variables, the presence of myocardial viability was no longer significantly associated with mortality. These findings bring into question whether left-ventricular ejection fraction recovery is completely dependent of myocardial viability, but might support the electrical or the 'reserve' hypothesis. In this hypothesis, patients with a CTO might be more prone to future cardiovascular events and have less reserve, especially during an acute occlusion in one of the remaining coronary arteries.[49]

PERCUTANEOUS TREATMENT OF CHRONIC TOTAL OCCLUSION

A detailed review of the techniques and materials available for CTO PCI are beyond the scope of this paper, however below is a summary of current recommendations and treatment algorithms which provide a useful introduction to the subject area.

Pre-Procedural Approach

The most widely used score to predict the overall likelihood of successful CTO PCI is the JCTO (Japanese Multicenter CTO Registry) score.[50] It uses independent angiographic predictors of failure (each given one point): prior failed attempt, angiographic evidence of heavy calcification, bending within the occluded segment, blunt proximal stump, and occlusion length >20 mm. CTO were graded as easy, intermediate, difficult, and very difficult (JCTO scores of 0, 1, 2, and ≥3, respectively). In addition to crossing times, the JCTO score appears to correlate with long-term success.[16]

In addition, other independent predictors of failure were derived from the use of coronary computed tomography angiography (CCTA): occlusion length >20 mm, multiple occlusions, blunt stump, bending, and severe calcification in the CTO segment. Clinical predictors of failure included a previously failed PCI revascularisation and duration of CTO >12 months or unknown duration of occlusion. The use of CCTA is controversial because the indication of treating a CTO is a clinical one, and should not be made on the basis of the ease or difficulty of the case. As such, these scores are useful for identifying highly complex cases that should be referred to expert centres.

Although CCTA is generally seen as having limited clinical value, it offers assessment of:

- The length and three dimensional course of the occluded arterial segment
- The presence of calcium at the CTO
- The vessel size and vessel remodelling (either positive or negative)
- The quality of the vessel distal to the CTO

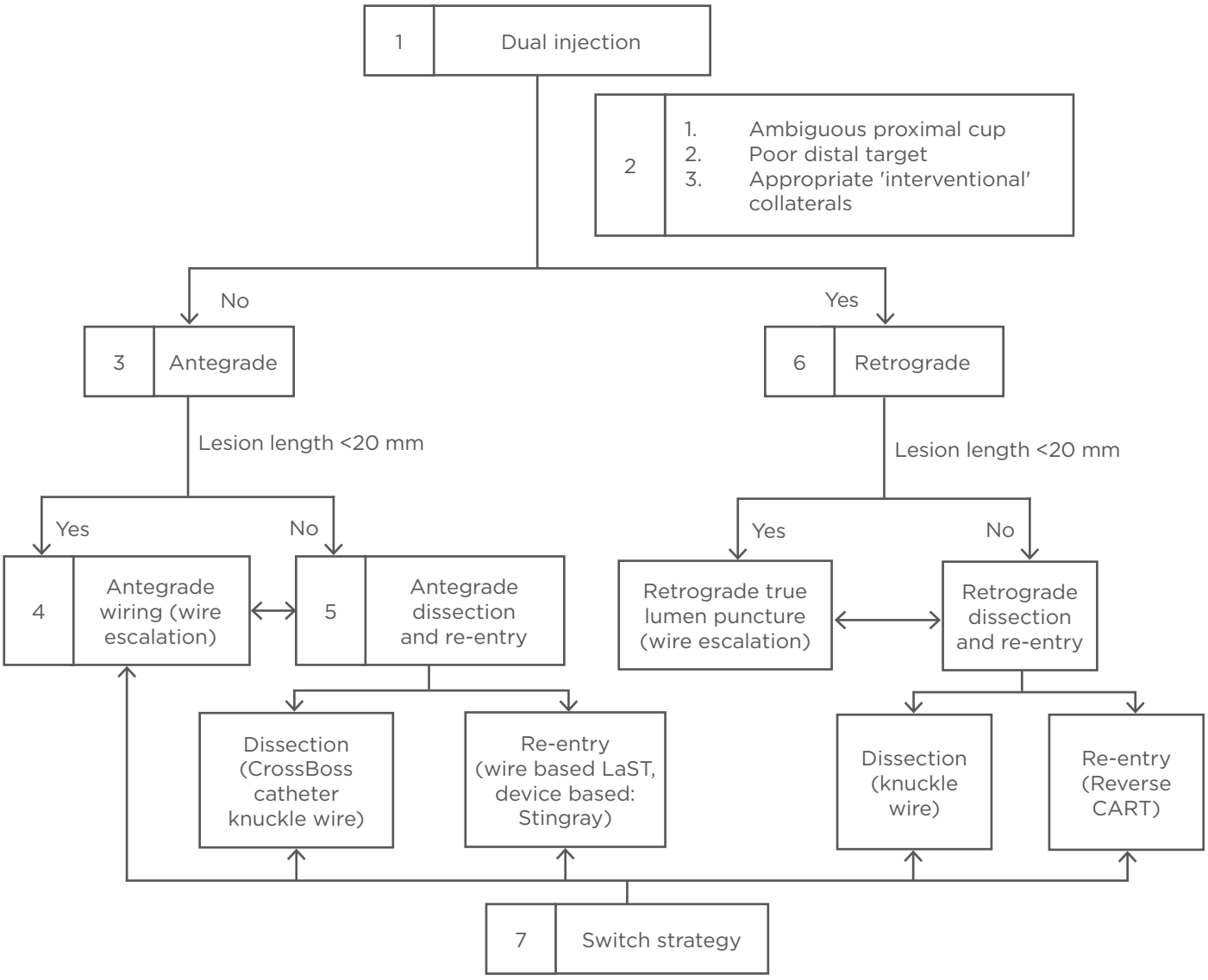


Figure 2: The American hybrid approach.

According to point 5 the 'move the cap' technique can facilitate antegrade crossing of CTO with ambiguous or impenetrable cap using either a stiff guidewire (scratch and go), or a proximal balloon inflation to cause limited dissection to facilitate subintimal guidewire entry (balloon assisted technique). This entry in the subintimal space is followed by antegrade dissection re-entry lesion crossing.[59] Stingray, Boston Scientific, Marlborough, Massachusetts, USA; Crossboss catheter knuckle wire, Boston Scientific.
CTO: chronic total occlusion; LaST: limited antegrade subintimal tracking; CART: controlled antegrade and retrograde tracking.
Adapted from Brilakis et al.[51] and Touma et al.[56]

Patients presenting with an acute coronary syndrome require expedited recanalisation of the culprit vessel. Whenever a CTO in a non-culprit vessel is incidentally found, the patient should be given time to recover from the cardiac, vascular, and renal effects of acute coronary syndrome and PCI. A minimum of 1–2 weeks should elapse between treatment of the culprit lesion and planned treatment of a CTO. There is evidence that leaving a totally occluded artery untreated is associated with higher mortality at short and long-term follow-up post-ST-segment elevation myocardial infarction.[2,12]

Interventional procedures should be carefully planned; *ad hoc* angioplasty is not recommended. The operator should spend time examining the diagnostic films to decide if a unilateral or bilateral approach is required, to choose appropriate vascular access routes and dedicated equipment, and to guide catheter shape and size.

Finally, remember that time constraint in the catheterisation laboratory is one of the factors linked with procedural failure.[51] Proper catheterisation laboratory planning for a minimum of 2 hours is essential.[2]

The selection of the access route is dependent on the individual patient situation (e.g. severe peripheral vascular disease may mandate a radial approach). The radial artery could be used for either contralateral injection (5 or 6 Fr diagnostic catheters) or CTO treatment with 7 Fr sheathless guiding catheter.[52] However, most experts use the femoral approach for the target CTO vessel (90% in Europe).[2,12]

When the distal vessel is mainly filled by retrograde collaterals, or there are bridging collaterals originating near the occlusion that are likely to have their flow impaired after wire-catheter advancement, contralateral injection is essential from the beginning of the procedure.[2] When distal flow comes from a proximal branch of the occluded vessel, an 8 Fr catheter can be used to perform to perform selective injections in this branch with a microcatheter and cross in parallel the rest of the material to work in the occluded segment. Occasionally, single vascular access has been used to perform contralateral injections with different manoeuvres.[53,54] Furthermore, single catheter antegrade injection should be avoided once dissection occurs in the antegrade space with subintimal entry as it may result in haematoma expansion.[55] Bilateral access is therefore frequently needed.

Regarding a CTO there are two methodological approaches: the Japanese (proximal-to-distal) approach,[11] and the American hybrid approach (Figure 2).[51] The technical aspects, and pros and cons of each one were recently explained in an interesting review by Touma et al.[56] In Europe and America the hybrid strategy has more followers, and it has also been used in CTO caused by in-stent restenosis.[57,58]

The hybrid approach is a systematic algorithm-led PCI strategy based on the identification of key anatomical features on baseline angiography.[51] It introduces a structured approach, the main aim being to provide a reproducible, easily taught, and proctored technique for CTO PCI.[60]

This approach requires operator familiarity with all the available CTO PCI materials, techniques, and skillsets (antegrade wire escalation, antegrade dissection/re-entry with dedicated devices,[61] and retrograde wire escalation and dissection re-entry). Flexibility with the various approaches, and timely change of strategies, is at the heart of the hybrid algorithm.

The limitations of disseminating the Japanese approach relate to cost and laboratory time. This approach is also highly individualised, making it difficult to teach and disseminate. Unique to Japan is the situation where patient preference results in low rates of CABG and this results in preferential treatment with PCI. Long case-duration may not be feasible when laboratory time is limited. Concerns have been raised over radiation and contrast volume during protracted cases.[56]

Lesion Crossing

In addition to strategies to facilitate lesion crossing and lesion modification, guidewire selection greatly influences the ability of an operator to successfully cross a lesion and wire the distal vessel true lumen. A variety of guidewires[56] and supplementary manoeuvres specific to lesion subsets are available. In the JCTO trial, utilisation of advanced guidewires facilitated successful lesion crossing in 88.6% of CTO cases.[50] It should be remembered that CTO-specific guidewires are more prone to enter subintimal channels, and may increase the risk of perforation. In order to increase the support to cross the lesion different techniques and devices can be used, including: anchor balloon support techniques, extension catheters, and microcatheters.

Lesion Modification

Once the lesion has been successfully crossed, further challenges related to lesion modification can arise. These modifications should be considered last resort measures where standard techniques have proved unsuccessful, taking into account the fact that in CTO they are all off-license settings;[62,63] very high pressure non-compliant balloon dilation, balloon assisted micro-dissection, excimer laser coronary atherectomy, and/or high speed rotational ablation.

Stent Implantation

After successful procedures, implantation of drug-eluting stents (DES) is recommended. DES lead to an incremental 60% reduction in the relative risk of repeat revascularisation after CTO PCI.[64] Clinical and angiographic restenosis rates are

higher after DES of CTO compared to non-CTO, at least in part due to the diffuseness of disease, calcification, and number and length of stents required. Current generation DES may improve upon the results of first-generation DES after successful CTO recanalisation. The patency rate after CTO PCI at 69-month follow-up is approximately 90% for first-generation DES (sirolimus and paclitaxel-eluting stents), 97% for everolimus-eluting stents,[65] and 94.3% for bioresorbable everolimus-eluting vascular scaffold (BVS).[66] Before BVS can be recommended for routine application to CTO several issues must be addressed, these include their greater profile, tendency toward more recoil, and healing properties (particularly with subintimal implantation).[67] Recently, similar clinical and angiographic outcomes in CTO revascularisation with zotarolimus and everolimus-eluting stents have also been discovered. Stent length, but not type of stent, was predictive for in-stent late loss and target lesion revascularisation rate.[68]

For the clinical community there are two interesting trials in progress: the EuroCTO and the DECISION-CTO,[69,70] both of which compare PCI with DES and optimal medical therapy or optimal medical therapy alone. After these are complete we will have more evidence of the best option for treatment.

Complications and Outcomes in Chronic Total Occlusion Percutaneous Coronary Intervention

There are several general and specific complications related to this procedure such as contrast induced nephropathy (CIN) and radiodermatitis. The overall rates of adverse short-term clinical outcomes after percutaneous CTO intervention are declining (Table 2) and the current rates are approaching that of non-CTO PCI (Table 3).[3]

Of paramount significance is the prevention of CIN during the CTO recanalisation procedure. Most operators would wish to keep dye load even in patients with normal estimated glomerular filtration rate (GFR) <400 mL, in the EuroCTO Club consensus the maximal amount is defined as 4 x GFR (mL). When planning a second attempt, it is advised to wait between 3 and 4 weeks.[2] The risk of incidence of CIN was not different between the successful and failed CTO PCI group (7.2% versus 6.5%, p=0.45).[44]

Table 2: Evolution of success and procedural complications in large registries of chronic total occlusion percutaneous coronary intervention.

Author	Year	CTO lesions (n)	Retrograde (%)	Technical success (%)	Major complications (%)	Death (%)	Tamponade (%)
Rathore et al.[71]	2009	904	17	87.5	1.9	0.6	0.6
Morino et al.[72]	2010	528	26	86.6	NR	0.4	0.4
Galasi et al.[37]	2011	1,983	14	82.9	1.8	0.3	0.5
Michael et al.[73]	2013	1,361	34	85.5	1.8	0.22	0.6

CTO: chronic total occlusion; PCI: percutaneous coronary intervention; NR: not reported.

Table 3: Comparison of in-hospital clinical outcomes between chronic total occlusion and elective non-chronic total occlusion percutaneous coronary intervention.

Clinical outcomes	Elective non-CTO PCI (%)	Current rates with successful CTO PCI (%)	Current rates with failed CTO PCI (%)
Death	0.2–0.3	0.1	0.8
Myocardial infarction	2.0	2.0	2.3
Urgent CABG	0.1–0.3	0.13	0.7

CTO: chronic total occlusion; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft. *Adapted from Khan et al.[3]*

The Mehran score[74] suggested that 'very high-risk group' (≥16) classification and angiographic severe tortuosity were the predictors of CIN in CTO PCI. In daily practice, more careful hydration before and after the procedure, lower contrast volumes during the procedure, and precise follow-up after the procedure should be applied to these high-risk patients.[2,74,75] Use of limited pre-procedural multislice spiral computed tomography, retrogradely positioned wires as markers (rather than using contrast injections), and intravascular ultrasound may all help to reduce dye load.[2]

Exposure to radiation is an important consideration; during CTO PCI it is necessary to make every effort to reduce radiation exposure (to the patient and the operator) and to document radiation exposure during the procedure. The procedure should be stopped when radiation reaches a maximum of 10 Gy. Strategies to reduce exposure could include using a frame rate for fluoroscopy of 7.5 pulses/s and changing projection.[2]

Urgent CABG in patients undergoing PCI for CTO could be needed in three common scenarios. Firstly, mechanical trauma to a vessel resulting in frank perforation and/or tamponade requires emergency cardiac surgery. Secondly, the inability to recanalise a CTO in the presence of MVD even in the absence of complications prompts a need for urgent bypass surgery in some symptomatic patients. Thirdly, in some patients with MVD and successful CTO intervention, post-PCI acute stent thrombosis can be managed with urgent CABG.

Complications unique to the retrograde approach may involve the occluded vessel (retrograde perforation/dissection), the collaterals (rupture/haematoma of the septal or epicardial collaterals, perforation to the right or left ventricle, septal wire trapping, epicardial flow disruption with ischaemia), and the donor artery (potentially life-threatening dissection/thrombosis, spasm leading to ischaemia). The most common of these are related to the collateral vessels, but they tend to be minor and easily treatable in the majority of cases. However, perforation of epicardial collaterals, particularly in patients without prior open heart surgery, can be associated with tamponade and rapid haemodynamic compromise.

Although coronary perforations are common in CTO PCI (27.6%),[71] most perforations are related to localised wire exit from the vessel architecture and are limited to angiographic evidence of contrast staining. As most perforations do not have serious clinical consequences, the risk of tamponade is low (0.3%).[76] However, clinically significant coronary perforations can be associated with significant morbidity and mortality, with reported rates of death of 42%, emergency surgery of 39%, myocardial infarction of 29%, and transfusion of 65% in series not limited to CTO PCI.[77] Management of perforations includes:

- prolonged balloon inflation across the perforation
- reversal of anticoagulation (not completely to avoid target and donor vessel thrombosis)
- covered stent placement, emergency surgery, or embolisation (coils, microsphere injection)
- pericardiocentesis

Experience in managing vascular and haemorrhagic complications is required since most CTO PCIs are performed through 8 Fr femoral sheaths, and the activated clotting time is kept in the 300 secs range during retrograde procedures.[2] When feasible, the radial approach has fewer access site complications.[78]

Post-procedural deaths in patients can be broadly divided into two main categories: those directly related to procedural complications (perforation and tamponade), and those secondary to stent related complications such as acute stent thrombosis. However, deaths in patients with failed CTO intervention seem to be closely related to procedural complications as evidenced by higher rates of coronary perforation and cardiac tamponade (7.4% and 1.9% versus 1.16% and 0.2%, respectively) in this group. The risk of peri-procedural death as a result of a failed CTO PCI attempt ranges from 0.8–1.4%, which is still lower than the peri-operative mortality for CABG (1.76–3.5%).[79]

Outcomes following PCI CTO have been improving during recent years. Success rates in the treatment of complex CTO are 90–95%. They remain in the hands of a few dedicated expert operators, however the spreading of the hybrid approach algorithm, including the proctor's help in difficult cases, is promising.[60,80,81] These rates imply a huge knowledge about antegrade and retrograde techniques, dedicated materials such as catheters, guidewires, microcatheters, and catheter extensions, and how to manage complementary techniques such as CCTA and intravascular ultrasound.[7] A recently published meta-analysis[3] showed that,

compared with a successful percutaneous CTO intervention, a failed CTO PCI is associated with higher rates of procedural complications: in-hospital mortality (1.44% versus 0.5%; relative risk [RR]: 2.88; p<0.001), peri-procedural major adverse cardiac event (8.88% versus 3.75%; RR: 2.25), myocardial infarction (3.17% versus 2.4%; RR: 1.35; p=0.032), and urgent revascularisation with bypass surgery (4.0% versus 0.5%; RR: 6.67; p<0.001).

Outcomes after CTO PCI may be enhanced by proper patient selection (resistant angina, large areas of ischaemia, and anatomic suitability for antegrade, retrograde, and/or subintimal recanalisation) and by reliance on expert operators using a flexible incremental approach to recanalisation.

CONCLUSIONS

There is evidence that successful CTO PCI results in improved long-term outcomes; however, a failed procedure is also associated with a higher risk of complications and adverse short-term outcomes. Therefore, patient selection for percutaneous CTO intervention should be individualised based on the risks of complications (probability of failed intervention) versus the benefits of improved long-term outcomes (in cases of successful PCI). Careful assessment of lesion morphology and other scores of risk, along with operator's personal experience to deal with the specific lesion subtype is paramount before embarking on the procedure. Successful revascularisation correlates strongly with operator experience. For senior operators in high-risk complex CTO, proctoring and referral centres should be considered.

REFERENCES

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

2. Sianos G et al. Recanalisation of chronic total coronary occlusions: 2012 consensus document from the EuroCTO club. EuroIntervention. 2012;8(1):139-45.

3. Khan MF et al. Comparison of procedural complications and in-hospital clinical outcomes between patients with successful and failed percutaneous intervention of coronary chronic total occlusions: a meta-analysis of observational studies. Catheter Cardiovasc Interv. 2015;85(5):781-94.

4. Brilakis ES et al. The retrograde approach to coronary artery chronic total occlusions: a practical approach. Catheter Cardiovasc Interv. 2012;79(1):3-19.

5. Carlino M et al. Treatment of the chronic total occlusion: a call to action for the interventional community. Catheter Cardiovasc Interv. 2015;85(5):771-8.

6. Hoebers LP et al. Contemporary overview and clinical perspectives of chronic total occlusions. Nat Rev Cardiol. 2014;11(8):458-69.

7. Habara M et al. Comparison of percutaneous coronary intervention for chronic total occlusion outcome according to operator experience from the Japanese retrograde summit registry. Cathet Cardiovasc Intervent. 2016;87(6): 1027-35.

8. Stone GW et al. Percutaneous recanalization of chronically occluded coronary arteries: procedural techniques, devices, and results. Catheter Cardiovasc Interv. 2005;66(2):217-36.

9. Singbal Y, Lim R. Training Standards and Recommendations for Intervention on Chronic Total Occlusions. Curr Cardiol Rev. 2015. [Epub ahead of print].

10. Werner GS, "Chronic total occlusions," Eeckhout E et al. (eds.), Percutaneous Interventional Cardiovascular Medicine The PCR-EAPCI Textbook. II. (2012) 1st edition, Toulouse:PCR, pp.407-53.

11. Galassi AR et al. Appropriateness of percutaneous revascularization of coronary chronic total occlusions: an overview. Eur Heart J. 2015. [Epub ahead of print].

12. Windecker S et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541-619.

13. Levine GN et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol. 2011;58(24):e44-122.

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

15. Karmpaliotis D, Green P. Chronic total occlusion percutaneous coronary intervention in 2014 beyond the J-CTO score (Japanese Multicenter CTO Registry): chance favors the prepared mind. JACC Cardiovasc Interv. 2015;8(2):268-70.

16. Tanaka H et al. Impact of J-CTO score on procedural outcome and target lesion revascularisation after percutaneous coronary intervention for chronic total occlusion: a substudy of the J-CTO Registry (Multicentre CTO Registry in Japan). EuroIntervention. 2016;11(9):981-8.

17. Zhang Z et al. The cost-effectiveness of percutaneous coronary intervention as a function of angina severity in patients with stable angina. Circ Cardiovasc Qual Outcomes. 2011;4(2):172-82.

18. Gada H et al. Establishing the cost-effectiveness of percutaneous coronary intervention for chronic total occlusion in stable angina: a decision-analytic model. Heart. 2012;98(24):1790-7.

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

20. Veen G et al. Culprit lesion morphology and stenosis severity in the prediction of reocclusion after coronary thrombolysis: angiographic results of the APRICOT study. Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis.

J Am Coll Cardiol. 1993;22(7):1755-62.

21. Grines CL et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med. 1993;328(10):673-9.

22. Stone GW et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med. 2002;346(13):957-66.

23. Habib GB et al. Influence of coronary collateral vessels on myocardial infarct size in humans. Results of phase I thrombolysis in myocardial infarction (TIMI) trial. The TIMI Investigators. Circulation. 1991;83(3):739-46.

24. Sakakura K et al. Comparison of pathology of chronic total occlusion with and without coronary artery bypass graft. Eur Heart J. 2014;35(25):1683-93.

25. Srivatsa SS et al. Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. J Am Coll Cardiol. 1997;29(5):955-63.

26. Karrowni W et al. Coronary collateral circulation: its relevance. Catheter Cardiovasc Interv. 2013;82(6):915-28.

27. Werner GS et al. Collateral function in chronic total coronary occlusions is related to regional myocardial function and duration of occlusion. Circulation. 2001;104(23):2784-90.

28. Gensini G. "Arterial anastomoses in the Coronary Circulation: The Coronary Collaterals", Gensini G (ed.), Coronary arteriography (1975) 1st edition, New York: Futura Publishing, pp.321-54.

29. Werner GS et al. The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction. Eur Heart J. 2006;27(20):2406-12.

30. Cheng AS et al. Percutaneous treatment of chronic total coronary occlusions improves regional hyperemic myocardial blood flow and contractility: insights from quantitative cardiovascular magnetic resonance imaging. JACC Cardiovasc Interv. 2008;1(1):44-53.

31. Bucciarelli-Ducci C et al. CMR Guidance for Recanalization of Coronary Chronic Total Occlusion. JACC Cardiovasc Imaging. 2016. [Epub ahead of print].

32. Rossello X et al. Assessment of Inducible Myocardial Ischemia, Quality of Life, and Functional Status After Successful Percutaneous Revascularization in Patients With Chronic Total Coronary Occlusion. Am J Cardiol. 2016;117(5):720-6.

33. Stuijfzand WJ et al. Value of Hybrid Imaging with PET/CT to Guide Percutaneous Revascularization of Chronic Total Coronary Occlusion. Curr Cardiovasc Imaging Rep. 2015;8(7):26.

34. Cho JS et al. Usefulness of the parameters of quantitative myocardial perfusion contrast echocardiography in patients with chronic total occlusion and collateral flow. Echocardiography. 2015;32(3):475-82.

35. Galassi AR et al. Prognostic value of exercise myocardial scintigraphy in patients with coronary chronic total occlusions. J Interv Cardiol. 2010;23(2):139-48.

36. Werner GS et al. Determinants of target vessel failure in chronic total coronary occlusions after stent implantation. The influence of collateral function and coronary hemodynamics. J Am Coll Cardiol. 2003;42(2):219-25.

37. Galassi AR et al. In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. EuroIntervention. 2011;7(4):472-9.

38. Claessen BE et al. Gender differences in long-term clinical outcomes after percutaneous coronary intervention of chronic total occlusions. J Invasive Cardiol. 2012;24(10):484-8.

39. Grantham JA et al. Quantifying the early health status benefits of successful chronic total occlusion recanalization: Results from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) Trial. Circ Cardiovasc Qual Outcomes. 2010;3(3):284-90.

40. Nombela-Franco L et al. Ventricular arrhythmias among implantable cardioverter-defibrillator recipients for primary prevention: impact of chronic total coronary occlusion (VACTO Primary Study). Circ Arrhythm Electrophysiol. 2012;5(1):147-54.

41. Khan MF et al. Effects of percutaneous revascularization of chronic total occlusions on clinical outcomes: a meta-analysis comparing successful versus failed percutaneous intervention for chronic total occlusion. Catheter Cardiovasc Interv. 2013;82(1):95-107.

42. Kirschbaum SW et al. Combining magnetic resonance viability variables better predicts improvement of myocardial function prior to percutaneous coronary intervention. Int J Cardiol. 2012;159(3):192-7.

43. Roifman I et al. The effect of percutaneous coronary intervention of chronically totally occluded coronary arteries on left ventricular global and regional systolic function. Can J Cardiol. 2013;29(11):1436-42.

44. Borgia F et al. Improved cardiac survival, freedom from MACE and angina-related quality of life after successful percutaneous recanalization of coronary artery chronic total occlusions. Int J Cardiol. 2012;161(1):31-8.

45. Jolicœur EM et al. Percutaneous coronary interventions and cardiovascular outcomes for patients with chronic total occlusions. Catheter Cardiovasc Interv. 2012;79(4):603-12.

46. Jones DA et al. Successful recanalization of chronic total occlusions is associated with improved long-term survival. JACC Cardiovasc Interv. 2012;5(4):380-8.

47. Mehran R et al. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. JACC Cardiovasc Interv. 2011;4(9):952-61.

48. Niccoli G et al. Late (3 years) follow-up of successful versus unsuccessful revascularization in chronic total coronary occlusions treated by drug eluting stent. Am J Cardiol. 2012;110(7):948-53.

49. Bonow RO et al. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med. 2011;364(17):1617-25.

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

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

52. Kwan TW et al. Feasibility and safety of 7F sheathless guiding catheter during transradial coronary intervention. Catheter Cardiovasc Interv. 2012;80(2):274-80.

53. Ferrer-Gracia MC et al. Sequential contralateral injection through the same transradial vascular approach in a chronic total occlusion. Postepy Kardiol Interwencyjnej. 2015;11(2):152-3.

54. Kiemeneij F. Simultaneous transradial coronary angioplasty and contralateral coronary angiography with a single guide catheter for total coronary occlusions. J Invasive Cardiol. 2014;26(2):87-90.

55. Yamane M. Current percutaneous recanalization of coronary chronic total occlusion. Rev Esp Cardiol (Engl Ed). 2012;65(3):265-77.

56. Touma G et al. Chronic total occlusions - Current techniques and future directions. Int J Cardiol Heart Vascul. 2015;7:28-39.

57. Wilson WM et al. A novel approach to the management of occlusive in-stent restenosis (ISR). EuroIntervention. 2014;9(11):1285-93.

58. Christopoulos G et al. The efficacy of "hybrid" percutaneous coronary

intervention in chronic total occlusions caused by in-stent restenosis: insights from a US multicenter registry. Catheter Cardiovasc Interv. 2014;84(4):646-51.

59. Vo MN et al. "Move the cap" technique for ambiguous or impenetrable proximal cap of coronary total occlusion. Catheter Cardiovasc Interv. 2016;87(4):742-8.

60. Sharma V et al. Impact of proctoring on success rates for percutaneous revascularisation of coronary chronic total occlusions. Open Heart. 2015;2(1): e000228.

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

62. Fairley SL et al. Adjunctive strategies in the management of resistant, 'undilatable' coronary lesions after successfully crossing a CTO with a guidewire. Curr Cardiol Rev. 2014;10(2):145-57.

63. Fernandez JP et al. Beyond the balloon: excimer coronary laser atherectomy used alone or in combination with rotational atherectomy in the treatment of chronic total occlusions, non-crossable and non-expansible coronary lesions. EuroIntervention. 2013;9(2):243-50.

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

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

66. Vaquerizo B et al. Bioresorbable everolimus-eluting vascular scaffold for the treatment of chronic total occlusions: CTO-ABSORB pilot study. EuroIntervention. 2015;11(5):555-63.

67. Goldman S et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. J Am Coll Cardiol. 2004;44(11):2149-56.

68. Markovic S et al. Zotarolimus compared with everolimus eluting stents-angiographic and clinical results after recanalization of true coronary chronic total occlusions. Catheter Cardiovasc Interv. 2016. [Epub ahead of print].

69. Euro CTO Club. A Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions (EuroCTO). Clinical Trial: NCT01760083. clinicaltrials.gov/ct2/show/NCT01760083.

70. Park SJ; CardioVascular Research Foundation, Korea. Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients With Chronic Total Occlusion (DECISION-CTO). Clinical trial: NCT01078051. clinicaltrials.gov/ct2/show/NCT01078051.

71. Rathore S et al. Procedural and in-hospital outcomes after percutaneous coronary intervention for chronic total occlusions of coronary arteries 2002 to 2008: impact of novel guidewire techniques. JACC Cardiovasc Interv. 2009; 2(6):489-97.

72. Morino Y et al. In-hospital outcomes of contemporary percutaneous coronary intervention in patients with chronic total occlusion insights from the J-CTO Registry (Multicenter CTO Registry in Japan). JACC Cardiovasc Interv. 2010; 3(2):143-51.

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

74. Mehran R et al. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol. 2004;44(7): 1393-9.

75. Abellas-Sequeiros RA et al. Mehran contrast nephropathy risk score: Is it still useful 10 years later? J Cardiol. 2016; 67(3):262-7.

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

77. Fejka M et al. Diagnosis, management, and clinical outcome of cardiac tamponade complicating percutaneous coronary intervention. Am J Cardiol. 2002; 90(11):1183-6.

78. Rathore S et al. A comparison of the transradial and the transfemoral approach in chronic total occlusion percutaneous coronary intervention. Catheter Cardiovasc Interv. 2009;73(7):883-7.

79. Hannan EL et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. N Engl J Med. 2005; 352(21):2174-83.

80. Shammas NW et al. The learning curve in treating coronary chronic total occlusion early in the experience of an operator at a tertiary medical center: The role of the hybrid approach. Cardiovasc Revasc Med. 2016;17(1):15-8.

81. Vo MN et al. Adoption of the hybrid CTO approach by a single non-CTO operator: procedural and clinical outcomes. J Invasive Cardiol. 2015;27(3):139-44.

UPCOMING EVENTS

SOLACI-CACI '17: 23rd Annual Meeting of the Latin American Society of Interventional Cardiology and 27th National Annual Meeting of the Argentinian School of Interventional Cardiologists

2nd–4th August 2017

Buenos Aires, Argentina

Attendees can expect a warm welcome from this established annual congress. The organisers have opted for a tried-and-tested venue and have filled the scientific programme with a range of sessions and opportunities to catch up with peers on the latest research advances. Some of the hot topics include innovations for peripheral interventions and structural heart disease interventions. There will also be a selection of live demonstrations and interactive discussions.

59th Annual World Congress International College of Angiology (ICA)

7th–9th September 2017

Vienna, Austria

Hosted in the historic city of Vienna, Austria, the ICA's 59th Annual World Congress is an unmissable event for any interventional cardiologist. The scientific programme includes training workshops, special lectures, and abstract presentations, which offer opportunities for interactive discussion and cover important topics such as atrial fibrillation and carotid stenosis. Attendees will also be treated to a welcome dinner and concert in keeping with the city's global renown.

Catheter Interventions in Structural, Valvular and Congenital Heart Disease, Atrial Fibrillation and Heart Failure (CSI-UCSF)

8th–9th September 2017

San Francisco, California, USA

In this joint annual meeting, the key theme is interaction. The organisers of the congress are excited to be working together to create an open space for discussion and learning, and they actively encourage attendees to submit cases for presentation and to question one another in order to advance understanding about the latest techniques and guidelines in interventional cardiology. This is sure to be a worthwhile visit for interventional cardiologists worldwide.

9th Experts "Live" CTO Workshop

24th–26th September 2017

London, UK

This event is designed for those with a keen interest in chronic total occlusion (CTO) and its optimal treatment, because it will provide a specialised and focussed study of this aspect of interventional cardiology. Hosted in the vibrant city of Berlin, attendees will gain a thorough understanding of CTO and its most effective treatments, touching on subjects such as continuous education, product development, and current research objectives.

PCR London Valves 2017

24th–26th September 2017

London, UK

This event focusses on transcatheter therapies for valvular heart disease for the heart team and is the largest training course of its kind in the world. As an official course of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), attendees can expect world-class education in the care of patients with valvular heart disease, with particular attention given to percutaneous valve interventions.

DCB III: The Balloons are Back in Town!

28th September 2017

Birmingham, UK

Back for its third event, DCB will feature popular debate sessions enabling the exchange of ideas and discussion on a variety of topics. These sessions have been extended this year, so attendees can expect plenty of opportunities to have their voices heard. Lectures and presentations will be given by world-renowned interventional cardiologists and case studies will also be considered. The hot topics for the event include percutaneous coronary interventions, in-stent restenosis, and coronary bifurcations.

29th French Congress of Interventional Cardiology (CFCI Paris)

4th–6th October 2017

Paris, France

This event will be one of reflection and celebration, as it coincides not only with the 20th anniversary of the French Society of Interventional Cardiology congress, but also the 40th anniversary of the very first percutaneous coronary intervention, which was performed by Andreas Grüntzig on 16th September 1977. The event comprises live demonstrations, educational sessions, abstract and poster presentations, and an exhibition of state-of-the-art products.

EuroPCR 2018

22nd–25th May 2018

Paris, France

Quite possibly the biggest event in the European Interventional Cardiology calendar, EuroPCR will return again to Paris, France with >12,000 attendees expected. The course functions as a forum for interventional cardiologists from across Europe and the world to share their knowledge and research with the wider medical community. If you enjoyed our congress review of EuroPCR 2017, you will not want to miss this exceptional event!

Buyer's Guide

- AACHEN RESONANCE
- ABBOTT
- ABIOMED
- ACIST
- ACROSTAK
- ALVIMEDICA
- ANDANZA
- ANGIOLINE
- APT MEDICAL
- ARAN BIOMEDICAL
- ASAHI INTECC
- B. BRAUN MELSUNGEN
- BALTON
- BIOSENSORS INTERNATIONAL
- BIOTRONIK
- BOSTON SCIENTIFIC
- CARDIALYSIS
- CELONOVA BIOSCIENCES
- CIRCLE CARDIOVASCULAR IMAGING
- COMED BV
- CONCEPT MEDICAL INC.
- CONTROL MEDICAL TECHNOLOGY
- CORDIS, A CARDINAL HEALTH COMPANY
- DEMAX MEDICAL TECHNOLOGY
- EDWARDS LIFESCIENCES
- ENVISION SCIENTIFIC
- ESAOTE
- EUCATECH
- EUROCOR GMBH
- FISO TECHNOLOGIES
- FRYMIRE & ASSOCIATES
- GE HEALTHCARE
- GENAE
- GOODMAN CO.
- GUIDEWAVE
- HEARTSTITCH
- HENGYI MEDICAL
- HEXACATH
- HLT
- IHT – CORDYNAMIC
- IMDS
- INC RESEARCH
- iVASCULAR
- JMC CORPORATION
- JOLINE
- KOSSEL MEDTECH
- LEMER PAX INNOVATIVE

Interventional Cardiology

- LEPU MEDICAL TECHNOLOGY
- LIVENOVA
- MAVIG
- MDT X-RAY
- MEDIS MEDICAL IMAGING SYSTEMS BV
- MEDTRONIC
- MENTICE
- MERIL LIFE SCIENCES
- MERIT MEDICAL
- MICROPORT
- MINVASYS
- MIRACOR MEDICAL SYSTEMS
- MITRALIGN
- MULTIMEDICS
- NATEC MEDICAL
- NOVELLA CLINICAL
- NVT
- OCCLUTECH
- OPSENS MEDICAL
- ORBUSNEICH
- PANGOLIN MEDICAL
- PEROUSE MEDICAL
- PHILIPS VOLCANO
- PIE MEDICAL IMAGING
- QUALIMED
- RD GLOBAL
- RENALGUARD
- REVA MEDICAL
- ROBOCATH
- RONTIS
- SIEMENS HEALTHINEERS
- SINOMED
- SIS MEDICAL
- SMT
- STENTYS
- SUNGWON MEDICAL
- SURMODICS/CREAGH MEDICAL
- SVELTE MEDICAL SYSTEMS
- SYMETICS
- TELEFLEX
- TERUMO MEDICAL CORPORATION
- TORAY
- TRANSLUMINA
- VASMED
- VIVASURE MEDICAL LTD.
- ZOLL MEDICAL
- 3D SYSTEMS, SIMBIONIX
- 4TECH LTD.