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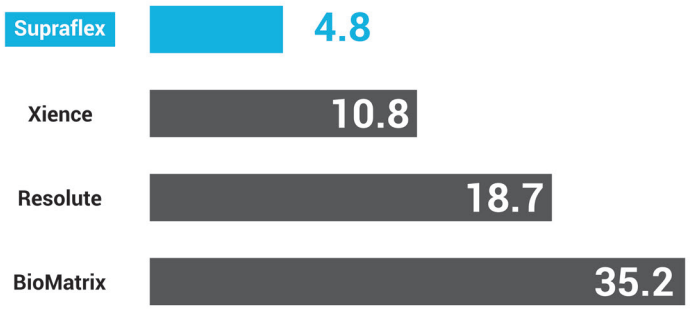

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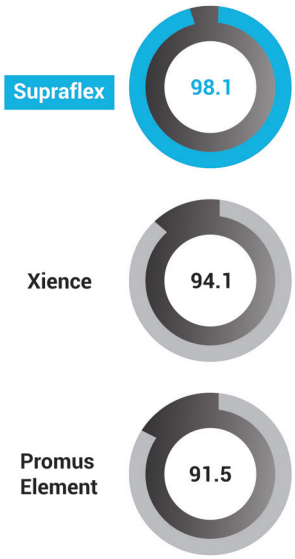

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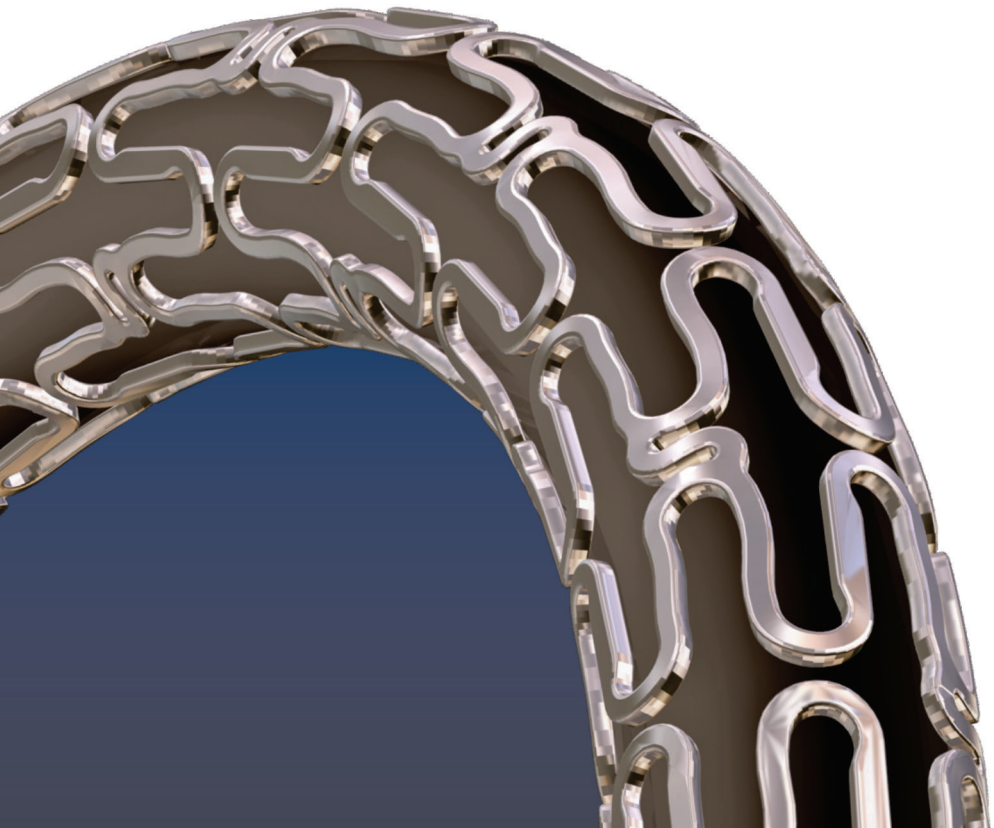

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AsiaIntervention 2016;2:73-74

Singapore: a tradition of "state of the art" cardiology

Huay Cheem Tan*, MBBS, *Co-Chief Editor, AsiaIntervention*

Department of Cardiology, National University Heart Centre, Singapore

In less than 50 years, Singapore has established itself as a centre for cardiovascular excellence. With a population of approximately 5.5 million people, great attention has been paid to the creation of our healthcare and emergency healthcare system and, today, Singapore has the third highest life expectancy in the world with an average lifespan for both males and females of 84.6 years.

Within the realm of interventional cardiology, Singapore has long been seen as a leader in Asia in the adoption of percutaneous technologies. The first balloon angioplasty was performed in 1984 in our country by our pioneering interventionalist Richard Ng in 19 patients. The first drug-eluting stent implantation in Singapore and Asia occurred during the 11th Singapore LIVE Course in 2002. Asia's first percutaneous aortic valve replacement was performed in Singapore in 2009.

Interventional cardiovascular care today

Relative to the rest of the world, Singapore has a healthy population. Still, there is an increased number of patients with cardiovascular disease but, when this is adjusted for age, it is seen that this is not increasing statistically in terms of the population as a whole. At present, there are six public hospitals and an equal number of private hospitals certified to perform angioplasty. Concerning the evolution of interventional treatments, the number of angioplasties continues to grow, while the numbers of CABG are dropping. Reviewing the trend from 2010-2014 concerning PCI, a 5% growth can be seen. However, with respect to CABG, from 2013-2014, a decrease of 3.4% is evident. Taken together, this amounts to a 6:1 ratio in terms of PCI to CABG procedures. Most of this increase originates in emergency PCI rather than elective PCI.

In Singapore, an active structural programme has matured over the last six or seven years – more than 300 TAVIs have now been performed. Also, MitraClip and left atrial appendage closure are standard procedures. As the number of patients receiving these treatments has increased, Singapore has concurrently become an international centre of reference with patients coming from, amongst other countries, India and Indonesia.

Challenges

The challenge today is not the number of qualified operators, which in itself is very good considering that the volume of PCI procedures continues to rise. In fact, for Singapore, the biggest challenge today is in the management of patients with myocardial infarction. Primary PCI is the universally accepted modality for the treatment of myocardial infarction in this country with 99.9% of patients receiving primary angioplasty coupled with impressive reductions in the overall mortality rate. Currently, the mortality rate for treatment within 12 hours of onset is 6.6% – and that includes patients with cardiogenic shock – and the 30-day mortality, excluding cardiogenic shock, is 4%. The Singaporean reduction in mortality rates is due to two important factors, firstly the national healthcare system, including the well-developed

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emergency care system. The average time in which an ambulance will reach the site of call is eight minutes, and 90% of the time the ambulance will reach the site of the call in less than 11 minutes. Secondly, overall door-to-balloon time has been reduced. This reduction is due to refinements in our organisation: when an ambulance picks up a patient with a suspected heart attack, an ECG is performed immediately and transmitted to the nearest PCI-capable hospital so that, by the time the patient arrives at that hospital, the team is already activated and ready. This pre-hospital, ambulance-based and transmissible ECG significantly shortens the time to treatment for the patient with a myocardial infarction.

Education and the future

The educational value of live case demonstration meetings has been an important element of Singapore's professional development and indeed Singapore was the first country to host live case demonstration courses in this part of the world in 1989 (known as Singapore LIVE). It also started the Asian Interventional Cardiovascular Therapeutics (AICT) meeting, along with several regional member countries, which has evolved to become the official scientific meeting of the Asia-Pacific Society of Interventional Cardiology (APSIC). Furthermore, Singapore has a tradition of sharing its know-how and expertise with physicians from around the world and has established itself as the training centre for many developing countries. Indeed, the interventional training programme at the National University Heart Centre, Singapore (NUHCS) started in 2000 with over 50 interventional cardiologists trained from all over the world, including China, India and recently also Europe and South America.

In the near future, more comprehensive programmes in interventional training will be developed. Considering that the interventional field has flourished beyond the initial expectations from coronary to structural interventions, what is now imperative is an evolving educational approach that will be inclusive of every different aspect of interventional cardiology as these aspects develop over the coming years. The modern-day fellows in interventional cardiology should not limit themselves to coronary, but should also be required to have a grasp of other endovascular procedures, structural as well as peripheral.

The future requires that we continue to build from the strong foundations we have created at present, to ensure the ongoing evolution of our practice, here in Singapore, and throughout our region and the world.

Conflict of interest statement

The author has no conflicts of interest to declare.

AsiaIntervention 2016;2:75-77

"What's past is prologue": the saga of percutaneous coronary intervention

José Ribamar Costa Jr[1,2], MD, PhD; Alexandre Abizaid[1,2,3]*, MD, PhD; J. Eduardo Sousa[1,2], MD, PhD

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Drug-eluting stents (DES) were conceived to reduce in-stent neointimal formation, minimising the occurrence of restenosis. Their development was pioneered through a combination of the increased understanding of the biology of restenosis, the selection of drugs that target one or more pathways in the restenotic process, controlled-release drug delivery strategies, and the use of the stent as a delivery platform.

The first successful DES programme, the CYPHER® sirolimus-eluting stent (Cordis Corporation, Johnson & Johnson, Warren, NJ, USA), was initiated in our centre in São Paulo, Brazil. Between December 1999 and January 2000, 30 patients were enrolled in the sirolimus-eluting FIM trial and received the moderate (n=15) and slow-release (n=15) formulations of this device. Four months later, in only two days, we performed the follow-up of both cohorts, with quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) evaluation[1]. At that moment, with no sophisticated study design (not even a control group!), we were sure we were looking at a new technology which would revolutionise the interventional coronary field, as was later confirmed in hundreds of randomised clinical trials and "real-world" registries[2-4].

In parallel to the broad incorporation of such devices into clinical practice, reports of new varieties of adverse events, such as very late stent restenosis and thrombosis, started to appear, raising concerns about the durability and long-term safety of the first generation of DES[5-9].

In the current edition of the AsiaIntervention Journal, Kuramitsu et al[10] present the very long-term results of their "real-world experience" with the CYPHER DES, including 985 consecutive patients

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(1,307 lesions) treated solely with this device. The authors should be congratulated for their meticulous scientific work. Important observations can be derived from their experience.

First, invasive follow-up with angiography was obtained in 88% of the total cohort. Although currently routine repeat angiography is not recommended for the majority of patients treated with PCI, at the time of the recruitment (more than a decade ago!) little was known about the performance of that novel technology in complex scenarios, which explains the interest of our colleagues in obtaining this valuable information. We did the same with the first patients treated with CYPHER, who generously agreed to undergo

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angiography at 4, 12, 24 and 48 months[1,11-13]. On the other hand, this systematic approach of routine invasive follow-up, combined with the high complexity angiographic profile enrolled in their registry (including bifurcations, coronary total occlusions, previous ISR, left main stem, etc.), might explain the relatively high target lesion restenosis (TLR) rates described in this publication (11.8% within the first year). Most of the "real-world" publications, including our local DESIRE registry[14], pointed to a single digit TLR rate within 12 months of the procedure. Of note, due to the systematic invasive follow-up, the authors were able to identify stent fracture as one of the main determinants of CYPHER failure.

A recurrent criticism in the interventional cardiology field is that the results of studies are limited to midterm follow-up. In the present manuscript, our Japanese colleagues have shown that it is possible to deliver high-quality, very long-term clinical data (median of 8.6 years). Among their main observations, the authors observed a continuous growth in target lesion revascularisation after the first year of the PCI (2.2%/year) as well as in the incidence of definitive very late stent thrombosis (0.22%/year). The incidence of these events was not tempered by the years, still occurring up to ten years after the index procedure. Although many other registries have been able to demonstrate the steady increase in thrombosis and restenosis of first-generation DES after one year of their deployment, most of them have their follow-up limited to five years. Again, we think it is interesting to establish a parallel to our DESIRE registry, in São Paulo. Our registry, currently with close to 7,000 patients, was initiated in May 2002 and has successfully clinically followed 98.2% of the entire population treated with DES (first- and second-generation) in a single-centre tertiary institution (Hospital do Coração, São Paulo, Brazil). As in the present study, we observed a continual increase in the occurrence of DES thrombosis and TLR of 0.3%/year and 1.6%/year, respectively, after the first year of the procedure, with cases happening after the first decade of the PCI. Likewise, the predictors of MACE varied according to the time point. In **Table 1**, we present the independent MACE predictors in the DESIRE registry.

It is important to highlight that, despite these untoward events experienced with the first generation of DES, these devices were instrumental in positioning PCI where it is nowadays - the preferred revascularisation strategy for the majority of patients with coronary artery disease. Also, the drawbacks observed with those devices were necessary to prompt the development of a next generation of DES, combining thinner and more flexible platforms made of new alloys (cobalt-chromium, platinum chromium, etc.), more biocompatible (e.g., fluoro polymer, phosphorylcholine, etc.) or even absorbable polymers (PLLA, PGLA, etc.) and novel antiproliferative agents (mostly sirolimus analogues or derivatives) or reduced doses of currently approved antiproliferative drugs.

The efficacy and long-term safety achieved with the current new generation of DES systems are very high and difficult to surpass; therefore, we believe that PCI will continue to play a pivotal role in the treatment of coronary artery disease. The current focus on metallic DES research is based on the development of technologies to promote faster and safer vessel healing, allowing the shortening of dual antiplatelet therapy and therefore minimising the bleeding risks associated with these medications.

Table 1. Independent predictors of acute, mid and very long-term MACE (cardiac death, non-fatal myocardial infarct and ischaemia-driven target lesion revascularisation) in the DESIRE registry.

Acute DES performance (in-hospital phase)			
Variable	**HR**	**95% CI**	***p*-value**
Stent length	1.02	1.020-1.028	<0.001
Age	1.02	1.01-1.04	<0.001
Residual stenosis	1.04	1.01-1.06	0.003
Use of first-generation DES	1.45	1.15-1.84	0.002
Treatment of SVG lesions	1.82	1.29-2.56	0.001
Midterm DES performance (>hospital discharge <365 days)			
Variable	**HR**	**95% CI**	***p*-value**
Age	1.02	1.0-1.02	0.04
Residual stenosis	1.02	1.0-1.04	0.04
Stent length	1.86	1.29-2.67	0.01
Smoking	1.98	1.31-2.97	0.01
Treatment of SVG lesions	3.0	1.86-4.86	<0.001
Very long-term DES performance (>365 days [up to 13 years, median of 7.2 years])			
Variable	**HR**	**95% CI**	***p*-value**
Age	1.01	1.0-1.03	0.004
Residual stenosis	1.02	1.0-1.04	0.009
Stent length	1.23	1.1-1.48	<0.001
Smoking	1.46	1.4-1.9	0.003
Previous CABG	1.54	1.12-2.11	0.007
Renal insufficiency	1.66	1.18-2.31	0.003
ACS	1.72	1.28-2.30	<0.001
Treatment of SVG	1.87	1.3-2.7	0.001
Use of second-generation DES	0.77	0.58-0.99	0.04

ACS: acute coronary syndrome; CABG: coronary artery bypass graft; CI: confidence interval; DES: drug-eluting stent; HR: hazard ratio; SVG: saphenous vein graft

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, Seixas AC, Staico R, Mattos LA, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation.* 2001;103:192-5.

2. Stettler C, Allemann S, Wandel S, Kastrati A, Morice MC, Schömig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ,

Park SJ, Sabaté M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, De Carlo M, Erglis A, Chechi T, Ortolani P, Schalij MJ, Diem P, Meier B, Windecker S, Jüni P. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ.* 2008;337:a1331.

3. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schömig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabaté M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Jüni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet.* 2007;370:937-48.

4. Kirtane AJ, Gupta A, Iyengar S, Moses JW, Leon MB, Applegate R, Brodie B, Hannan E, Harjai K, Jensen LO, Park SJ, Perry R, Racz M, Saia F, Tu JV, Waksman R, Lansky AJ, Mehran R, Stone GW. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation.* 2009;119:3198-206.

5. Feres F, Costa JR Jr, Abizaid A. Very late thrombosis after drug-eluting stents. *Catheter Cardiovasc Interv.* 2006;68:83-8.

6. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation.* 2007;115:2426-34.

7. Siqueira DA, Abizaid AA, Costa Jde R, Feres F, Mattos LA, Staico R, Abizaid AA, Tanajura LF, Chaves A, Centemero M, Sousa AG, Sousa JE. Late incomplete apposition after drug-eluting stent implantation: incidence and potential for adverse clinical outcomes. *Eur Heart J.* 2007;28:1304-9.

8. Tajiri K, Sato A, Hoshi T, Kimura T, Nakagawa Y, Sakai S, Aonuma K, Watanabe S. Mechanisms explaining the late "catch-up" phenomenon after sirolimus-eluting stent implantation. *Int J Cardiol.* 2014;177:44-5.

9. Billinger M, Räber L, Hitz S, Stefanini GG, Pilgrim T, Stettler C, Zanchin T, Pulver C, Pfäffli N, Eberli F, Meier B, Kalesan B, Jüni P, Windecker S. Long-term clinical and angiographic outcomes of diabetic patients after revascularization with early generation drug-eluting stents. *Am Heart J.* 2012;163:876-86.e2.

10. Kuramitsu S, Matsuda H, Jinnouchi H, Yamaji K, Hiromasa T, Matsumura Y, Yamaji Y, Miura M, Domei T, Shirai S, Ando K, Kimura T. Long-term (7 to 10 years) clinical outcome after first-generation sirolimus-eluting stent implantation. *AsiaIntervention.* 2016;2:93-100.

11. Sousa JE, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, Kozuma K, Van Langenhove G, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation.* 2001;104:2007-11.

12. Sousa JE, Costa MA, Sousa AG, Abizaid AC, Seixas AC, Abizaid AS, Feres F, Mattos LA, Falotico R, Jaeger J, Popma JJ, Serruys PW. Two-year angiographic and intravascular ultrasound follow-up after implantation of sirolimus-eluting stents in human coronary arteries. *Circulation.* 2003;107:381-3.

13. Sousa JE, Costa MA, Abizaid A, Feres F, Seixas AC, Tanajura LF, Mattos LA, Falotico R, Jaeger J, Popma JJ, Serruys PW, Sousa AG. Four-year angiographic and intravascular ultrasound follow-up of patients treated with sirolimus-eluting stents. *Circulation.* 2005;111:2326-9.

14. Sousa A, Costa JR Jr, Moreira AC, Cano M, Maldonado G, Costa RA, Pavanello R, Romano ER, Campos C, Haddad N, Abizaid A, Feres F, Mattos LA, Staico R, Sousa JE. Long-term clinical outcomes of the Drug-Eluting Stents in the Real World (DESIRE) Registry. *J Interv Cardiol.* 2008;21:307-14.

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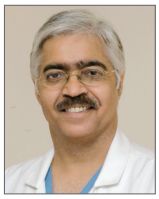
Bioresorbable scaffold use in the "real world" – mantras from the East



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The Absorb bioresorbable vascular scaffold (A-BVS) (Abbott Vascular, Santa Clara, CA, USA) represents a significant advance in the treatment of coronary artery disease. In use increasingly around the world, over the last year it has had to its credit three seminal trials (ABSORB China, ABSORB Japan and ABSORB III) which have demonstrated that A-BVS is as good as the best in class second-generation metallic drug-eluting stent (DES) both for safety and effectiveness at one year. These findings have also led to its approval in the USA two months ago. Over the last three years, clinical uptake of this revolutionary therapy has fluctuated between scepticism and optimism, confidence and caution and clarity and confusion – and all this because of the single fact that the A-BVS does not behave like the thin-strut, lower-profile user-friendly third-generation DES, which makes life so "simple" for the busy interventional cardiologist, even in complex lesions. The dreaded complication of stent thrombosis is also rare for DES as they are "technically forgiving" despite, in many instances, suboptimal implantation. The A-BVS is a "new device" and has a unique set of deployment and implantation characteristics, hence it requires its own set of "tips and tricks" for safe and effective implantation.

In this issue of AsiaIntervention, Sengottuvelu et al[1] publish a review of A-BVS use in the Asia-Pacific region. This review is

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important, especially as this region has a high prevalence of diabetes, and advanced and diffuse coronary artery disease in smaller vessels. Experience with the A-BVS is rapidly expanding in this region, and the lessons learnt by some of the experienced users and key opinion leaders provide not just insights, but important guidance for the interventional community at large for its safe and effective use. The document is originally based on a meeting which was convened in order to come up with a consensus around important "practice points". This meeting took place nearly a year and a half ago (April 2015), after GHOST-EU[2] had created an atmosphere of fear regarding higher scaffold thrombosis rates. Today, however, we are far wiser and certainly more confident. The document emphasises what we have said before:

- Firstly, there is a learning curve and operators should gradually make the transition from simple to more complex cases. This helps the operator get the "feel" of the device, its crossability and deliverability characteristics, the nuances of gradual inflation, recrossing with balloons and wires, its appearance on intravascular imaging with OCT/IVUS, etc. After approximately 15-20 cases, one can then progress to more "real-world" complex cases.
- Secondly, meticulous attention to implantation techniques affects outcomes. Clearly the "seven mantras" to success with the BVS are strongly amplified in this document **(Figure 1)**. Of these, for me the most important is high-pressure post-dilatation of the scaffold with a 0.25 mm larger non-compliant balloon up to 18-20 atm. This optimises the expansion, enlarges the lumen and also embeds the thick struts into the vessel wall[3] resulting in low thrombosis rates and improved outcomes similar to the latest-generation DES[4].

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Seven "mantras" to success with BVS

1. Have good guide catheter and guidewire support
2. Size the vessel accurately after intracoronary nitroglycerine
3. Prepare the lesion well with near optimal size balloon dilatation
4. Deploy the BVS slowly and appropriately matched to the vessel size
5. Post-dilate with a 0.25 mm larger non-compliant balloon to high pressures
6. Use OCT/IVUS when in doubt regarding vessel size or result
7. Pay meticulous attention to antiplatelet therapy

Figure 1. *Seven "mantras" to success with BVS.*

– Thirdly, while I strongly recommend imaging by OCT in specific clinical scenarios such as for accurate sizing of large vessels to determine if they are greater than 4 mm (which would preclude the use of the A-BVS), for bifurcation lesions, where a two-scaffold strategy is deployed, for "full plastic jacket" and small vessels diffuse disease, the routine use of intravascular imaging is not necessary if high-pressure post-dilatation is routinely performed as advised above. One should keep in mind that intravascular imaging is not available at all centres and also adds to cost. The more practical philosophy is to "post-dilate all and image a few" rather than "image all and post-dilate a few".

Despite exciting technical promise and robust scientific proof, the uptake of the A-BVS will remain slow until those concerns which brought about this era of caution are further clarified in order to achieve confidence. There is also a reluctance related to the greater time and hardware spent in deploying an invisible device with meticulous, painstaking precision and a routine that requires post-dilatation interspersed with imaging – and all this in an age when we have become used to the rapid "deploy and done" technique with the latest-generation DES where we have no need to remember any "mantras". I would argue that the potential long-term benefits of this temporary scaffold are physiologically sound, and clinically attractive (though this will only be proven through ongoing, long-term studies). Therefore, really, what is a few more minutes of your time if it gives the patient a "lifetime".

Finally, the consensus regarding type and duration of DAPT therapy in the Asia-Pacific region remains unclear and seems to follow that of the West. This is despite the fact that many studies from the West show an increased incidence of clopidogrel resistance in patients of Asian origin. There are no systematic studies today regarding this from Asia. While this may not be so important for the "forgiving DES", it takes on a different and important connotation for the thick-strutted A-BVS where DAPT using the newer $P2Y_{12}$ inhibitors, at least initially, could be more predictable and safe in complex "real-world" patients. This is clearly an area for prospective investigation.

It is heartening that the initial clinical experience with first-generation BVS has led to the evolution of an "optimal technique" of BVS implantation which offers us third-generation DES-like safety and outcomes. Further refinements in technology, iterations in design, and the thinning of struts and pruning of costs would overcome many of the present limitations and concerns, hopefully making BVS the strategy of choice for most patients with coronary artery disease rather than just the select few.

Conflict of interest statement

A. Seth is a member, ABSORB, Global Advisory Board, Abbott Vascular.

References

1. Sengottuvelu G, Schultz C, Chandra P, Santoso T, Mcclean D, Chanana BB, Dick R, Cheng JJ, Gwon HC, Hiremath S, Huan DQ, Jeamanukoolkit A, Jiang T, Kwok OH, Lim M, Low AF, Mathew R, Mathew SK, , Nakamura S, Nguyen M, Patel T, Qiao S, Saxena S, Soo CS, Tsai CT, Wasan U, Whelan A, Wong C, Yap YG, Simonton CA, Sudhir K. Bioresorbable vascular scaffold use in the Asia-Pacific region: current practices, technical considerations and key recommendations. *AsiaIntervention.* 2016;2:82-92.

2. Capodanno D, Gori T, Nef H, Latib A, Mehilli J, Lesiak M, Caramanno G, Naber C, Di Mario C, Colombo A, Capranzano P, Wiebe J, Araszkiewicz A, Geraci S, Pyxaras S, Mattesini A, Naganuma T, Münzel T, Tamburino C. Percutaneous coronary intervention with everolimus-eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry. *EuroIntervention.* 2015;10:1144-53.

3. Seth A, Kumar V, Rastogi V. BRS in complex lesions: massaging (and messaging) the right pressure points. *EuroIntervention.* 2015;11:131-5.

4. Puricel S, Cuculi F, Weissner M, Schmermund A, Jamshidi P, Nyffenegger T, Binder H, Eggebrecht H, Münzel T, Cook S, Gori T. Bioresorbable Coronary Scaffold Thrombosis: Multicenter Comprehensive Analysis of Clinical Presentation, Mechanisms, and Predictors. *J Am Coll Cardiol.* 2016;67:921-31.

AsiaIntervention 2016;2:80-81

Proceedings from an AsiaIntervention think tank meeting, May 2016

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Introduction

Under the leadership of the Chief Editors of AsiaIntervention, Runlin Gao, Upendra Kaul, Takeshi Kimura, Seung-Jung Park and Huay Cheem Tan, the Editorial Board of AsiaIntervention convoked a "think tank" meeting during the recent EuroPCR meeting in Paris, France, May 2016. The objective of this think tank meeting was to stimulate discussions concerning the promotion of the journal and, equally, encourage a further increase of manuscript submissions to AsiaIntervention.

Unique to this meeting was the request from the Chief Editors that young interventionalists should be the focus group of the meeting, something which was reflected in the invitees list along with consideration for their geographical origin which encompassed a broad spectrum of experiences within the Asia-Pacific region. Furthermore, Huay Cheem Tan provided insights and guidance in his role as Co-Chief Editor of AsiaIntervention, complemented by the experience of EuroIntervention Editorial Board members Robert Byrne and Christoph Naber, who were also present.

A brief history

The first issue of AsiaIntervention was published in Januay 2015 and – to date – it remains the only journal in the Asia-Pacific region dedicated soley to interventional cardiology. The Journal's editorial structure, although challenging, is unique in that it is led by the five Chief Editors as opposed to what is generally considered the norm, a single Chief Editor. The publisher's rationale for this structure is their desire to embrace "inclusiveness", ensuring as best as possible that all the major countries of the region are represented.

Echoing a growing movement within the European Society of Cardiology (ESC) with the formation of the ESC Young Community and its subgroups – and, in particular the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Young subgroup – the AsiaIntervention think tank attendees aimed to develop new initiatives for the journal through open and frank discussions.

Promotion

The AsiaIntervention website, http://www.asiaintervention.org, was launched in September 2015 together with social media platforms such as Facebook, Twitter and LinkedIn. Furthermore, through the publisher's links to the Europa Organisation and the PCR meetings, AsiaIntervention has enjoyed the benefit of Europa's mailing list (>70,000 worldwide). Moreover, AsiaIntervention is promoted at several key Asia-Pacific regional meetings (such as CIT, TCTAP, ACIT, AsiaPCR, CVIT). Nonetheless, the consensus

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of the think tank attendees was that a presence at other meetings is required to increase exposure. Currently the AsiaIntervention is not linked to any meeting or professional working groups in the region. This aspect was considered to fall outside the remit of the think tank meeting; nevertheless, it was deemed important that the publisher recognise that this could be a positive strategy to pursue in order to move forward.

Presently, AsiaIntervention is invited yearly to build a "how to write/review a medical paper" session at AsiaPCR/SingLIVE. The group proposed that other congress meetings in the region should be approached to investigate if similar sessions under the AsiaIntervention branding could be considered, noting the mutual benefit for both parties. Also, the suggestion to invite the authors of the best abstracts at these meetings to submit their work in full as complete articles to AsiaIntervention was positively welcomed.

Encouragement of manuscript submissions

The group discussed the current culture of scientific output in the region. The culture of medical writing has not yet matured to the levels of the West and to reach this level it will take time. The writing sessions discussed above are a compelling tool to aid younger interventionalists in understanding the publication process and its maturation. Furthermore, a significant element to promote submissions for the group is the importance of PubMed indexing for accepted papers and, although at the time of this report the application for AsiaIntervention indexing has been submitted, the group stressed that it was critical to emphasise that previously published papers will also be indexed retrospectively. Furthermore, a promotional strategy should be developed so that the community becomes aware when the indexing application has been successful.

Concerning the Impact Factor, it was noted that this generally takes three years after the journal has obtained indexed coverage such as PubMed. In a future think tank meeting, the group would like to develop a strategy for obtaining a high first impact factor and, hereafter, to increase its value systematically.

Initally, AsiaIntervention received submissions via a transfer recommendation system from its sister journal, EuroIntervention. However, while it was reported that this route accounts for 40% of submissions at present, this figure carries with it the positive implication that 60% of submissions now come directly to AsiaIntervention itself.

A number of proposals for submissions were further discussed including soliciting expert reviews with a focus on the Asia-Pacific community. Similar to EuroIntervention, international consensus documents and international surveys relevant to the local interventional community should be encouraged. Also, and once again similar to EuroIntervention, the group proposed dedicating a page within the journal for the promotion of each national interventional working group.

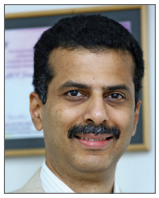
With respect to supplements, further thought was recommended concerning the feasibility of linking AsiaIntervention supplement publications with dedicated meetings such as bifurcation PCI and valvular interventions in both China and Japan.

Conclusion

Huay Cheem Tan, Co-Chief Editor, concluded that the first AsiaIntervention think tank meeting was fruitful in developing proposals for advancing the growth of the journal. Secondary to the goals of the meeting, he thanked the invitees for their attendance, noting that this platform will certainly help to increase their profile within their international networks and hopefully be the foundation for new friendships and professional relationships. A second meeting will be held in early 2017 during AsiaPCR/SingLIVE.

AsiaIntervention 2016;2:82-92

Technical considerations and practical guidance on the use of bioresorbable vascular scaffolds in the Asia-Pacific region: recommendations from an Asia Pacific Expert Group meeting 2015



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KEYWORDS

- Absorb
- Asian
- bioresorbable vascular scaffold

Abstract

Aims: Although the use of the bioresorbable vascular scaffold (BVS) in percutaneous coronary intervention (PCI) has been under investigation in clinical trials and real-world settings since its launch in 2010, these reports have come largely from the perspectives of European patients and physicians. Patient characteristics and physician preferences often differ in the Asia-Pacific region with respect to device implantation techniques, lesion complexity, access to intravascular imaging and patient management strategies. This has led to the need for a consensus on recommendations for deployment in Asia-Pacific populations. This document therefore serves as an overview of region-customised recommendations describing the best practices for these populations, in order to achieve more consistent and optimal clinical outcomes.

Methods and results: A comprehensive multiple choice questionnaire was disseminated to 28 interventional cardiologists from 13 countries in the Asia-Pacific region. The collated survey results then provided a backdrop to detailed discussion at a scientific meeting, the goal of which was accurate evaluation and understanding of the current BVS implantation and patient management practices of this group of physicians. Critical information from the discussions at the meeting was then compiled to generate technical recommendations, the purpose of which is to educate other cardiologists, both in the region and globally.

Conclusions: Practices, tips and techniques for the successful use of the Absorb BVS (A-BVS) in Asia were examined and used to assemble key recommendations that would foster confidence and encourage wider implementation of the device in the region. This included considerations for lesion selection, predilatation, deployment, post-dilatation, antiplatelet therapy, and management of complications. Additionally, the techniques used by interventional cardiologists in the Asia-Pacific region for specific complex lesion subtypes were also discussed.

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Background and introduction

Important advances have been made in the last thirty years in the management and treatment of cardiovascular disease, through the use of coronary artery bypass, balloon angioplasty and other surgical and percutaneous interventions. However, as heart disease continues to be the leading cause of death globally[1], the approach to its management must be regularly updated and optimised. Over 75% of deaths from cardiovascular disease now occur in low- and middle-income countries[2], with the Asia-Pacific region accounting for nearly 50% of the worldwide burden of mortality[3].

Bioresorbable vascular scaffolds (BVS) represent a significant advance in coronary interventional technology. Although guidelines exist for the use of BVS in European patients[4], no specific recommendations are available for the Asia-Pacific region. This document therefore seeks to provide clarity on the best practices for the implementation of the Absorb BVS (A-BVS) (Abbott Vascular, Santa Clara, CA, USA) in percutaneous coronary intervention (PCI) in Asian patients, by leveraging the combined clinical experiences and professional opinions of 28 of the region's interventional cardiologists ("the authors").

Editorial, see page 78

The A-BVS has undergone extensive preclinical testing[5] and clinical evaluation in Europe in simple coronary lesion settings[6,7] and has received the CE mark of approval (2010). It is now used increasingly in complex clinical settings such as ST-segment elevation myocardial infarctions (STEMI), long lesions, chronic total occlusions (CTO) and bifurcations.

Survey methodology

Twenty-eight interventional cardiologists from 13 countries in the Asia-Pacific region (Australia, New Zealand, Thailand, Malaysia, Vietnam, Singapore, Taiwan, Indonesia, India, China, Hong Kong, Japan and South Korea) who had prior experience with the implantation of coronary stents were invited to complete a survey. Briefly, the detailed survey comprised both quantitative and qualitative questions to determine the level of their experience and expertise with coronary scaffold technology and, in particular, their usage of the A-BVS device. The primary results of the survey have been published elsewhere[8]. Following the completion of the survey, the physicians gathered at a meeting sponsored by the device manufacturer (Abbott Vascular) in Singapore in April 2015. This meeting was also attended by the company's own representatives. The goal of the meeting was to understand the rationale and motivation behind the physicians' responses, in order to provide a more accurate perspective of scaffold delivery practices by physicians in the region. Importantly, the information derived from discussions during the meeting was used to drive recommendations for A-BVS deployment and use in the Asia-Pacific region, based on the collective experience of these physicians. The goal was to allow further education of physicians in these countries who are either new to, less experienced with, or encountering problems with the implementation of the A-BVS in their own practice. The following is a detailed account of the discussions at the meeting.

Potential benefits of BVS

Asia-Pacific interventional cardiologists perceived the A-BVS as effective in restoring the treated vessel's natural architecture and functionality, and potentially lowering long-term adverse event (AE) rates compared to drug-eluting stents (DES). Its most significant benefit is its temporary nature, allowing vessel enlargement through expansive vascular remodelling upon its disappearance. Many authors suggested that a scaffold would only be needed for three to six months to treat the lesion, and a temporary device that disappeared completely after two to three years was ideal.

BVS use would preserve future treatment options, such as coronary artery bypass graft (CABG) surgery in patients with progressive coronary artery disease (CAD) and replace the use of full-metal jackets with full-polymer ones in diffuse lesions (the so-called endoluminal bypass). It was also considered potentially beneficial for patients with diabetes mellitus and for young patients who might suffer from progressive and often aggressive CAD, and thus require repeat reinterventions. In such recurrent disease, implantation of additional BVS is feasible. In cases of in-scaffold restenosis (ISR), the use of metal-over-metal could be avoided by using BVS instead. With no permanent metal implant, concerns over very late stent thrombosis (ST) could potentially be reduced in the long term, especially beyond the time of complete resorption. In principle, the administration of long-term dual antiplatelet therapy (DAPT) may also be unnecessary beyond the period of resorption, although this would need to be confirmed in longer-term trials. BVS can also be used with computed tomography (CT), which is emerging as a non-invasive approach for evaluating patients with CAD **(Table 1)**.

Table 1. Perceived benefits of BVS.

Twenty-eight interventional cardiologists from countries in the Asia-Pacific region were asked to state the advantages of implanting BVS compared to alternatives such as drug-eluting metallic stents.	
Benefits of BVS as perceived or experienced by Asian interventional cardiologists	
Restores vessel's natural architecture and function	Could potentially reduce risk of late adverse events beyond the time of complete resorption
Temporary implant	Restores vasomotor function
Capping off of vulnerable plaques	Late lumen gain
Preserves future therapeutic options	Avoids full-metal jacket in diffuse lesions
Use of multiple BVS is beneficial for recurrent or progressive disease	May avoid need for long-term DAPT
Avoids metal-over-metal in ISR cases	Allows imaging, e.g., CT

Possible reasons for heterogeneous clinical outcomes

Utilisation of A-BVS varied among the authors, with one of the major concerns being the incidence of acute or subacute ST. Success with BVS was thought to be primarily dependent on adequate lesion preparation and post-dilatation **(Table 2)**. Authors agreed that

Table 2. Reasons for heterogeneous clinical outcomes.

Authors were asked to consider the problems faced in their own practices with A-BVS deployment, in order to understand the reason for heterogeneous clinical outcomes.
Possible reasons for heterogeneous clinical outcomes
Irregular use of post-dilatation
Inadequate lesion preparation
Operator inexperience with new device
DAPT non-compliance or discontinuation
Residual stenosis, suboptimal procedural result
Inadequate post-dilatation pressures
Operator skill
Incorrect vessel sizing
DAPT resistance

a large majority of the ST observed in the early post-market experience appeared to be due to a lack of or inadequate post-dilatation, or inadequate vessel and scaffold sizing. A smaller proportion is due to DAPT discontinuance, interruption or resistance.

General recommendations for BVS implantation

PATIENT AND LESION SUITABILITY

Ideal lesions for physicians to begin A-BVS implantation practices would be simple, straightforward, focal ones, e.g., type A/B1 lesions without heavy calcification or a major side branch (SB). The authors recommend successfully treating at least 20 simple lesions before attempting more complex ones (e.g., long diffuse lesions, CTOs, bifurcations). Only confident operators should attempt tortuous, extremely angulated and heavily calcified lesions. Left main (LM) and SB implantations should also be avoided initially, or until more suitable A-BVS sizes become available.

At the beginning of their practice, physicians should learn the "feel" of A-BVS deployment (i.e., pushability, strut flexibility) prior to progressing to more complicated lesions. The use of imaging techniques such as optical coherence tomography (OCT) is especially helpful when treating such lesions. For calcified lesions, the use of cutting balloons and rotablation is important in lesion preparation **(Table 3)**.

Due to the device's relative newness in the Asia-Pacific region (or unavailability so far, as in Japan and China), and the need to master implantation techniques, it is important that newer operators understand the patient and lesion types that may not benefit from A-BVS. Ideal lesions for treatment with A-BVS would be those which can be optimally expanded. Complex lesions would require more preparation and post-dilation and operator experience, and include heavily calcified lesions, long vein grafts, and true ostial lesions in either the right coronary artery or LM that are also fibrotic.

A-BVS may be less beneficial to elderly patients with numerous metallic implants. Operators must consider the currently available device lengths and diameters, expansion limits and profiles during deployment in challenging settings (e.g., in small vessels and tapering arteries). Patients who cannot be prescribed or comply with DAPT should not be treated with A-BVS.

Table 3. General guidelines for BVS implantation.

The 28 authors surveyed listed their personal experience and learning from the use of the A-BVS in their own patients to create a set of general guidelines for new users of the device.	
General guidelines for BVS implantation	
Lesions to begin with	Simple
	Focal
	A/B1
	Not heavily calcified
Lesions to progress to	Long, diffuse lesions
	STEMI/ACS
	Simple bifurcations
	CTOs
Lesions or cases to avoid	Heavily calcified
	Long vein grafts
	True ostial lesions
	Larger than 4 mm
	Smaller than 2.25 mm
Tools & techniques to use	Imaging (IVUS, OCT) when necessary/available
	Plaque modification (with cutting balloons, Rotablator™)

PREDILATATION AND SIZING

Vessel sizing and scaffold selection, lesion preparation and intravascular imaging are important pre-implantation considerations **(Figure 1)**. Proper scaffold selection is essential and depends on accurate target vessel sizing, for example, by intravascular imaging (IVUS and OCT), especially for complex lesions. However, due to the cost and limited availability of intravascular imaging, some authors preferred visual estimation against a catheter or predilatation balloon, quantitative coronary angiography or a pre-procedural CT coronary angiogram. For angiography, either proximal, interpolated or distal vessel reference diameters may be used for sizing. Sizing could also be facilitated by prior administration of nitrates. To determine whether an A-BVS could be advanced across a tough lesion, the lesion could be initially crossed and sized using a winged or deflated non-compliant balloon. Predilatation to the same size as the vessel (1:1), or to slightly less, could be performed with a non-compliant balloon dilatation catheter, especially if the lesion does not open with a semi-compliant balloon. Direct A-BVS implantation may rarely be performed in acute coronary syndromes (ACS) after thrombus aspiration.

For lesion preparation, predilatation with a non-compliant balloon was the most preferred method. For severely calcified lesions, the use of a cutting or scoring balloon or rotablation was highly advised. The authors recommended that the maximum amount of residual stenosis before scaffold implantation be at least less than 40% and, ideally, less than 20%.

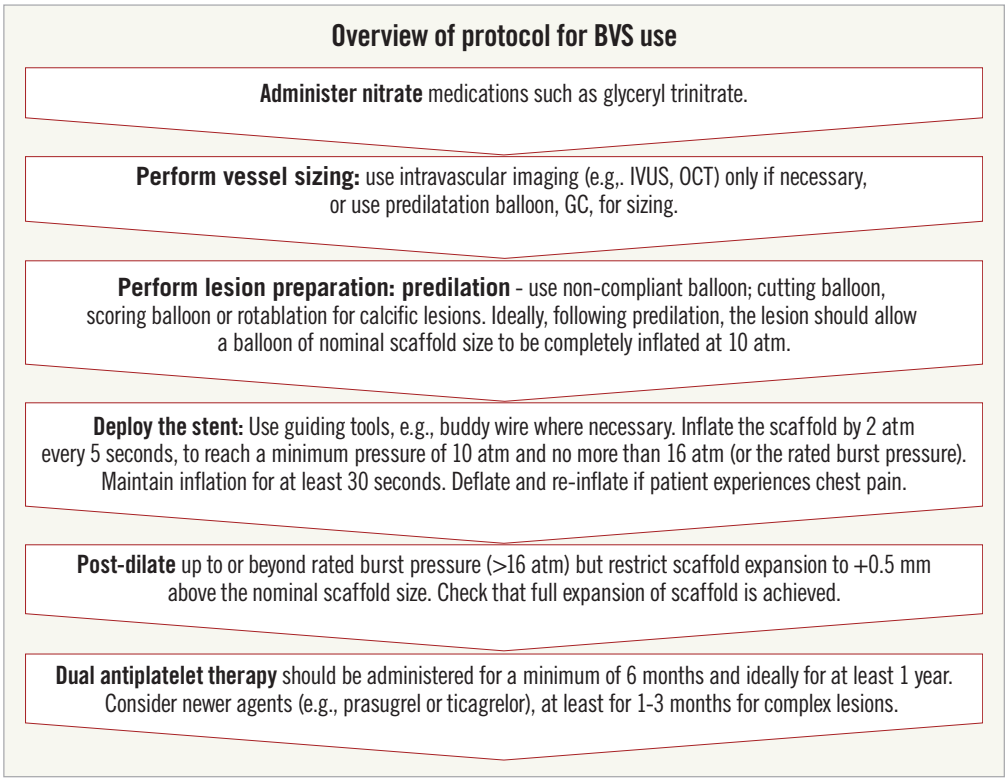

Figure 1. *Flow chart of treatment algorithm. Key steps in the deployment of the A-BVS device are summarised, following in-depth discussions by the authors to derive practical guidance on the most important aspects for practice.*

DEPLOYMENT: SCAFFOLD IMPLANTATION AND LESION CROSSING

The use of guidance tools can be integrated into BVS deployment practice. Buddy wires are often used to assist with tracking BVS deployment, as are GuideLiners® (Vascular Solutions Inc., Minneapolis, MN, USA), extra support wires or mother-and-daughter catheters. Optimal expansion and slow, gradual inflation during deployment were the most critical factors in ensuring successful implantation **(Figure 1)**. Although the scaffold should not be excessively overexpanded beyond its limits, expansion must be optimised. Balloon inflation should be maintained for at least 30 seconds and up to one minute, with pressures of 11-16 atm. Physicians must also be mindful of risking edge dissections, especially when deploying at very high pressures. To avoid this, the use of 8-10 atm for inflation was recommended by some authors, although expansion up to rated burst pressures is feasible.

The use of overlapping scaffolds may be necessary to ensure full coverage of the lesion and area treated by the balloon. The manufacturer recommends that the scaffolds be overlapped by at least 1 mm and up to 4 mm, to prevent gap-related restenosis. Overlapping should be performed by placing the balloon marker bands of the second A-BVS device on the inside of the first, already deployed scaffold, before expansion. This prevents gaps occurring between scaffolds.

Where possible, marker-to-marker overlapping should be used, although marker-over-marker and scaffold-to-scaffold techniques are also used. Precision is essential to avoid geographic miss. Physicians must understand that malapposition occurs more frequently at overlapping regions and calcified lesions. Overlapping A-BVS should also be avoided in small vessels.

POST-DILATATION: SCAFFOLD OPTIMISATION AND INTRAVASCULAR IMAGING

Post-dilatation using a high-pressure non-compliant balloon is recommended by both the manufacturer and the authors. The authors suggest a post-dilatation balloon that is slightly larger (by 0.25 to 0.5 mm) than the selected A-BVS device. Non-compliant balloons should be inflated to a maximum pressure of 15-20 atm, but expansion must be kept to no greater than 0.5 mm above the nominal scaffold diameter **(Figure 1)**. Higher pressures may be required in tough fibrocalcific lesions. The preferred duration for post-dilatation balloon inflation is 15-30 seconds but, depending on lesion complexity and the patient's tolerance to pain, inflation for either 31-60 seconds or less than 15 seconds may be preferred. Physicians are advised that balloon expansion *in vivo* differs from that shown in compliance charts.

ADJUNCTIVE ANTITHROMBOTIC THERAPY (DAPT)

DAPT recommendations currently in use by cardiologists in the Asia-Pacific region are adapted from those formulated by the American College of Cardiology, the American Heart Association and/or the European Society of Cardiology, for Caucasian patients.

East Asian patients may have different drug responses, and this must be considered when devising PCI strategies for ACS. These differences include ethnic-specific proclivities for thrombogenicity and bleeding, and a different window of time for optimal DAPT efficacy.

East Asian patients may have risk profiles for both thrombosis and bleeding which differ from Western populations[9]. In Asia, DAPT is usually prescribed for at least one year for complex lesions, with patients often maintained on DAPT long-term as secondary prevention. If clopidogrel therapy was initiated and resistance subsequently detected, transition to ticagrelor or prasugrel would be necessary. This highlights the necessity of customising DAPT prescriptions to the patient's clinical and genetic profile to ensure safety and efficacy.

For stable angina patients, a period of six months to one year or one to two years of DAPT **(Table 4)** was preferred. In ACS presentations, namely NSTEMI and STEMI, the authors were divided almost equally between durations of six months, six months to one year, one to two years, or more than two years, and there was no agreement on the optimal duration of DAPT. For patients with complex lesions such as CTO, long lesions or bifurcations, longer DAPT duration should be considered. In patients with ACS or STEMI, prasugrel or ticagrelor was preferred over clopidogrel **(Table 4)**.

If long-term OCT data in humans (in excess of three years) successfully confirm the total resorption of A-BVS, then there might be no need for long-term DAPT, i.e., beyond 2.5-3 years. More general descriptions of antiplatelet strategies and best practices for East Asian patients are available in recently published reviews[10].

Table 4. DAPT duration preferences for the treatment of A-BVS-implanted patients with stable angina, complex lesions, NSTE-ACS and STEMI complex lesions by authors surveyed for this manuscript.

In general, more authors chose either six months to one year or one to two years, rather than choosing up to six months or more than two years. Usage of prasugrel or ticagrelor was also surveyed.	
Rank order of preferred DAPT durations for cardiovascular indications treated with A-BVS	
Stable angina (1: most preferred, 4: least preferred, *: tie)	
Up to 6 months	2*
6 months - 1 year	1*
1 - 2 years	
More than 2 years	2*
Complex lesions (bifurcations, long, CTO) (1: most preferred, 4: least preferred)	
Up to 6 months	4
6 months - 1 year	1
1 - 2 years	3
More than 2 years	2
NSTE-ACS and STEMI (1: most preferred, 4: least preferred)	
Up to 6 months	4
6 months - 1 year	1
1 - 2 years	3
More than 2 years	2
Use of prasugrel or ticagrelor (%)	
Patient lesion type	% of authors who prescribe prasugrel or ticagrelor
NSTE-ACS or STEMI	66
All patients regardless of symptoms	26
N/A (physician only prescribes clopidogrel)	8

Recommendations for specific lesion subsets

LONG LESIONS

To avoid full-metal jackets in long lesions, the use of A-BVS is attractive, especially in young patients with long, diseased left anterior descending arteries (LAD), when options for future surgery need to be preserved and the anastomotic site must remain metal-free. Pre-implantation imaging is helpful for initial assessments in long lesions, as well as in the evaluation of tapering in such vessels. Imaging can help choose between implanting a single scaffold (using the interpolated diameter), or using two scaffolds instead. When sizing long lesions in tapering vessels, two scaffolds of different sizes may be used. Two different non-compliant balloons, one to treat the distal site, and a larger one to treat the proximal site, may also be used.

The treatment of long lesions with BVS requires suitable support (e.g., at least 7 Fr guide catheter, buddy wires, etc.) and meticulous vessel preparation **(Table 5)**. For deployment, the distal scaffold should be implanted first and all scaffolds should be optimally expanded. In general, implanting scaffolds distally to proximally is recommended. However, proximal A-BVS deployment can also be performed first when accurate placement is essential, e.g., in ostial lesions that require overlap and avoidance of a large side branch. This can be followed by post-dilatation and subsequent crossing with a distal scaffold.

Table 5. Factors to consider for the use of A-BVS in long lesions.

Treatment of long lesions with A-BVS	
Imaging	Assess extent of taper
	Verify possibility of use of 1 interpolated size scaffold
	Verify need for 2 different-sized scaffolds
Sizing	If >1 mm disparity, use 2 different-sized scaffolds
	Use interpolated diameter
	Use 2 different-sized non-compliant balloons
Preferred tools and techniques	Use good guide support
	Prepare vessel thoroughly
	Marker-to-marker overlap
Issues to note	If using multiple BVS, ensure precise positioning and optimal inflation
	Avoid or minimise scaffold overlap
	Overlap is not recommended in smaller vessels (<2.5 mm)

For overlapping, marker-to-marker was the most recommended approach. Ideally, the distal scaffold is deployed first, and the marker of the A-BVS scaffold checked to ensure appropriate overlap with the marker of the proximal scaffold balloon. When implanting full-polymer jackets, overlap should be minimal, and the technique of scaffold-to-scaffold placement (edge-to-edge) can be used. With small vessel diameters, layering of thick struts may compromise the lumen; therefore, overlap of A-BVS is not recommended in smaller vessels (<2.5 mm) **(Table 5)**.

CHRONIC TOTAL OCCLUSION (CTO)

As most CTOs are long lesions, using A-BVS keeps them free from full-metal jacketing for future surgical interventions. However, A-BVS is best avoided in certain CTO-associated lesions, e.g., heavily calcified lesions. The use of subintimal dissection and re-entry techniques for A-BVS in CTO is feasible. The regular use of invasive imaging techniques (IVUS and OCT) is advocated for BVS selection and follow-up in CTOs. In addition, when long CTOs are treated with overlapping BVS, optimal implantation can be verified with intravascular imaging during the index procedure, and at follow-up.

At six-month follow-up, the CTO-ABSORB pilot study[11] of BVS in 35 CTO lesions demonstrated the safety of A-BVS in this setting, as there were no MACE events in that study. Importantly, this trial emphasised adequate lesion preparation in these lesions to facilitate BVS expansion.

THROMBOTIC LESIONS (e.g., ACS, STEMI)

Real-world data from Singapore show that A-BVS can safely be used in patients with STEMI undergoing primary PCI[12]. The European multicentre randomised TROFI-II trial[13] demonstrated that stenting of culprit lesions with Absorb in the setting of STEMI resulted in a nearly complete arterial healing, which was comparable with that of the XIENCE EES at six months. In thrombotic lesions, using A-BVS may prevent late malapposition. Moreover, the greater intimal coverage afforded by the struts of A-BVS may potentially reduce distal embolisation. In younger patients with ACS and STEMI, the use of A-BVS can restore long-term vasomotion, lumen gain and vessel remodelling. Although the authors felt that A-BVS was appropriate for thrombotic lesions, the need for larger trials and more long-term data was emphasised.

To size STEMI lesions, the proximal reference diameters should be used after restoring flow and size recovery of the vessel following thrombus aspiration and nitrate treatment. Optimal sizing could be achieved using a larger balloon, although some oversizing (the largest scaffold that can be tolerated by the vessel) may be necessary. Imaging was also recommended to assist in determining the level of thrombus burden or whether plaque rupture had occurred.

The authors advised using the proximal reference marker, and deploying the scaffold slowly and gradually, to slightly higher than nominal pressures, visually verifying expansion, and performing post-dilatation to ensure optimal proximal apposition. Aggressive post-dilatation (over 14-16 atm) was generally not recommended due to the risk of no reflow, which can be minimised by thorough thrombus aspiration and/or intracoronary glycoprotein IIb/IIIa administration **(Table 6)**.

Direct scaffolding of STEMI lesions should only be performed if the level of plaque burden and proximal and distal vessel segments can be clearly seen following thrombus aspiration, and the

Table 6. Factors to consider for the use of A-BVS in thrombotic lesions (ACS, STEMI).

Treatment of thrombotic lesions with A-BVS		
Techniques	Prepare lesion:	Thorough thrombus aspiration
		Restore flow to vessel
	Sizing:	Use proximal reference diameter
		Size after restoring flow to vessel
	Implantation and post-dilatation:	Deploy scaffold slowly
		Implant a slightly oversized or largest size scaffold possible
		Direct scaffold only if thrombus aspiration is optimal, vessel is clearly visible and lesion is short, with little residual stenosis
		Avoid aggressive post-dilatation, >14-16 atm is not recommended
DAPT recommendations	1 year of DAPT is advised, e.g., one year of clopidogrel	
	Preload with DAPT	
	Use newer drugs or change to ticagrelor or prasugrel	
	Start with combinations such as aspirin and ticagrelor or prasugrel	
Issues to note	Reference vessel may be difficult to observe and size	
	Undersizing may occur	
	Plaque morphology may be unclear	
	Plaque resists expansion or ruptures	
	Risk of no reflow can be minimised by thrombus aspiration and/or intracoronary GP IIb/IIIa administration	

lesion is short with minimal residual stenosis. This would ensure that the lesion is sized accurately and thoroughly covered by the scaffold. Concerns included highly fibrotic and expansion-resistant plaques, or situations where the morphology of the plaque is unclear, especially if direct scaffolding with A-BVS is planned.

The consensus on the duration of antiplatelet therapy in thrombotic lesions following A-BVS implantation was one year of DAPT, with preloading and the use of newer thienopyridine medications such as ticagrelor or prasugrel. The manufacturer currently advocates at least six months of DAPT. Asia-Pacific interventional cardiologists preferentially use prasugrel and ticagrelor for ACS and STEMI. In complex lesions in general, the threshold for using prasugrel and ticagrelor tends to be lower. Patients can also begin with ticagrelor or prasugrel with aspirin but change to clopidogrel and aspirin during the first year, or after one year.

Potential issues with the use of A-BVS in thrombotic lesions include inflammation, spasm, occlusion and difficulties in visualising the vessel reference, which would affect vessel sizing. Importantly, these factors are also similarly present with the use of DES. Patients in cardiogenic shock should not be treated with A-BVS, since proper vessel sizing is time-consuming and may jeopardise the patient.

CALCIFIED LESIONS

Since significant calcification probably disrupts intimal physiology, vasomotor benefits following A-BVS may be limited in calcified lesions. Such compromised physiology may also impair local delivery of drugs to the calcified lesion; therefore, lesion preparation is essential. In calcific settings, overstretching the device can cause adventitial strain; therefore, lesion preparation is an essential first step and will determine the extent of expansion that can be achieved. However, BVS can provide long-term benefits if proper apposition and scaffold expansion are achieved. In order to use A-BVS, the level of calcifications must be no more than mild to moderate.

The use of cutting or scoring balloon or rotablation is recommended for lesion preparation. High-pressure dilatation with a non-compliant balloon (over 20 atm) can be performed to attempt full balloon expansion (preferably a 1:1 balloon:artery ratio). Where possible, no residual stenosis should persist. After lesion preparation, imaging (OCT or IVUS) is useful to assess the level of residual calcification, and whether it spans the entire circumference of the vessel, or is focal or eccentric. IVUS can determine if the calcification has cracked following balloon dilatation, which would make it more suitable for A-BVS. Besides sizing, IVUS can also be used post implantation to verify that, in all arterial segments, the implanted A-BVS is well expanded, and all struts circumferentially and longitudinally well apposed. Analysis of the lesion by CT angiography prior to the implantation procedure is also helpful in calcified lesions. The CT angiogram provides information on the extent and distribution of calcification **(Table 7)**.

BIFURCATIONS

In bifurcation lesions, the use of A-BVS over DES would prevent long-term stent jailing of the side branch. However, this lesion type should be treated by operators with significant expertise and experience. Due to the discrepancy between proximal and distal vessels, the operator should select the proximal vessel diameter

Table 7. Guidelines and considerations for the treatment of calcified lesions with the A-BVS.

Treatment of calcified lesions with A-BVS		
Techniques	Lesion preparation:	Use balloon dilatation to crack calcified plaque
		Cutting balloon, scoring balloon or rotablation can also be used on plaques
		Attempt to achieve no residual stenosis
	Imaging & sizing:	Use imaging for assessment of plaque density and distribution
		Use imaging for vessel sizing
		Size artery using non-compliant balloon to get 1:1 dimensions
		CT angiography may be helpful in assessing extent and distribution of calcium
	Deployment and post-deployment:	Gentle manipulation must be used for deployment
		Use high-pressure dilatation (>20 atm) with non-compliant balloon
		Use IVUS imaging to confirm that struts are well apposed, concentric and exposed
Issues to note	Overstretching can cause adventitial straining	
	Suboptimal deployment increases restenosis and thrombosis risk	
	Compromised DAPT delivery to calcified lesion	
	Not for highly calcified lesions	
	Disruption of intimal physiology	
	Early restenosis	
	Strut disruption/fractures if forcefully deployed	
	Lower vasomotor benefits	
	Diabetic patients may have more restenosis	

for scaffold sizing for bifurcation lesions, keeping in mind the limits of post-dilatation of the scaffold. Adequate imaging should be strongly considered, to establish vessel size and plaque distribution. If the distal vessel is small, it is critical not to oversize and risk distal vessel edge dissection; therefore, two overlapping scaffolds should be considered where possible, particularly in highly tapered vessels.

The use of kissing dilatation should also be minimised, and single, provisional scaffolding is the recommended strategy. Sequential non-compliant balloon inflations in the side branch and subsequently in the main branch may be used. Another option is to use snuggle balloon dilatation with two non-compliant balloons, and minimal overlapping of the balloons. While the use of final kissing balloon dilatation is generally not preferred, in selected cases low-pressure kissing balloon dilatation can be cautiously performed, preferably with imaging guidance.

Recommended strategies include the provisional 1-scaffold technique[14] with a side branch balloon, and the 2-scaffold technique with either TAP (with two BVS, or one BVS and one DES) or T stenting. If the anatomy is suitable for Medina 0,1,1 bifurcations, the V-scaffold technique is advocated. The "keep it open" approach is recommended for bifurcations with the side branch under 2.5 mm. If pinching of the side branch is significant, sequential balloon dilatation with low pressures (<10 atm) is advised, beginning with the side branch and finishing with the proximal optimisation technique (POT) in the main vessel. Kissing balloon dilatation with low pressures may be used, while a drug-eluting balloon (DEB) can be used for treatment of the side branch.

To treat the side branch, ballooning or DEBs could be used if the side branch is less than 2.5 mm in diameter. For wider side branches, either a DES or a BVS could be used, depending on the degree of angulation, diffuseness of disease or extent of calcification. To facilitate side branch treatment, the main branch BVS must be post-dilated optimally first, followed by gradual dilatation of the side branch through the struts using a balloon not more than 2.5 mm in diameter, after which a second BVS may be deployed in the side branch. The POT approach can also be used, as long as the expansion limits of the A-BVS are respected.

Post-procedure imaging, particularly with OCT, provides useful information on malapposition, underexpansion, scaffold fracture, edge dissection and side branch ostium, and should be strongly considered. Overdilatation of A-BVS in the main vessel can lead to issues including scaffold fracture, especially during proximal optimisation and final upsizing in the proximal vessel with an oversized balloon. Culotte or traditional crush techniques should generally be avoided in bifurcations. Ormiston et al[15] have shown in bench studies that dilatation through the side of an A-BVS scaffold displaced struts from the side branch lumen, but caused main branch malapposition opposite the side branch, main branch scaffold narrowing beyond the side branch, and protrusion of struts into the side branch. Scaffold distortion was corrected by main branch post-dilatation or by mini-kissing balloon post-dilatation (mini-KBPD). When 3.0 mm diameter balloons were used for side branch dilatation or mini-KBPD in 3.0 mm A-BVS, strut fracture did not occur at or below inflation pressures of 10 and 5 atm, respectively. Above these thresholds, the likelihood of strut fracture increased with increasing pressure. The clinical implications of scaffold fractures in bifurcations remain unclear, and use of a 3 mm balloon for side branch dilatation is not advocated by the manufacturers. Other considerations include malapposition, recrossing and calcifications. Scaffold malapposition in proximal vessels and/or severely tapered vessels may occur; therefore, the use of imaging techniques to assess vessel size and plaque distribution is recommended. When recrossing an implanted BVS with a second A-BVS is difficult, the authors advise using a short metallic DES. Calcification may impact on A-BVS deliverability (e.g., to side branches) and, in such situations, it must be used carefully or not used at all.

Management of complications

Data on the incidence of periprocedural scaffold thrombosis are conflicting; however, there is general consensus that the occurrence of such events is often related to suboptimal deployment. To treat early or late scaffold thrombosis, the preferred approach is plain balloon angioplasty with or without thrombectomy, followed by DES implantation (especially in cases of BVS fracture confirmed by OCT), and lastly by implantation of a new A-BVS. Also, the authors suggested administering glycoprotein inhibitors to dissolve the thrombus, since aggressive post-dilatation may also induce slow flow or no flow.

In dealing with in-scaffold restenosis (ISR), substantial plaque prolapse or associated thrombus is sometimes seen within the scaffold by IVUS/OCT. Since the occurrence of ISR after A-BVS implantation is still relatively uncommon, the best treatment strategy has not been evaluated. Use of a drug-eluting balloon or plain balloon angioplasty in this setting has the potential advantage of "leaving nothing behind", especially if the restenosis is early. Occasionally a second A-BVS has also been used in this setting for the same reason. However, many experts choose to treat restenosis following A-BVS with a metallic DES.

Limitations

This document was drafted based on the opinion of twenty-eight interventional cardiologists. Where there were differences of opinion, consensus was arrived at through thorough discussion. The opinions here reflect experience with optimal deployment and short-term outcomes. While all authors were comfortable with deploying A-BVS in simple lesions and patients, caution was recommended for more complex lesions where data are more limited. Long-term clinical studies are currently under way, and will help confirm whether such recommendations translate to the best long-term outcomes. A few pivotal trials have been published since the meeting; while the authors did not have the opportunity to discuss these, the additional trials are referenced in the discussion section below.

Summary of recommendations and discussion

BVS is generally regarded as the technology of the future by the authors and, in six to eight years, is expected to be widely used in the majority of cardiac catheterisation laboratories. Ongoing randomised controlled trials comparing A-BVS to the XIENCE stent include ABSORB II, III, CHINA, and JAPAN as well as ABSORB IV which is actively enrolling. In patients from Europe and New Zealand, ABSORB II[16] has thus far demonstrated comparable clinical event rates of A-BVS to XIENCE at one year, with reduced rates of angina, nitrate use and revascularisation in BVS-treated patients. ABSORB JAPAN, which compared A-BVS to XIENCE EES in Japanese patients with a maximum of two *de novo* target lesions in separate coronary arteries, has met the primary clinical and secondary angiographic endpoints of target lesion failure at one year and angiographic in-segment late lumen loss at 13 months, respectively[17]. Updated data from randomised controlled studies, including the large cohort (>2,000 patients) in ABSORB III at one year[18], demonstrated comparable target lesion failure and adverse event rates between the A-BVS and the XIENCE scaffold (TLF 7.8% vs. 6.1%, p<0.007), thus meeting the study's primary endpoint goals. The ABSORB China trial, which also compared A-BVS to XIENCE and was conducted to support device approval in China[19], achieved the one-year non-inferiority primary endpoint of in-segment late loss in 480 Chinese patients (A-BVS 0.19±0.38 mm vs. XIENCE 0.13±0.38 mm, p=0.01). In a patient-level, pooled meta-analysis of the above four randomised trials of 3,389 patients with stable coronary artery disease or a stabilised acute coronary syndrome, A-BVS event rates of composite patient-oriented and device-oriented adverse events did not differ at one-year follow-up compared with the XIENCE EES[20]. Together, these results indicate that A-BVS is non-inferior to the current best-in-class XIENCE metallic stent. Further results are anticipated from longer-term follow-up of these randomised trials.

In a prospective, real-world Australian study[21] of 152 lesions in 100 patients, A-BVS was associated with low rates of target lesion revascularisation, myocardial infarction, and scaffold thrombosis at 12 months. This was attributed to a strategy of meticulous lesion preparation, routine post-dilation, and 12 months of dual antiplatelet therapy. This Asia-Pacific experience supports the recommendations for optimising lesion preparation and post-dilatation procedures. Other real-world European studies have addressed the heterogeneity in patient outcomes reported by previous studies. In one small all-comers study by Costopoulos et al[22], where A-BVS-treated patients were lesion-matched to XIENCE-treated patients, no ST was detected. In that study, because post-dilatation was performed in >90% of A-BVS-treated patients and maximum inflation pressure was 21 atm, a reasonable inference is that high-pressure post-dilatation contributed to low to no adverse events. In another European study, the POLAR ACS study[23] in which post-dilatation was performed in 81% of patients, only one case of myocardial infarction (MI), attributed to scaffold thrombosis, was detected at one year. A single incidence of target lesion revascularisation (TLR) was observed, leading the investigators to conclude that the use of BVS for the treatment of acute coronary syndrome patients was both safe and effective. The controversial GHOST-EU trial[24] included all-comers with a fairly complex disease profile; the overall post-dilation rate in that report was only 52.3%, and the ST rate was 1.9% at six months and 2.0% at one year. More recently, however, a propensity-matched analysis of GHOST-EU patients versus those from the XIENCE V USA registry showed that the combined rate of ischaemic events at one year was low and not significantly different to matched patients treated with XIENCE EES[25]. Importantly, in a recent European all-comers registry, scaffold thrombosis could be significantly reduced with optimised implantation[26], a strategy now widely recognised as critical to the best clinical outcomes and lowest adverse event rates.

A summary of the recommendations of the group is as follows. Initial experience with A-BVS should consist of simple lesions and patients, such as type A/B1 lesions, the absence of heavy calcification and the avoidance of major side branches. A learning curve of approximately 20 procedures was considered reasonable, after which operators might expand their use to more complex lesion and patient types. Vessel sizing and scaffold selection, lesion preparation and intravascular imaging were emphasised as important pre-implantation considerations. Proper scaffold selection is essential and depends on accurate target vessel sizing, for example, by intravascular imaging, especially for complex lesions. However, due to the cost and limited availability of IVUS and OCT, many authors preferred visual estimation, quantitative coronary angiography or a pre-procedural CT coronary angiogram. Adequate predilatation to the same size as the vessel (1:1) is critical, if necessary with a non-compliant balloon catheter. Cutting or scoring balloons or rotablation were strongly recommended for calcified lesions. Post-dilatation was strongly recommended using non-compliant balloons inflated to a maximum pressure of 15-20 atm, or higher if necessary, with expansion limited to 0.5 mm above the nominal diameter of the scaffold. A period of six to 12 months of DAPT was considered ideal for simple lesion and patient types, whereas 12 months or longer was recommended for complex lesions. Many authors preferred newer $P2Y_{12}$ inhibitors, namely ticagrelor or prasugrel, especially in ACS and STEMI patients. These recommendations are very similar to those from Europe by Tamburino et al, in which consensus criteria for patient and lesion selection, BVS implantation and optimisation, use of intravascular imaging guidance, approach to multiple patient and lesion scenarios, and management of complications, were identified[4]. The authors noted that the current A-BVS device has thicker struts than current-generation DES, and noted that future generations of the device with a thinner strut profile would probably be easier to use, with a potential for even better clinical outcomes.

This document highlights how the current practice and experience of Asia-Pacific interventional cardiologists mirror those in Europe, regardless of lesion complexity. It is expected that long-term clinical trial data will support the present results, potentially showing improvements in long-term efficacy and safety over DES.

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K. Sudhir and C. Simonton are employees of Abbott Vascular. The other authors have no conflicts of interest to declare.

References

1. World Health Organization (WHO). Cardiovascular diseases (CVDs). 2009: Fact sheet N°317. http://www.who.int/mediacentre/factsheets/fs317/en/

2. World Health Organization (WHO). Global atlas on cardiovascular disease prevention and control. Policies, strategies and interventions. 2011. http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/

3. World Health Organization (WHO) Global Infobase. https://apps.who.int/infobase/mortality.aspx

4. Tamburino C, Latib A, van Geuns RJ, Sabate M, Mehilli J, Gori T, Achenbach S, Alvarez MP, Nef H, Lesiak M, Di Mario C, Colombo A, Naber CK, Caramanno G, Capranzano P, Brugaletta S, Geraci S, Araszkiewicz A, Mattesini A, Pyxaras SA, Rzeszutko L, Depukat R, Diletti R, Boone E, Capodanno D, Dudek D. Contemporary practice and technical aspects in coronary intervention with bioresorbable scaffolds: a European perspective. *EuroIntervention.* 2015;11:45-52.

5. Nakatani S, Ishibashi Y, Sotomi Y, Perkins L, Eggermont J, Grundeken MJ, Dijkstra J, Rapoza R, Virmani R, Serruys PW, Onuma Y. Bioresorption and Vessel Wall Integration of a Fully Bioresorbable Polymeric Everolimus-Eluting Scaffold: Optical Coherence Tomography, Intravascular Ultrasound, and Histological Study in a Porcine Model With 4-Year Follow-Up. *JACC Cardiovasc Interv.* 2016;9:838-51.

6. Serruys PW, Onuma Y, Ormiston JA, de Bruyne B, Regar E, Dudek D, Thuesen L, Smits PC, Chevalier B, McClean D, Koolen J, Windecker S, Whitbourn R, Meredith I, Dorange C, Veldhof S, Miquel-Hebert K, Rapoza R, García-García HM. Evaluation of the second generation of a bioresorbable everolimus drug eluting vascular scaffold for treatment of de novo coronary artery stenosis: six-month clinical and imaging outcomes. *Circulation.* 2010;122:2301-12.

7. Serruys PW, Onuma Y, Dudek D, Smits PC, Koolen J, Chevalier B, de Bruyne B, Thuesen L, McClean D, van Geuns RJ, Windecker S, Whitbourn R, Meredith I, Dorange C, Veldhof S, Hebert KM, Sudhir K, Garcia-Garcia HM, Ormiston JA. Evaluation of the second generation of a bioresorbable everolimus-eluting vascular scaffold for the treatment of de novo coronary artery stenosis: 12-month clinical and imaging outcomes. *J Am Coll Cardiol.* 2011;58:1578-88.

8. Chanana BB, Chandra P, Cheng JJ, Dick R, Gwon HC, Hiremath MS, Huan DQ, Jeamanukoolkit A, Jiang T, Kwok OH, Lim MC, Low AF, Mathew R, Mathew SK, McClean D, Nakamura S, Nguyen M, Qiao S, Santoso T, Saxena S, Schultz C, Sengottuvelu G, Seth A, Simonton CA, Soo CS, Sudhir K, Tsai CT, Wasan U, Whelan A, Wong C, Yap YG. Current practices of Asia-Pacific cardiologists in the utilization of bioresorbable scaffolds. *Int J Cardiol.* 2016;222:832-40.

9. Kwon TJ, Tantry US, Park Y, Choi YM, Ahn JH, Kim KH, Koh JS, Park JR, Hwang SJ, Kwak CH, Hwang JY, Gurbel PA, Smith SC Jr, Jeong YH. Influence of platelet reactivity on BARC classification in East Asian patients undergoing percutaneous coronary intervention. Results of the ACCEL-BLEED study. *Thromb Haemost.* 2016;115:979-92.

10. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC Jr. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol.* 2014;11:597-606.

11. Vaquerizo B, Barros A, Pujadas S, Bajo E, Estrada D, Miranda-Guardiola F, Rigla J, Jiménez M, Cinca J, Serra A. Bioresorbable everolimus-eluting vascular scaffold for the treatment of chronic total occlusions: CTO-ABSORB pilot study. *EuroIntervention.* 2015;11:555-63.

12. Kajiya T, Liang M, Sharma RK, Lee CH, Chan MY, Tay E, Chan KH, Tan HC, Low AF. Everolimus-eluting bioresorbable vascular scaffold (BVS) implantation in patients with ST-segment elevation myocardial infarction (STEMI). *EuroIntervention.* 2013;9:501-4.

13. Sabaté M, Windecker S, Iñiguez A, Okkels-Jensen L, Cequier A, Brugaletta S, Hofma SH, Räber L, Christiansen EH, Suttorp M, Pilgrim T, Anne van Es G, Sotomi Y, García-García HM, Onuma Y, Serruys PW. Everolimus-eluting bioresorbable stent vs. durable polymer everolimus-eluting metallic stent in patients with ST-segment elevation myocardial infarction: results of the randomized ABSORB ST-segment elevation myocardial infarction-TROFI II trial. *Eur Heart J.* 2016;37:229-40.

14. Kraak RP, Grundeken MJ, de Winter RJ, Wykrzykowska JJ. ABSORB BVS Implantation in Bifurcation Lesions - Current Evidence and Practical Recommendations. *Interventional Cardiology Review.* 2014;9:84-8.

15. Ormiston JA, Webber B, Ubod B, Webster MW, White J. Absorb everolimus-eluting bioresorbable scaffolds in coronary bifurcations: a bench study of deployment, side branch dilatation and post-dilatation strategies. *EuroIntervention.* 2015;10:1169-77.

16. Serruys PW, Chevalier B, Dudek D, Cequier A, Carrié D, Iniguez A, Dominici M, van der Schaaf RJ, Haude M, Wasungu L, Veldhof S, Peng L, Staehr P, Grundeken MJ, Ishibashi Y, Garcia-Garcia HM, Onuma Y. 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; 385:43-54.

17. Kimura T, Kozuma K, Tanabe K, Nakamura S, Yamane M, Muramatsu T, Saito S, Yajima J, Hagiwara N, Mitsudo K, Popma JJ, Serruys PW, Onuma Y, Ying S, Cao S, Staehr P, Cheong WF, Kusano H, Stone GW; 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;36:3332-42.

18. Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, Litt MR, Kini A, Kabour A, Marx SO, Popma JJ, McGreevy R, Zhang Z, Simonton C, Stone GW; ABSORB III Investigators. Everolimus-Eluting Bioresorbable Scaffolds for Coronary Artery Disease. *N Engl J Med.* 2015;373:1905-15.

19. Gao R, Yang Y, Han Y, Huo Y, Chen J, Yu B, Su X, Li L, Kuo HC, Ying SW, Cheong WF, Zhang Y, Su X, Xu B, Popma JJ, Stone GW; ABSORB China Investigators. Bioresorbable Vascular Scaffolds Versus Metallic Stents in Patients With Coronary Artery Disease: ABSORB China Trial. *J Am Coll Cardiol.* 2015;66: 2298-309.

20. Stone GW, Gao R, Kimura T, Kereiakes DJ, Ellis SG, Onuma Y, Cheong WF, Jones-McMeans J, Su X, Zhang Z, Serruys PW. 1-year outcomes with the Absorb bioresorbable scaffold in patients with coronary artery disease: a patient-level, pooled meta-analysis. *Lancet.* 2016;387:1277-89.

21. Robaei D, Back L, Ooi SY, Pitney M, Jepson N. Twelve-Month Outcomes With a Bioresorbable Everolimus-Eluting Scaffold: Results of the ESHC-BVS Registry at Two Australian Centers. *J Invasive Cardiol.* 2016;28:316-22.

22. Costopoulos C, Latib A, Naganuma T, Miyazaki T, Sato K, Figini F, Sticchi A, Carlino M, Chieffo A, Montorfano M, Colombo A. Comparison of early clinical outcomes between ABSORB bioresorbable vascular scaffold and everolimus-eluting stent implantation in a real-world population. *Catheter Cardiovasc Interv.* 2015;85:E10-5.

23. Dudek D, Rzeszutko Ł, Zasada W, Depukat R, Siudak Z, Ochała A, Wojakowski W, Przewłocki T, Żmudka K, Kochman J, Lekston A, Gąsior M. Bioresorbable vascular scaffolds in patients with acute coronary syndromes: the POLAR ACS study. *Pol Arch Med Wewn.* 2014;124:669-77.

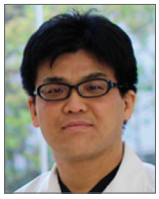
24. Capodanno D, Gori T, Nef H, Latib A, Mehilli J, Lesiak M, Caramanno G, Naber C, Di Mario C, Colombo A, Capranzano P, Wiebe J, Araszkiewicz A, Geraci S, Pyxaras S, Mattesini A, Naganuma T, Münzel T, Tamburino C. Percutaneous coronary intervention with everolimus-eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry. *EuroIntervention.* 2015;10:1144-53.

25. Tamburino C, Capranzano P, Gori T, Latib A, Lesiak M, Nef H, Caramanno G, Naber C, Mehilli J, Di Mario C, Sabaté M, Münzel T, Colombo A, Araszkiewicz A, Wiebe J, Geraci S, Jensen C, Mattesini A, Brugaletta S, Capodanno D. 1-Year Outcomes of Everolimus-Eluting Bioresorbable Scaffolds Versus Everolimus-Eluting Stents: A Propensity-Matched Comparison of the GHOST-EU and XIENCE V USA Registries. *JACC Cardiovasc Interv.* 2016;9:440-9.

26. Puricel S, Cuculi F, Weissner M, Schmermund A, Jamshidi P, Nyffenegger T, Binder H, Eggebrecht H, Münzel T, Cook S, Gori T. Bioresorbable Coronary Scaffold Thrombosis: Multicenter Comprehensive Analysis of Clinical Presentation, Mechanisms, and Predictors. *J Am Coll Cardiol.* 2016;67:921-31.

AsiaIntervention 2016;2:93-100

Long-term (7 to 10 years) clinical outcome after first-generation sirolimus-eluting stent implantation



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KEYWORDS

- coronary artery disease
- sirolimus-eluting stent
- stent thrombosis
- target lesion revascularisation

Abstract

Aims: Late adverse events such as very late stent thrombosis (VLST) or late target lesion revascularisation (TLR) after sirolimus-eluting stent (SES) implantation remain an important concern. However, clinical outcomes beyond five years after SES implantation remain unclear. We sought to assess the very long-term (7-10 years) clinical outcome after SES implantation.

Methods and results: Between April 2004 and March 2008, a total of 985 consecutive patients with 1,307 lesions underwent percutaneous coronary intervention only with SES. Cumulative incidence of TLR within the first year was 11.8%. Late TLR beyond one year continued to occur without attenuation or acceleration up to 10 years (2.6%/year, and cumulative 10-year incidence, 35.2%). Cumulative incidence of definite stent thrombosis was low (30 days, 0.31%; one year, 0.63%; five years, 1.1%; and 10 years, 2.6%), whereas definite VLST also continued to occur without attenuation or acceleration (0.22%/year).

Conclusions: Late adverse events such as VLST and late TLR beyond one year after SES implantation continue to occur up to 10 years without attenuation or acceleration of their annual incidences. Careful clinical follow-up is mandatory in patients who have already been treated with SES.

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Abbreviations

ARC	Academic Research Consortium
CABG	coronary artery bypass graft
CREDO-Kyoto	Coronary Revascularisation Demonstrating Outcome study in Kyoto
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
eGFR	estimated glomerular filtration rate
ISA	incomplete stent apposition
IVUS	intravascular ultrasound
LST	late stent thrombosis
MI	myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
PSS	persistent contrast staining
SES	sirolimus-eluting stent
SF	stent fracture
ST	stent thrombosis
TLR	target lesion revascularisation
VLST	very late stent thrombosis

Introduction

The sirolimus-eluting stent (SES) was the most widely used first-generation drug-eluting stent (DES) and dramatically reduced the rate of in-stent restenosis and subsequent target lesion revascularisation (TLR) compared with bare metal stents (BMS)[1]. Pivotal randomised clinical trials have demonstrated that the efficacy of SES was sustained without any significant increase of stent thrombosis (ST) up to four to five years after implantation[2,3]. However, in real-world clinical practice, late adverse events such as very late ST (VLST) and late TLR beyond one year have emerged as unsolved issues after SES implantation[4-8]. The j-Cypher Registry demonstrated that VLST and late TLR beyond one year continued to occur without attenuation up to five years after SES implantation (0.26%/year and 2.2%/year, respectively)[8]. Furthermore, the CREDO-Kyoto (Coronary Revascularisation Demonstrating Outcome study in Kyoto) percutaneous coronary intervention (PCI)/coronary artery bypass graft (CABG) registry cohort-2 also reported that VLST and late TLR beyond one year after SES implantation occurred constantly and without attenuation up to seven years (0.24%/year and 2.0%/year, respectively)[9]. Although these findings suggested that late adverse events such as VLST and late TLR beyond one year are a continuous hazard, lasting at least up to seven years after SES implantation, there is a paucity of reports evaluating clinical outcomes beyond seven years after SES implantation. Therefore, we sought to assess very long-term (7 to 10 years) clinical outcomes of SES in the present single-centre study.

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Methods

PATIENT POPULATION AND PROCEDURAL PROTOCOL

From April 2004 to March 2008, a total of 4,603 consecutive patients with 5,514 lesions underwent percutaneous coronary intervention with stent implantation in Kokura Memorial Hospital, Kitakyushu, Japan. Of these, 985 consecutive patients (1,307 lesions) treated only with SES (CYPHER®; Cordis, Johnson & Johnson, Warren, NJ, USA) were enrolled in the present study **(Figure 1)**. All interventions were performed using standard techniques. Predilatation, post-dilatation, and the use of intravascular ultrasound (IVUS) were left to the operator's discretion. After the procedure, all patients were advised to continue aspirin (81-162 mg daily) for life unless contraindicated. Either ticlopidine (200 mg daily) or clopidogrel (75 mg daily) was also prescribed for at least three months after stent implantation. A routine follow-up angiography six to 12 months after SES implantation was recommended to the patients regardless of clinical symptoms. All patients gave written informed consent for the procedure and the follow-up protocol, which was approved by the ethics committee of Kokura Memorial Hospital.

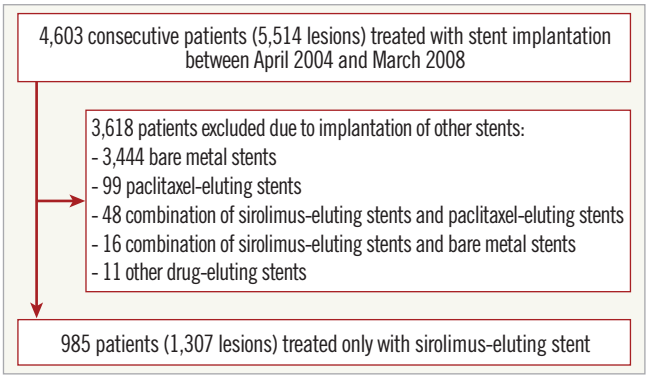


Figure 1. *Study flow chart.*

STUDY ENDPOINTS AND DEFINITIONS

The major study endpoints included VLST, late TLR beyond one year, and clinically driven late TLR beyond one year. All-cause death, cardiac death, non-cardiac death, myocardial infarction (MI), stroke, CABG, and any coronary revascularisation were also assessed as endpoints. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. MI was defined according to the Academic Research Consortium (ARC) definition[10]. TLR was defined as either PCI or CABG resulting from restenosis or thrombosis of the SES-treated target lesion that included the proximal and distal edge to the stent (within 5 mm) and the ostium of side branches[8]. Clinically driven TLR was defined as TLR performed because of ischaemic symptoms, electrocardiographic changes at rest or positive stress test results[8]. Clinically driven TLR on a patient basis was censored when non-clinically driven TLR was performed in all the target lesions. The timing and diagnostic certainty of ST were assessed according to the ARC definition[10]. Stroke during the follow-up was defined as ischaemic or haemorrhagic stroke requiring hospitalisation with symptoms lasting >24 hours.

CLINICAL FOLLOW-UP

Clinical follow-up data were obtained either from a review of the hospital records or by telephone contacts with the patients, relatives,

or referring physicians. Patients who were lost to follow-up were censored on the last day with follow-up information. Follow-up intervals were calculated from the day of the index procedure.

STATISTICAL ANALYSIS

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean±SD or median (interquartile range). Cumulative incidences were estimated by the Kaplan-Meier method. To evaluate the late events beyond one year, we used landmark analysis at one year. Those patients with individual endpoint events before one year were excluded in the landmark analysis. A Cox proportional hazards model was used to identify independent risk factors of TLR (within the first year and beyond one year). We used the 23 variables listed in **Table 1** as potential independent variables **(Online Table 1)**. The continuous variables were dichotomised by clinically meaningful reference values. To determine the independent risk factors, we first selected variables with p-values <0.10 in the univariate Cox models. We then included them simultaneously in the multivariable models and obtained the adjusted hazard ratios and their 95% confidence intervals. To evaluate the risk factors for TLR beyond one year, we included only those patients who completed the one-year follow-up without TLR. Statistical analysis was performed with the use of JMP software, version 10.0 (SAS Institute Inc., Cary, NC, USA). A two-sided p-value of <0.05 was considered statistically significant.

Results

BASELINE CHARACTERISTICS

The current study population included predominantly patients with stable coronary artery disease. However, the great majority of patients had high-risk features such as advanced age, diabetes mellitus, prior PCI, prior MI, and multivessel disease **(Table 1)**. Also, the great majority of patients had AHA/ACC type B2/C lesions with complex lesion characteristics such as bifurcation, in-stent restenosis, severe calcification, and chronic total occlusion **(Table 2)**. The prevalence of post-dilatation after SES implantation was low, and intravascular ultrasound was used infrequently **(Table 2)**. The prescription rates of the evidence-based medications such as statins and beta-blockers were low at the time of hospital discharge **(Table 1)**. Median follow-up duration of survivors was 8.6 (first and third quartiles [Q1-Q3]: 7.6-9.4; and range: 0-11.0) years. Ten-year clinical follow-up was completed in 138 patients (90.2%) among 153 patients eligible for 10-year follow-up.

Table 1. Patient characteristics.

Characteristics		
Number of patients		985
Age (years)		68.7±9.6
>80 years		103 (10.5%)
Male		756 (76.8%)
Hypertension		756 (76.8%)
Diabetes mellitus		479 (48.6%)
Insulin-treated		83 (8.4%)
Dyslipidaemia		534 (54.2%)
Chronic kidney disease	eGFR <30 ml/min/1.73 m^2 without haemodialysis	48 (4.9%)
	Haemodialysis	61 (6.2%)
Current smoker		151 (15.3%)
Multivessel disease		350 (35.5%)
Target lesion involving chronic total occlusion		116 (11.8%)
Target lesion involving in-stent restenosis		331 (33.6%)
Target lesion involving bifurcation treated with two stents		38 (3.9%)
Target lesion involving ostial right coronary artery		68 (6.9%)
Target lesion involving severe calcification		69 (7.0%)
Total stent length >28 mm		298 (30.3%)
Number of diseased vessels	1	635 (64.5%)
	2	272 (27.6%)
	≥3	78 (7.9%)
Prior myocardial infarction		333 (33.8%)
Prior percutaneous coronary intervention		664 (67.4%)
Prior coronary artery bypass grafting		67 (6.8%)
Prior stroke		77 (7.8%)
Clinical status	Stable coronary artery disease	962 (97.7%)
	Acute coronary syndrome	23 (2.3%)
Left ventricular ejection fraction (%)		61.0 (50.0-68.0)
≤40%		106 (10.8%)
Medications at discharge	Aspirin	985 (100%)
	Thienopyridine	985 (100%)
	Beta-blockers	264 (26.9%)
	ACE-I/ARB	544 (55.2%)
	Statins	512 (52.1%)
	Oral hypoglycaemic agent	317 (32.1%)

Data are presented as mean±SD, median (interquartile range), or number (%). ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker

CLINICAL OUTCOMES

The cumulative 10-year incidence of all-cause death and cardiac death was 30.3% and 8.1%, respectively **(Table 3, Figure 2A)**. Cardiac death constituted 23.9% of all-cause death. The cumulative 10-year incidence of MI was low (annual incidence of 0.6%).

In this cohort, 88.0% of patients underwent angiographic follow-up within one year. The cumulative incidence of TLR within the first year was relatively high (11.8%). Among the 201 patients undergoing TLR within the first year, 74 patients (66.7%) underwent plain old balloon angioplasty, 27 patients (24.3%) another SES implantation, eight patients (7.2%) coronary artery bypass graft, and two patients (1.8%) paclitaxel-eluting stent implantation. Late TLR beyond one year also continued to occur constantly without attenuation or acceleration up to 10 years (2.6%/year) **(Figure 2B, Figure 3)**. Clinically driven TLR within the first year was relatively low (5.2%), but it continued to occur with

Table 2. Lesion and procedural characteristics.

Characteristics		
Number of lesions		1,307
Location of target lesion	LAD	628 (48.1%)
	RCA	385 (29.5%)
	LCX	328 (25.1%)
	LMCA	38 (2.9%)
	SVG	6 (0.5%)
AHA/ACC lesion type	A	34 (2.6%)
	B1	304 (23.2%)
	B2	385 (29.5%)
	C	584 (44.7%)
In-stent restenosis		368 (28.2%)
Severe calcification		89 (6.8%)
Bifurcation		454 (34.7%)
Treated with two stents		53 (4.1%)
Ostial location		93 (7.1%)
Chronic total occlusion		119 (9.1%)
Procedural characteristics		
Number of stents per lesion	1	1,003 (76.8%)
	2	244 (18.7%)
	≥3	60 (4.5%)
Total stent length (mm)		23.0 (18.0-33.0)
Overlapping stent		313 (24.0%)
Post-dilatation		463 (37.3%)
Maximal inflation pressure (atm)		16.5±2.6
IVUS use		217 (16.6%)

Data are presented as mean±SD, median (interquartile range), or number (%). AHA/ACC: American Heart Association/American College of Cardiology; IVUS: intravascular ultrasound; LAD: left anterior descending coronary artery; LCX: left circumflex artery; LMCA: left main coronary artery; RCA: right coronary artery; SVG: saphenous vein graft

a constant rate of 1.6%/year beyond one year **(Figure 2B)**. Non-TLR continued with a similar frequency to TLR with an annual incidence of 2.3% **(Figure 2B)**.

The cumulative incidence of definite ST was also low (30-day, 0.31%; one-year, 0.63%; five-year, 1.1%; and 10-year, 2.6%). VLST continued to occur constantly without attenuation or acceleration up to 10 years after SES implantation (0.22%/year) **(Table 3, Figure 4A, Figure 4B)**. Among 19 ST events up to 10 years, 18 (94.7%) resulted in MI. ST was the cause of MI during follow-up in 39.1% of 46 MI episodes. All patients with early ST and late ST had continued dual antiplatelet therapy (DAPT) at the time of ST, whereas DAPT had been continued in seven (53.8%) of 13 patients with VLST. No patient had discontinued both aspirin and thienopyridine before the onset of ST.

Stent fracture (SF) was observed in 43 (13.3%) of 323 TLR lesions and in four (21.1%) of 19 ST lesions (one LST and three VLST). The incidence of SF as a cause for TLR or ST was higher in the right coronary artery than in other vessels (30 [69.8%] of 43 SF-related TLR lesions; three [75.0%] of four SF-related ST lesions).

Independent risk factors for TLR within one year included such target lesions as the ostial RCA, total stent length >28 mm, in-stent restenosis, age >80 years, bifurcation lesions treated with two stents **(Table 4)**. Independent risk factors for late TLR beyond one year included such target lesions as in-stent restenosis, total stent length >28 mm, estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 without haemodialysis **(Table 4)**.

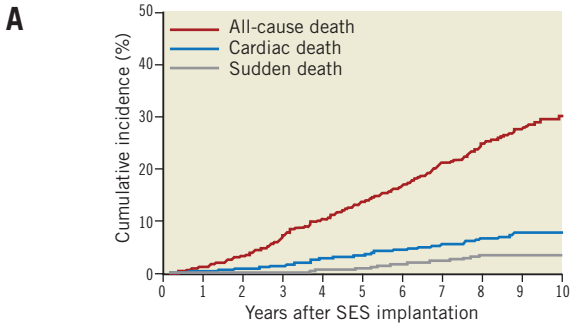
Discussion

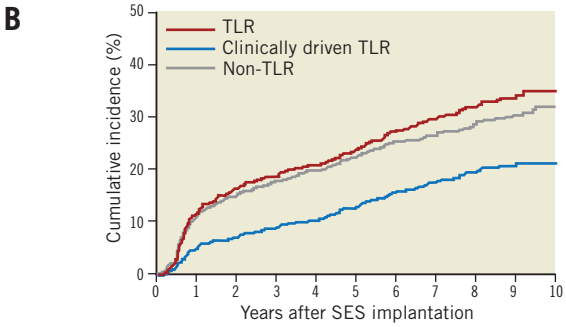
The main finding of the present study is that late adverse events such as VLST and late TLR beyond one year after SES implantation continue to occur up to 10 years without attenuation or acceleration of their annual incidences.

Table 3. Clinical event rates up to 10 years.

		Number of patients with events (Cumulative incidence)			
		30-day	1-year	5-year	10-year
Death	All-cause death	0 (0%)	13 (1.4%)	128 (14.0%)	244 (30.3%)
	Cardiac death	0 (0%)	5 (0.51%)	32 (3.7%)	60 (8.1%)
	Sudden death	0 (0%)	1 (0.11%)	9 (1.1%)	27 (3.7%)
Myocardial infarction		3 (0.31%)	10 (1.2%)	25 (2.9%)	46 (6.5%)
Stent thrombosis	Definite	3 (0.31%)	6 (0.63%)	10 (1.1%)	19 (2.6%)
	Definite/probable	3 (0.31%)	7 (0.73%)	11 (1.2%)	20 (2.7%)
	Definite/probable/possible	3 (0.31%)	7 (0.73%)	22 (2.5%)	46 (6.4%)
Stroke		4 (0.41%)	6 (0.63%)	24 (2.7%)	36 (6.2%)
Target lesion revascularisation		4 (0.41%)	111 (11.8%)	220 (24.2%)	290 (35.2%)
Clinically driven target lesion revascularisation		4 (0.41%)	48 (5.2%)	112 (13.5%)	159 (21.7%)
Non-target lesion revascularisation		5 (0.51%)	107 (11.6%)	207 (23.0%)	259 (32.5%)
Coronary artery bypass grafting		1 (0.10%)	13 (1.5%)	27 (4.3%)	58 (7.4%)
Any coronary revascularisation		8 (0.82%)	217 (23.0%)	381 (41.7%)	475 (57.0%)

Cumulative incidences of events were calculated by the Kaplan-Meier method.



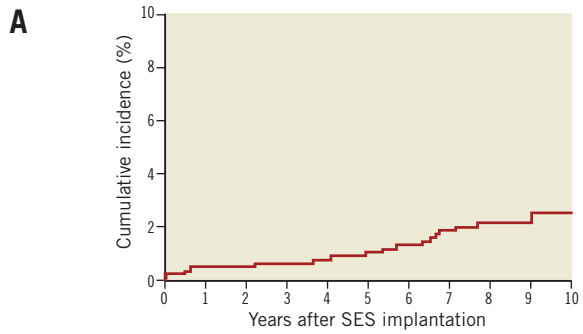


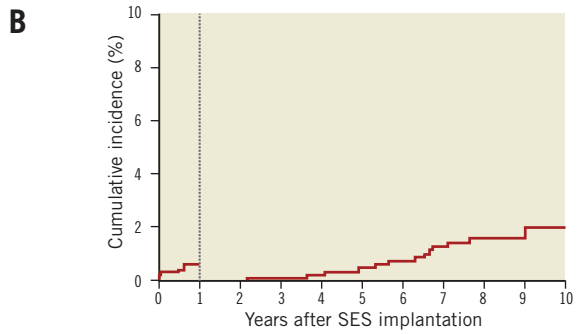
Intervals	0 day	30 days	1 year	5 years	10 years
All-cause death					
No. of patients at risk	985	964	918	775	87
No. of patients with events	0	4	13	128	251
Cumulative incidence	0%	0.41%	1.4%	14.0%	30.3%
Cardiac death					
No. of patients at risk	985	964	915	774	87
No. of patients with events	0	4	5	32	60
Cumulative incidence	0%	0.41%	0.51%	3.7%	8.1%
Sudden death					
No. of patients at risk	985	967	924	780	87
No. of patients with events	0	0	1	9	27
Cumulative incidence	0%	0%	0.11%	1.1%	3.7%

Intervals	0 day	30 days	1 year	5 years	10 years
TLR					
No. of patients at risk	985	964	817	604	53
No. of patients with events	0	4	111	220	290
Cumulative incidence	0%	0.41%	11.8%	24.2%	35.2%
Clinically driven TLR					
No. of patients at risk	985	964	817	605	52
No. of patients with events	0	4	48	112	159
Cumulative incidence	0%	0.41%	5.2%	13.5%	21.7%
Non-TLR					
No. of patients at risk	985	963	813	608	55
No. of patients with events	0	5	107	207	259
Cumulative incidence	0%	0.51%	11.6%	23.0%	32.5%

Figure 2. *Cumulative incidence of clinical events up to 10 years after SES implantation. A) All-cause death, cardiac death and sudden death. B) TLR, clinically driven TLR, and non-TLR. SES: sirolimus-eluting stent; TLR: target lesion revascularisation*

Widespread use of first-generation DES has raised several unresolved, clinically relevant issues. Particular concerns have been the late complications including VLST and late TLR. VLST is a reassuringly rare, but potentially life-threatening complication. Recently, several large-scale DES registries have demonstrated that the annual incidences of VLST were 0.21 to 0.53%/year up to three to five years[3-8]. More recently, Natsuaki et al reported from the CREDO-Kyoto 2 registry that VLST beyond one year after SES implantation occurred constantly and without attenuation up to seven years (0.24%/year)[9]. Although these results suggested that the risk of VLST is sustained without attenuation up to seven years after SES implantation, there are few data evaluating >7 years' follow-up of SES. In the present study, VLST continued to occur without attenuation up to 10 years after SES implantation (0.22%/year). This annual incidence of VLST is consistent with that reported from the j-Cypher Registry and the CREDO-Kyoto 2 registry[8,9]. Considering these findings, VLST remains a concerning problem at least up to 10 years after SES implantation, while it was reassuring that we did not see a signal suggesting acceleration in the occurrence of VLST, although a pathological study

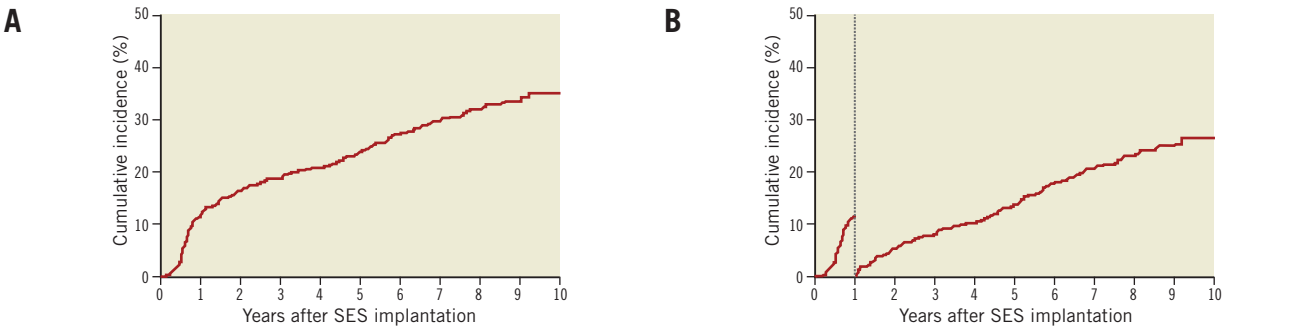




Intervals	0 day	30 days	1 year	5 years	10 years
No. of patients at risk	985	965	918	774	86
No. of patients with events	0	3	6	10	19
Cumulative incidence	0%	0.31%	0.63%	1.1%	2.6%

Intervals	0 day	30 days	1 year	5 years	10 years
No. of patients at risk	985	965	918	774	86
No. of patients with events	0	3	6	4	13
Cumulative incidence	0%	0.31%	0.63%	0.49%	2.0%

Figure 3. *Cumulative incidence of TLR during the entire follow-up period (A), within one year, and between one and 10 years by the one-year landmark analysis (B). SES: sirolimus-eluting stent; TLR: target lesion revascularisation*



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No. of patients with events	0	4	111	109	179
Cumulative incidence	0%	0.4%	11.8%	14.2%	26.7%

Figure 4. *Cumulative incidence of definite stent thrombosis during the entire follow-up period (A), within one year, and between one and 10 years by the one-year landmark analysis (B). SES: sirolimus-eluting stent*

suggested more pronounced neoatherosclerosis formation with longer time intervals after coronary stent implantation[11-13].

In the present study, late TLR beyond one year also continued to occur constantly without attenuation up to 10 years after SES implantation with an annual incidence of 2.6%/year. This annual incidence of late TLR is also consistent with that reported from previous large-scale DES registries[8,9]. Recently, Palhais et al were the first to report a 10-year clinical follow-up of 200 patients with SES implantation, demonstrating that the cumulative 10-year incidence of TLR was 8% and the risk of TLR was maximal at three to six years after SES implantation and decreased thereafter[14]. Compared with the present study, the cumulative incidence of TLR was much lower and the trend was quite different. The current study had a larger study population with a higher-risk patient profile and more complex lesion characteristics, such as a high prevalence of DM, ISR, bifurcation lesion, chronic total occlusion, and long total stent length. After the introduction of SES in real-world clinical practice, SES were widely used in high-risk patients as shown in the current study, which might have led to the sustained occurrence of late TLR.

The underlying mechanisms for the continuous occurrence of late adverse events after SES implantation have not been fully understood. Previous studies have demonstrated that inflammatory reaction, hypersensitivity, endothelial dysfunction, and

Table 4. Univariate and multivariable Cox models for target lesion revascularisation.

Variables	Present events/ patients, n (%)	Absent events/ patients, n (%)	Univariate		Multivariable	
			HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
TLR within 1 year						
Target lesion involving ostial RCA	22/68 (35.0)	88/917 (10.0)	3.92 (2.40-6.13)	<0.001	3.60 (2.17-5.75)	<0.001
Total stent length >28 mm	48/298 (16.8)	62/687 (9.5)	1.81 (1.24-2.64)	0.002	1.84 (1.24-2.72)	0.003
Target of ISR	50/331 (15.9)	60/654 (9.6)	1.73 (1.19-2.52)	0.005	1.72 (1.17-2.52)	0.006
Age ≥80 years	5/103 (5.2)	105/882 (12.4)	0.41 (0.14-0.90)	0.02	0.38 (0.13-0.85)	0.02
Target of a bifurcation lesion treated with two stents	10/38 (26.3)	100/947 (11.1)	2.58 (1.26-4.69)	0.01	2.43 (1.17-2.52)	0.02
Haemodialysis	14/61 (25.8)	96/924 (10.8)	2.73 (1.49-4.62)	0.002	1.92 (0.99-3.49)	0.054
Insulin use	16/83 (19.7)	94/902 (10.9)	1.90 (1.08-3.13)	0.03	1.74 (0.97-2.91)	0.06
Target lesion involving severe calcification	13/69 (21.4)	97/916 (11.0)	2.10 (1.12-3.61)	0.02	1.40 (0.72-2.55)	0.31
TLR beyond 1 year						
Target lesion involving ISR	70/257 (34.0)	108/560 (22.9)	1.44 (1.06-1.94)	0.02	1.43 (1.05-1.93)	0.02
Total stent length >28 mm	59/234 (29.6)	119/583 (25.1)	1.35 (0.98-1.83)	0.07	1.41 (1.02-1.92)	0.036
eGFR <30 ml/min/1.73 m^2 without haemodialysis	10/33 (48.0)	167/783 (25.7)	2.09 (1.03-3.76)	0.04	2.06 (1.01-3.71)	0.046
Target lesion involving ostial RCA	13/40 (46.2)	165/777 (25.3)	1.83 (0.99-3.09)	0.056	1.71 (0.92-2.89)	0.09
Prior stroke	18/62 (36.3)	160/755 (25.7)	1.62 (0.96-2.57)	0.07	1.48 (0.87-2.35)	0.14

Only variables with univariate $p<0.10$ are shown. Incidences of events were calculated by the Kaplan-Meier method. CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ISR: in-stent restenosis; RCA: right coronary artery.

neoatherosclerosis could be suggested as the causes of VLST as well as late TLR beyond one year[15-19]. Recently, an OCT analysis in 50 patients with ISR after DES implantation demonstrated that 52% of lesions had at least one thin-cap fibroatheroma containing neointima, 58% had in-stent neointimal rupture, and 58% showed intraluminal thrombi[20]. More recently, Kang et al reported that, using OCT, VLST was associated with in-stent neointimal rupture in 63% of DES-treated lesions[21]. Furthermore, stent fracture (SF) is also one of the risk factors for ST and TLR after DES implantation and may be likely to occur due to increased metallic fatigue over time[22,23]. Indeed, Ohya et al reported that SF after SES implantation was consistently associated with higher rates of VLST and TLR during eight-year follow-up[24]. In the present study, SF was observed in a significant proportion of lesions with TLR and/or ST. Furthermore, persistent contrast staining (PSS), which might be related to inflammation and remodelling of the stented vessel, was reported to be a potent risk factor for VLST of SES[25]. These findings support the belief that neoatherosclerosis, SF and PSS are the causes of late adverse events in some SES-treated patients. Long-term DAPT after SES implantation might be necessary in some selected patients with potent angiographic risk factors of VLST such as SF and/or PSS.

The current study showed that late adverse events such as VLST and late TLR beyond one year after SES implantation continue to occur up to 10 years without attenuation or acceleration of their annual incidences. These findings indicate that there may be no end in sight for the late adverse events after SES implantation. Therefore, further careful follow-up is mandatory to assess the very long-term outcomes of patients who have already received SES implantation. Although the mechanisms for late adverse events after SES implantation are multifactorial, the most significant contributing factor might be different according to the timing and type of late adverse events. Indeed, the j-Cypher Registry suggested that the risk factors of late TLR are similar to those of early TLR, whereas the predictors for VLST are quite different from those for early ST and LST[8]. Although the current study could not provide the predictors for VLST, target lesions involving in-stent restenosis, total stent length, and eGFR <30 ml/min/1.73 m^2 without haemodialysis were independent predictors for late TLR beyond one year. Therefore, more careful follow-up may be required in those patients.

Limitations

There are several limitations in the present study. First, this study was a retrospective, single-centre study that did not include a control group. Therefore, we could not assess whether the very long-term outcomes of SES are different from those of BMS and/or second-generation DES based on the results of the current study. Second, the present study included a very small number of patients with acute coronary syndrome. Third, the overall incidence and clinical impact of SF and PSS, which are reported to be strong risk factors for ST after SES implantation, were not assessed in the present study[24,25]. Fourth, we did not have information on bleeding complications and antiplatelet therapy during the follow-up. Finally, first-generation SES are no longer used in current practice. However, many millions of patients have already undergone first-generation SES implantation. Therefore, it is important to continue evaluating the very long-term clinical outcomes of patients receiving first-generation SES implantation to improve the care of these patients.

Impact on daily practice

Late adverse events such as VLST and late TLR beyond one year after SES implantation continue to occur up to 10 years without attenuation or acceleration of their annual incidences. Careful clinical follow-up is mandatory in patients who have already been treated with SES.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnàr F, Falotico R; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomised comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-80.

2. Morice MC, Serruys PW, Barragan P, Bode C, Van Es GA, Stoll HP, Snead D, Mauri L, Cutlip DE, Sousa E. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. *J Am Coll Cardiol.* 2007;50:1299-304.

3. Weisz G, Leon MB, Holmes DR Jr, Kereiakes DJ, Popma JJ, Teirstein PS, Cohen SA, Wang H, Cutlip DE, Moses JW. Five-year follow-up after sirolimus-eluting stent implantation results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) Trial. *J Am Coll Cardiol.* 2009;53:1488-97.

4. de la Torre-Hernandez JM, Alfonso F, Hernandez F, Elizaga J, Sanmartin M, Pinar E, Lozano I, Vazquez JM, Botas J, Perez de Prado A, Hernandez JM, Sanchis J, Nodar JM, Gomez-Jaume A, Larman M, Diarte JA, Rodriguez-Collado J, Rumoroso JR, Lopez-Minguez JR, Mauri J; ESTROFA Study Group. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio ESpanol sobre TROmbosis de stents FArmacoactivos). *J Am Coll Cardiol.* 2008;51:986-90.

5. Wenaweser P, Daemen J, Zwahlen M, van Domburg R, Jüni P, Vaina S, Hellige G, Tsuchida K, Morger C, Boersma E, Kukreja N, Meier B, Serruys PW, Windecker S. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. *J Am Coll Cardiol.* 2008;52:1134-40.

6. Lagerqvist B, Carlsson J, Frobert O, Lindback J, Schersten F, Stenestrand U, James SK; Swedish Coronary Angiography and Angioplasty Registry Study Group. Stent thrombosis in Sweden: a report from the Swedish Coronary Angiography and Angioplasty Registry. *Circ Cardiovasc Interv.* 2009;2:401-8.

7. Costa JR Jr, Sousa A, Moreira AC, Costa RA, Cano M, Maldonado G, Campos C, Carballo M, Pavanello R, Sousa JE. Incidence and predictors of very late (>or=4 years) major cardiac adverse events in the DESIRE (Drug-Eluting Stents in the Real World)-LATE registry. *JACC Cardiovasc Interv.* 2010;3:12-8.

8. Kimura T, Morimoto T, Nakagawa Y, Kawai K, Miyazaki S, Muramatsu T, Shiode N, Namura M, Sone T, Oshima S, Nishikawa H, Hiasa Y, Hayashi Y, Nobuyoshi M, Mitudo K; j-Cypher Registry Investigators. Very late stent thrombosis and late target lesion revascularization after sirolimus- eluting stent implantation: five-year outcome of the j-Cypher Registry. *Circulation.* 2012;125:584-91.

9. Natsuaki M, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Yamaji K, Ando K, Shizuta S, Shiomi H, Tada T, Tazaki J, Kato Y, Hayano M, Abe M, Tamura T, Shirotani M, Miki S, Matsuda M, Takahashi M, Ishii K, Tanaka M, Aoyama T, Doi O, Hattori R, Kato M, Suwa S, Takizawa A, Takatsu Y, Shinoda E, Eizawa H, Takeda T, Lee JD, Inoko M, Ogawa H, Hamasaki S, Horie M, Nohara R, Kambara H, Fujiwara H, Mitsudo K, Nobuyoshi M, Kita T, Kimura T; CREDO-Kyoto PCI/CABG registry cohort-2 investigators. Late adverse events after implantation of sirolimus-eluting stent and bare-metal stent: long-term (5-7 years) follow-up of the Coronary Revascularization Demonstrating Outcome study-Kyoto registry Cohort-2. *Circ Cardiovasc Interv.* 2014;7:168-79.

10. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

11. Nakazawa G, Vorpahl M, Finn AV, Narula J, Virmani R. One step forward and two steps back with drug-eluting-stents: from preventing restenosis to causing late thrombosis and nouveau atherosclerosis. *JACC Cardiovasc Imaging.* 2009;2:625-8.

12. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J Am Coll Cardiol.* 2011;57:1314-22.

13. Otsuka F, Vorpahl M, Nakano M, Foerst J, Newell JB, Sakakura K, Kutys R, Ladich E, Finn AV, Kolodgie FD, Virmani R. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation.* 2014;129:211-23.

14. Palhais N, Arroyo D, Lehmann S, Togni M, Kaufmann U, Puricel SG, Stauffer JC, Goy JJ, Cook S. Ten-year clinical follow-up after sirolimus-eluting stent implantation. *Am Heart J.* 2014;167:893-9.

15. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.

16. Nakazawa G, Finn AV, Vorpahl M, Ladich ER, Kolodgie FD, Virmani R. Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. *J Am Coll Cardiol.* 2011;57:390-8.

17. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation.* 2007;115:2435-41.

18. Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, Togni M, Wenaweser P, Billinger M, Seiler C, Gay S, Meier B, Pichler WJ, Jüni P, Virmani R, Windecker S. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation.* 2009;120:391-9.

19. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation.* 2004;109:701-5.

20. Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, Lee SW, Kim YH, Whan Lee C, Park SW, Park SJ. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation.* 2011;123:2954-63.

21. Kang SJ, Lee CW, Song H, Ahn JM, Kim WJ, Lee JY, Park DW, Lee SW, Kim YH, Mintz GS, Park SW, Park SJ. OCT analysis in patients with very late stent thrombosis. *JACC Cardiovasc Imaging.* 2013;6:695-703.

22. Chakravarty T, White AJ, Buch M, Naik H, Doctor N, Schapira J, Kar S, Forrester JS, Weiss RE, Makkar R. Meta-analysis of incidence, clinical characteristics and implications of stent fracture. *Am J Cardiol.* 2010;106:1075-80.

23. Kuramitsu S, Iwabuchi M, Haraguchi T, Domei T, Nagae A, Hyodo M, Yamaji K, Soga Y, Arita T, Shirai S, Kondo K, Ando K, Sakai K, Goya M, Takabatake Y, Sonoda S, Yokoi H, Toyota F, Nosaka H, Nobuyoshi M. Incidence and clinical impact of stent fracture after everolimus-eluting stent implantation. *Circ Cardiovasc Interv.* 2012;5:663-71.

24. Ohya M, Kadota K, Tada T, Habara S, Shimada T, Amano H, Izawa Y, Hyodo Y, Miyake K, Otsuru S, Hasegawa D, Tanaka H, Maruo T, Katoh H, Fuku Y, Goto T, Mitsudo K. Stent Fracture After Sirolimus-Eluting Stent Implantation: 8-Year Clinical Outcomes. *Circ Cardiovasc Interv.* 2015;8:e002664.

25. Imai M, Kadota K, Goto T, Fujii S, Yamamoto H, Fuku Y, Hosogi S, Hirono A, Tanaka H, Tada T, Morimoto T, Shiomi H, Kozuma K, Inoue K, Suzuki N, Kimura T, Mitsudo K. Incidence, risk factors, and clinical sequelae of angiographic peri-stent contrast staining after sirolimus-eluting stent implantation. *Circulation.* 2011;123:2382-91.

Supplementary data

Online Table 1. Univariate Cox model for target lesion revascularisation.

This paper also includes supplementary data published online at: www.asiaintervention.org

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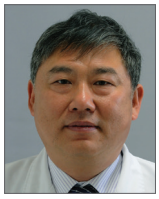
Three-year outcomes from an all-comers Chinese population treated with the Resolute zotarolimus-eluting stent: RESOLUTE China Registry



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KEYWORDS

- drug-eluting stent
- percutaneous coronary intervention
- Resolute zotarolimus-eluting stent

Abstract

Aims: The Resolute™ zotarolimus-eluting stent (ZES) has been associated with excellent and sustained safety and efficacy in real-world populations undergoing percutaneous coronary intervention (PCI). However, limited real-world clinical outcome data beyond one year are available in an Asian population. The aim of this article is to report the three-year outcomes of the RESOLUTE China Registry.

Methods and results: The RESOLUTE China Registry is a prospective, observational registry conducted among patients with symptomatic coronary artery disease at 30 sites in China with minimal exclusion criteria. Among 1,800 patients enrolled, mean age was 61±11 years, 29% had a history of diabetes and 68% underwent PCI of long lesions (≥18 mm), 43% of small vessels (≤2.75 mm), and 7% of chronic total occlusions. Total stent length was 42.2±28.3 mm per patient. At three years, target lesion failure was 6.3%, with a 2.4% incidence of clinically driven target lesion revascularisation, 4.4% incidence of cardiac death or target vessel myocardial infarction, and 0.8% definite or probable stent thrombosis. Clinical outcomes were favourable across complex subsets, including patients with diabetes, chronic total occlusion, and small vessel treatment.

Conclusions: In the largest study of Asian patients treated with the Resolute ZES, the incidence of adverse cardiac events was low and sustained at three years, highlighting the continued safety and efficacy of the Resolute ZES in a real-world Chinese population.

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Introduction

The Resolute™ zotarolimus-eluting stent (ZES) (Medtronic, Minneapolis, MN, USA) has been associated with excellent and sustained safety and efficacy in real-world populations undergoing percutaneous coronary intervention (PCI). In the RESOLUTE All-Comers trial of Resolute ZES (N=1,140) vs. XIENCE V™ everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, CA, USA; N=1,152), conducted in an all-comers population across Europe, target vessel failure (a composite of cardiac death, myocardial infarction [MI] not clearly attributable to a non-target vessel, and clinically indicated target vessel revascularisation) at five years was 20% with Resolute ZES (and no different from XIENCE V EES, 19%, p=0.60)[1]. Moreover, given the excellent safety and efficacy of current-generation drug-eluting stents, the stents are used to treat an increasingly complex patient population, including those with small vessels, bifurcation lesions, and chronic total occlusions. However, limited long-term real-world clinical outcome data are available in an Asian population, in particular among complex subsets. In contrast to the United States and Europe where mortality due to coronary artery disease is declining, mortality due to coronary artery disease is increasing in China[2]. Additionally, Asian patients are more likely to require re-admission to treat clinical restenosis as compared with white Europeans[3].

The RESOLUTE China Registry is a large trial of Chinese patients implanted with the Resolute ZES in an all-comers population, providing a large sample size across complex subsets. Outcomes at one year have been previously reported[4]. In this manuscript we report the three-year outcomes.

Methods

The design of and primary outcomes in the RESOLUTE China Registry have been previously reported[4]. Briefly, the RESOLUTE China Registry is a prospective, multicentre, observational study in an all-comers Chinese population. Limited inclusion/exclusion criteria were used. Subjects who were aged 18 years or older and eligible for elective implantation with Resolute ZES in at least one target lesion were included. Patient follow-up was planned at 30 days, six months, and annually up to five years.

The study conformed to the Declaration of Helsinki, and the protocol was approved by independent ethics committees for all sites. All patients provided written informed consent before enrolment and prior to the PCI procedure. The study design and oversight were directed by a steering committee comprising study investigators and a representative from the sponsor. Outcomes were adjudicated by an independent clinical events committee (CEC) composed of cardiologists who were not study participants. Safety oversight was provided by a data safety monitoring board.

Site monitoring (R&G Pharma Studies Co. Ltd., Shanghai, China) was conducted at all sites to verify 100% of informed consent forms and source data from at least 50% of patients. Additionally, all serious adverse events were source verified and also sent for CEC adjudication. The one-year report of the RESOLUTE China Registry showed no differences in outcomes between subjects who were monitored and those who were not[4]. Additional monitoring was conducted based on CEC-adjudicated events.

STATISTICAL ANALYSIS

The primary endpoint was one-year target lesion failure (TLF), defined as a composite of cardiac death, target vessel MI (Q-wave and non-Q-wave) or clinically driven target lesion revascularisation (TLR) by percutaneous or surgical methods. Major adverse cardiac events (MACE) were defined as the composite of all death, MI, emergent coronary artery bypass graft, or clinically driven TLR. Deaths were considered cardiac unless an unequivocal non-cardiac cause could be established. All MI, including target vessel MI, were adjudicated according to the extended historical definition[5].

The following pre-specified subset analyses are included: treatment of long lesions (≥18 mm length), small vessels (≤2.75 mm diameter), multiple vessels, and chronic total occlusion, as well as treatment in patients with a history of diabetes mellitus.

All analyses were conducted based on the intention to treat, and no data imputation for missing values was performed. Continuous variables are presented as mean±standard deviation and nominal variables as percentages. The incidence of clinical events was calculated using the Kaplan-Meier method. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS software, version 9.1 or later (SAS Institute, Cary, NC, USA).

Results

Between 23 December 2010 and 6 March 2012, a total of 1,800 subjects were enrolled at 30 sites across China. Follow-up was available on 1,701 patients (95%) at three years. **Table 1** shows baseline patient and lesion characteristics, as reported previously. Mean age was 61±11 years, 29% had a history of diabetes, 68% had acute coronary syndrome, 43% were treated for small vessels (≤2.75 mm), 68% for long lesions (≥18 mm), 28% of patients underwent multivessel treatment, 15% were treated for bifurcation lesions, and 7% for chronic total occlusions.

Total stent length was 42.2±28.3 mm per patient and 1.8±1.1 stents were implanted per patient. Predilatation was used in 82.8% of lesions. There was no post-procedure Thrombolysis In Myocardial Infarction (TIMI) grade 0 or 1, 0.3% grade 2 and 99.7% grade 3. Percent diameter stenosis was 0.3±2.4, based on operator estimate.

The three-year incidence of adverse cardiac events is shown in **Table 2** and **Figure 1**. At two years, TLF was 5.5% (96) and comprised 2.2% (39) clinically driven TLR and 3.7% (65) cardiac death or target vessel MI; between two and three years, there were two (0.1%) clinically driven TLRs and 10 (0.6%) cardiac deaths or target vessel MIs. Definite and probable stent thrombosis was low up to three years **(Table 2)**.

Table 1. Baseline patient and lesion characteristics.

		RESOLUTE China Registry (N=1,800 subjects; 2,321 lesions)
Patient characteristics		
Age, years		61±11
Men,%		76 (1,361)
Current smoker,%		36 (645)
Diabetes mellitus,%		29 (645)
Hyperlipidemia,%		41 (733)
Hypertension,%		64 (1,150)
Prior myocardial infarction,%		36 (638)
Reason for revascularisation,%	Unstable angina	59 (1,045)
	Acute myocardial infarction	31 (560)
	Stable angina	8 (134)
	Silent angina	3 (45)
Complex patients,%*		61 (1,102)
Lesion characteristics		
Vessel location (per lesion),%	Left anterior descending	51 (1,194)
	Left circumflex	19 (432)
	Right coronary artery	28 (642)
	Left main	2 (40)
	Saphenous vein graft or internal mammary artery	0.6 (13)
Lesion length, mm		24.9±13.7 (n=2,263)
Pre-procedure reference vessel diameter, mm		3.0±0.5
Pre-procedure TIMI,%	0	14.0
	1	4.1
	2	13.6
	3	68.3
Pre-procedure diameter stenosis,%		86.0±13.3 (2,321)
Long lesion (≥18 mm length), %		68 (1,230)
Small vessels (≤2.75 mm diameter), %		43 (769)
AHA/ACC Class B2/C lesion,%		68 (1,571)
Chronic total occlusion,%		7 (167)
Bifurcation lesion,%		15 (345)
Number of lesions treated per subject		1.4±0.7
Number of stents per subject		1.8±1.1
Total stent length per lesion, mm		29.5±15.4
Total stent length per subject, mm		42.2±28.3

Results presented as mean±standard deviation or % (n). *Subjects are considered "complex" if they have at least one of the following characteristics: total occlusion, bifurcation, saphenous vein graft, in-stent restenosis, acute myocardial infarction (≤72 hours from index procedure), left ventricular ejection fraction <30%, unprotected left main, more than two vessels stented, renal insufficiency or failure (creatinine ≥140 µmol/L), lesion length >27 mm, more than one lesion per vessel, or pre-procedure thrombus. AHA/ACC: American Heart Association/American College of Cardiology.

Dual antiplatelet use at one, two and three years was 94%, 51%, and 40%, respectively. Academic Research Consortium (ARC) definite or probable stent thrombosis at one year, and between one and three years was 0.5% and 0.3%, respectively.

SUBSET ANALYSES

Figure 2 demonstrates the incidence of adverse cardiac events across several complex subsets. The three-year rate of TLF was 7.4% in subjects with long lesions (≥18 mm length, total stent length 50±29 mm per subject), 8.4% in small vessels (≤2.75 mm diameter), 10.5% in multivessel treatment, 9.0% in subjects with diabetes mellitus, 11.1% in subjects treated at a bifurcation lesion, and 8.7% in subjects treated for chronic total occlusion (lesion length 31±18 mm).

Discussion

The RESOLUTE China Registry is the largest study of Asian patients (1,800 patients) treated with second-generation Resolute ZES in real-world clinical practice, allowing a robust evaluation of clinical outcomes across a broad spectrum of patients. Despite this complex patient population, the three-year incidence of all major adverse clinical events remained low. Between two and three years, only two subjects underwent TLR and, at three years, the incidence of TLF was 6.3% (due to 2.4% clinically driven TLR and 4.4% cardiac death or target vessel MI), and the incidence of ARC definite or probable stent thrombosis was 0.8%. These results highlight the long-term safety and efficacy of this second-generation drug-eluting stent in a large, real-world Chinese population.

The outcomes in the RESOLUTE China Registry are similar to those observed in studies of EES in a Chinese population. In PLATINUM China, TLR at one year was 2.2% with the PROMUS Element™ EES (Boston Scientific, Marlborough, MA, USA) (N=373)[6], similar to that observed with Resolute ZES in the RESOLUTE China Registry at one year (1.3%). Long-term outcomes in PLATINUM China are not available.

The RESOLUTE China Registry is unique in providing a large study population of all-comer subjects to analyse complex subsets in a Chinese population. In subjects with diabetes mellitus, clinically driven TLR and TLF were 2.9% and 9.0% at three years, respectively. TLF is similar to that observed in a meta-analysis from the SPIRIT Clinical Trial Program among subjects with diabetes mellitus treated with EES (11.7% TLF at three years)[7]. Additionally, in the RESOLUTE China Registry, 150 subjects were treated for chronic total occlusion with an average lesion length of 31±18 mm. Among these subjects, TLF at three years was 8.7%, which is similar to that reported at three years in subjects treated with the Resolute ZES for chronic total occlusion in both TWENTE (13.6% in a pooled analysis of Resolute ZES and XIENCE V EES)[8] and a pooled analysis in RESOLUTE All Comers and RESOLUTE International (9.1% at two years)[9]. Furthermore, in both TWENTE and the pooled analysis, TLF was similar in both subjects treated and not treated for

Table 2. Event rates at 1, 2 and 3 years in the RESOLUTE China Registry.

	1 year % (n) (n=1,774)	95% CI	2 years % (n) (n=1,742)	95% CI	3 years % (n) (n=1,701)	95% CI
Target lesion failure	3.9 (69)	(3.0%, 4.9%)	5.5 (96)	(4.5%, 6.7%)	6.3 (108)	(5.2%, 7.5%)
Target vessel failure	4.3 (76)	(3.4%, 5.3%)	6.0 (105)	(5.0%, 7.3%)	6.9 (118)	(5.8%, 8.3%)
MACE	4.5 (79)	(3.5%, 5.5%)	6.8 (119)	(5.7%, 8.1%)	8.2 (140)	(7.0%, 9.6%)
Cardiac death or target vessel MI	3.0 (53)	(2.3%, 3.9%)	3.7 (65)	(2.9%, 4.7%)	4.4 (75)	(3.5%, 5.5%)
Death	1.2 (22)	(0.8%, 1.9%)	2.8 (48)	(2.0%, 3.6%)	3.9 (67)	(3.1%, 5.0%)
Cardiac death	0.7 (12)	(0.4%, 1.2%)	1.3 (23)	(0.8%, 2.0%)	1.9 (33)	(1.3%, 2.7%)
Target vessel MI	2.3 (41)	(1.7%, 3.1%)	2.6 (45)	(1.9%, 3.4%)	2.8 (47)	(2.0%, 3.7%)
Clinically driven TLR	1.3 (23)	(0.8%, 1.9%)	2.2 (39)	(1.6%, 3.1%)	2.4 (41)	(1.7%, 3.3%)
Clinically driven TVR	1.8 (32)	(1.2%, 2.5%)	2.9 (50)	(2.1%, 3.8%)	3.1 (53)	(2.3%, 4.1%)
Stent thrombosis (ARC) definite/probable	0.5 (8)	(0.2%, 0.9%)	0.6 (11)	(0.3%, 1.1%)	0.8 (13)	(0.4%, 1.3%)
Acute (0-1 day) definite/probable	0.0 (0)	(0.0%, 0.2%)				
Definite	0.0 (0)	(0.0%, 0.2%)				
Probable	0.0 (0)	(0.0%, 0.2%)				
Subacute (2-30 days) definite/probable	0.4 (7)	(0.2%, 0.8%)				
Definite	0.2 (3)	(0.0%, 0.5%)				
Probable	0.3 (5)	(0.1%, 0.7%)				
Early (0-30 days) definite/probable	0.4 (7)	(0.2%, 0.8%)				
Definite	0.2 (3)	(0.0%, 0.5%)				
Probable	0.3 (5)	(0.1%, 0.7%)				
Late (31-360 days) definite/probable	0.1 (1)	(0.0%, 0.3%)				
Definite	0.1 (1)	(0.0%, 0.3%)				
Probable	0.0 (0)	(0.0%, 0.2%)				
Very late (>361 days) definite/probable					0.1 (6)	(0.1%, 0.8%)
Definite					0.0 (1)	(0.0%, 0.3%)
Probable					0.1 (5)	(0.1%, 0.7%)
Significant bleeding complications	1.5 (27)	(1.0%, 2.2%)	1.7 (29)	(1.1%, 2.4%)	1.9 (32)	(1.3%, 2.7%)
Stroke	0.8 (15)	(0.5%, 1.4%)	1.3 (23)	(0.8%, 2.0%)	1.9 (32)	(1.3%, 2.7%)

chronic total occlusion[8,9]. In the EXPERT CTO multicenter trial (Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions), TLF was 9.1%[10] at one year after implantation of XIENCE V EES in 250 subjects with chronic total occlusion.

The advent of drug-eluting stents has increased the use of stenting for more complex lesions, including small vessels[11]; however, historically, late lumen loss was more likely to result in the need for repeat revascularisation in small vessels as compared with large vessels[12]. Among subjects with small vessel treatment (≤2.75 mm reference vessel diameter) in the RESOLUTE China Registry, TLR was low at 3.4% (25/734) at three years, which is similar to the rate observed with EES implantation in small coronary vessels (RVD <2.77 mm) in a pooled analysis of SPIRIT II and III (3.0% [11/366] at one year)[13]. Given concerns about rising mortality due to coronary artery disease in China[2] and high re-admission rates to treat clinical restenosis among Asian patients[3], using drug-eluting stents to reduce the risk of restenosis is of critical importance in China. Treatment of small vessels can be problematic as late lumen loss may be less tolerated in small vessels. The low adverse event rates associated with Resolute ZES in the RESOLUTE China Registry, including among subjects with small vessels, makes Resolute ZES an important option in the treatment of coronary artery disease in China.

Dual antiplatelet use in the RESOLUTE China Registry at one, two, and three years was 94%, 51% and 40%, respectively. This rate is higher than that observed in RESOLUTE All Comers conducted in Europe, in which dual antiplatelet use after implantation with Resolute ZES at one, two, and three years was 84%, 18%, and 13%, respectively[14], suggesting that long-term dual antiplatelet therapy may be prescribed more commonly in Asian populations. Use of dual antiplatelet therapy in RESOLUTE Asia (conducted across Asia) at one and two years was 91% and 94% in the 38 mm cohort and 66% and 78% in the dual vessel cohort, respectively[15]. Despite possible geographical differences in dual antiplatelet usage, ARC definite or probable stent

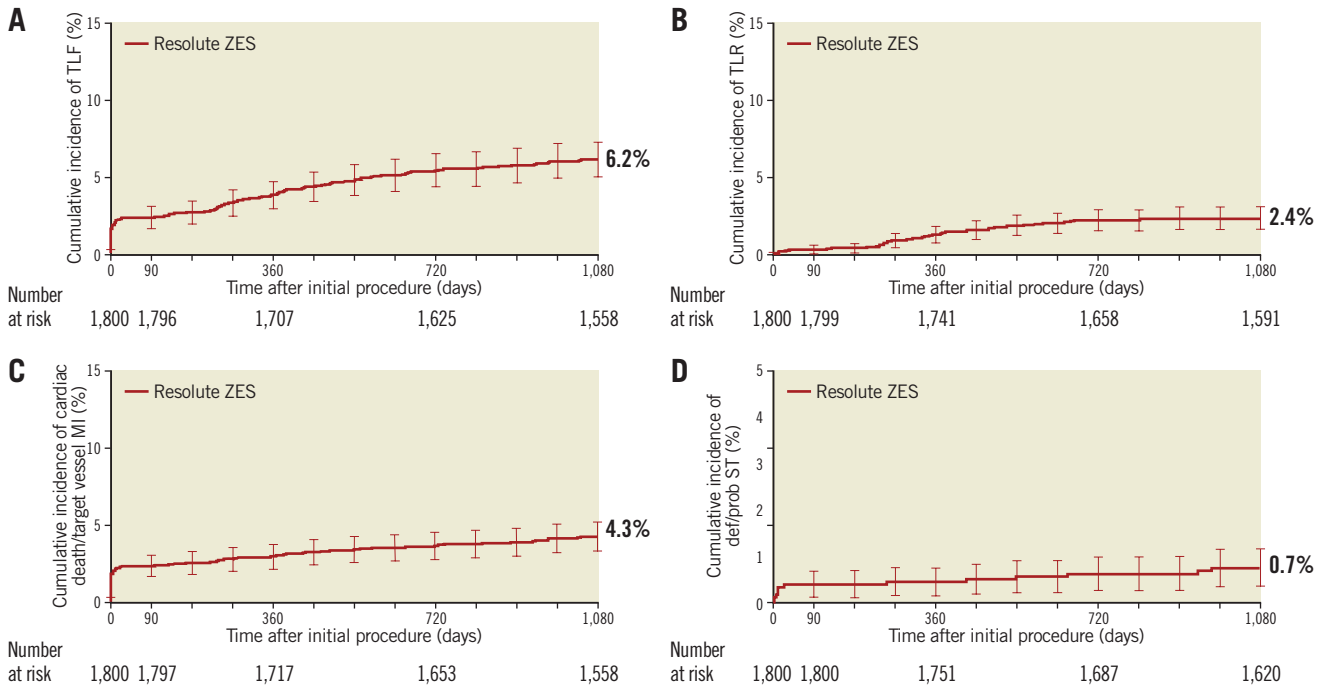

Figure 1. *Three-year cumulative incidence of events. A) Target lesion failure. B) Clinically driven target lesion revascularisation. C) Cardiac death/target vessel myocardial infarction. D) Academic Research Consortium definite or probable stent thrombosis.*

thrombosis remains low across the RESOLUTE Global Clinical Trial Program[1,16-18] including the RESOLUTE China Trial, in which stent thrombosis was 0.5% at one year and 0.3% between one and three years.

Limitations

As a registry, the RESOLUTE China Registry did not include a control group. The registry also did not collect intravascular ultrasound and optical coherence tomography data as these imaging procedures were not in common practice in China at the time this study was initiated. Additionally, clinical monitoring was not 100%; however, a previous analysis at one year found no differences in outcomes between the monitored and unmonitored subjects[4]. Furthermore, while subset analyses were prespecified, a randomised controlled trial comparing subsets would be required to confirm results. Results from this study may be specific to China and therefore may not necessarily be indicative of results in other Asian or Western countries.

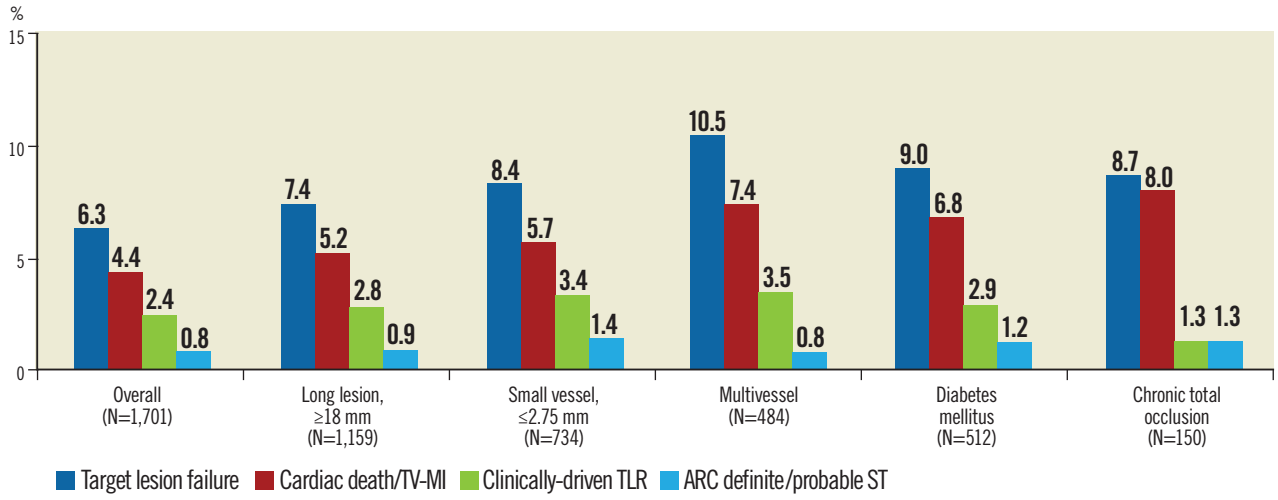

Figure 2. *Three-year events across complex subsets. ARC: Academic Research Consortium; TV-MI: target vessel myocardial infarction; ST: stent thrombosis; TLR: target lesion revascularisation*

Conclusion

The prospective, multicentre RESOLUTE China Registry is the largest study of Asian patients treated with the second-generation Resolute ZES. The incidence of adverse cardiac events remained low and sustained, demonstrating the three-year safety and efficacy of this second-generation DES in a large, real-world, complex patient population.

Impact on daily practice

Given concerns about rising mortality due to coronary artery disease in China and high re-admission rates to treat clinical restenosis among Asian patients, using drug-eluting stents to reduce the risk of restenosis is of critical importance in China. Unfortunately, clinical outcome data beyond one year for Asian populations undergoing percutaneous coronary intervention are limited. This study documented a low incidence of adverse cardiac events at three years among real-world Chinese patients treated with the Resolute zotarolimus-eluting stent, demonstrating the continued safety and efficacy of this stent.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Iqbal J, Serruys PW, Silber S, Kelbaek H, Richardt G, Morel MA, Negoita M, Buszman PE, Windecker S. Comparison of zotarolimus- and everolimus-eluting coronary stents: final 5-year report of the RESOLUTE all-comers trial. *Circ Cardiovasc Interv.* 2015;8:e002230.

2. Jiang G, Wang D, Li W, Pan Y, Zheng W, Zhang H, Sun YV. Coronary heart disease mortality in China: age, gender, and urban-rural gaps during epidemiological transition. *Rev Panam Salud Publica.* 2012;31:317-24.

3. Toor S, Jaumdally R, Lip GY, Pagano D, Dimitri W, Millane T, Varma C. Differences between South Asians and White Europeans in five year outcome following percutaneous coronary intervention. *Int J Clin Pract.* 2011;65:1259-66.

4. Qiao S, Chen L, Chen S, Wang W, Zhu G. One-year outcomes from an all-comers chinese population of patients implanted with the resolute zotarolimus-eluting stent. *Am J Cardiol.* 2014;113:613-20.

5. Vranckx P, Cutlip DE, Mehran R, Kint PP, Silber S, Windecker S, Serruys PW. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. *EuroIntervention.* 2010;5:871-4.

6. Gao R, Han Y, Yang Y, Zhang J, Hou Y, Wang H, Li H, Fang Q, Yu B, Xu B, Allocco DJ, Dawkins KD. PLATINUM China: a prospective, randomized investigation of the platinum chromium everolimus-eluting stent in de novo coronary artery lesions. *Catheter Cardiovasc Interv.* 2015;85 Suppl 1:716-23.

7. Dangas GD, Serruys PW, Kereiakes DJ, Hermiller J, Rizvi A, Newman W, Sudhir K, Smith RS Jr, Cao S, Theodoropoulos K, Cutlip DE, Lansky AJ, Stone GW. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv.* 2013;6:914-22.

8. van Houwelingen KG, Sen H, Lam MK, Tandjung K, Lowik MM, de Man FH, Louwerenburg JH, Stoel MG, Hartmann M, Linssen GC, Doggen CJ, von Birgelen C. Three-year clinical outcome after treatment of chronic total occlusions with second-generation drug-eluting stents in the TWENTE trial. *Catheter Cardiovasc Interv.* 2015;85:E76-82.

9. Kelbaek H, Holmvang L, Richardt G, Eberli FR, Stella P, Buszman PE, Neumann FJ, Serruys PW, Windecker S, Widimský P, Belardi JA, Silber S. Clinical results with the Resolute zotarolimus-eluting stent in total coronary occlusions. *EuroIntervention.* 2015;11:650-7.

10. Kandzari DE, Kini AS, Karmpaliotis D, Moses JW, Tummala PE, Grantham JA, Orr C, Lombardi W, Nicholson WJ, Lembo NJ, Popma JJ, Wang J, Larracas C, Rutledge DR. Safety and Effectiveness of Everolimus-Eluting Stents in Chronic Total Coronary Occlusion Revascularization: Results From the EXPERT CTO Multicenter Trial (Evaluation of the XIENCE Coronary Stent, Performance, and Technique in Chronic Total Occlusions). *JACC Cardiovasc Interv.* 2015;8:761-9.

11. Jabara R, Gradman M, Chen JP, King SB 3rd, Gadesam R, Chronos NA. Clinical and angiographic features of small vessel stenting in the drug-eluting stent era. *Clin Cardiol.* 2009;32:E40-5.

12. Hsieh IC, Chien CC, Chang HJ, Chern MS, Hung KC, Lin FC, Wu D. Acute and long-term outcomes of stenting in coronary vessel >3.0 mm, 3.0-2.5 mm, and <2.5 mm. *Catheter Cardiovasc Interv.* 2001;53:314-22.

13. Bartorelli AL, Serruys PW, Miquel-Hebert K, Yu S, Pierson W, Stone GW; SPIRIT II SPIRIT III Investigators. An everolimus-eluting stent versus a paclitaxel-eluting stent in small vessel coronary artery disease: a pooled analysis from the SPIRIT II and SPIRIT III trials. *Catheter Cardiovasc Interv.* 2010;76:60-6.

14. Taniwaki M, Stefanini GG, Silber S, Richardt G, Vranckx P, Serruys PW, Buszman PE, Kelbaek H, Windecker S; RESOLUTE All-Comers Investigators. 4-year clinical outcomes and predictors of repeat revascularization in patients treated with new-generation

drug-eluting stents: a report from the RESOLUTE All-Comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention). *J Am Coll Cardiol.* 2014;63:1617-25.

15. Zambahari R, Lee M, Hiremath S. Resolute zotarolimus-eluting coronary stent implantation in Asian patients with multivessel disease and long lesions: clinical outcomes in RESOLUTE Asia. *AsiaIntervention.* 2015;1:18-25.

16. Saito S, Maehara A, Vlachojannis GJ, Parise H, Mehran R; RESOLUTE Japan Investigators. Clinical and angiographic evaluation of the resolute zotarolimus-eluting coronary stent in Japanese patients – long-term outcome in the RESOLUTE Japan and RESOLUTE Japan small vessel study. *Circ J.* 2015;79:96-103.

17. Neumann FJ, Widimsky P, Belardi JA. One-year outcomes of patients with the zotarolimus-eluting coronary stent: RESOLUTE International Registry. *EuroIntervention.* 2012;7:1181-8.

18. Yeung AC, Leon MB, Jain A, Tolleson TR, Spriggs DJ, Mc Laurin BT, Popma JJ, Fitzgerald PJ, Cutlip DE, Massaro JM, Mauri L; RESOLUTE US Investigators. Clinical evaluation of the Resolute zotarolimus-eluting coronary stent system in the treatment of de novo lesions in native coronary arteries: the RESOLUTE US clinical trial. *J Am Coll Cardiol.* 2011;57:1778-83.

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The GRACE risk score predicts mortality in Middle Eastern patients undergoing percutaneous coronary intervention for acute coronary syndrome: results from the First Jordanian PCI Registry (JoPCR1)

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KEYWORDS

- acute coronary syndrome
- GRACE risk score
- percutaneous coronary intervention

Abstract

Aims: The Global Registry of Acute Coronary Events (GRACE) risk score (RS) estimates the probability of death in patients with acute coronary syndromes (ACS). The aim of the present study was to assess the GRACE RS predictability of cardiac mortality in Middle Eastern ACS patients following percutaneous coronary intervention (PCI).

Methods and results: The GRACE RS was calculated for each patient at admission and prior to hospital discharge. The correlation of the GRACE RS with the in-hospital, six- and 12-month mortality was evaluated according to the three risk groups (low, intermediate and high-risk) determined by the score tertiles in the GRACE study. The discriminative power of the score was tested using the receiver operating characteristic (ROC) curves. Of 2,426 patients, 1,870 (77.1%) patients had PCI for ACS. The RS demonstrated an excellent discrimination in predicting in-hospital mortality (area under the ROC curve [C-statistic] of 0.84, 95% CI: 0.82-0.86, p<0.001). The overall in-hospital and one-year mortality rates were 0.74% and 1.94%, respectively. Patients in the high-risk group had significantly higher mortality compared with those in the low-risk group during hospitalisation (2.9% vs. 27%; p<0.0001), and at one year (8.05% vs. 2.0%; p=0.0002).

Conclusions: In this first prospective, multicentre study of Middle Eastern patients undergoing PCI, the GRACE RS in ACS patients demonstrated an excellent discriminative power in predicting in-hospital and one-year cardiac mortality. It would be wise to calculate the GRACE RS for such patients in order to identify those at higher risk of death and treat them with an invasive management strategy.

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Abbreviations

ACS	acute coronary syndromes
CABG	coronary artery bypass graft
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DM	diabetes mellitus
EKG	electrocardiogram
GRACE	Global Registry of Acute Coronary Events
HR	heart rate
JoPCR1	First Jordanian Percutaneous Coronary Intervention Registry
MI	myocardial infarction
NSTEACS	non-ST-segment elevation acute coronary syndrome
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PURSUIT	Platelet glycoprotein IIb/IIIa inhibitors in Unstable angina: Receptor Suppression Using Integrilin
ROC	receiver operating characteristic
RS	risk score
SBP	systolic blood pressure
SC	stable coronary disease
STEMI	ST-segment elevation MI
TIMI	Thrombolysis In Myocardial Infarction
UA	unstable angina

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the Middle East[1-3]. In this region, patients admitted with acute coronary syndromes (ACS) are seven to 10 years younger than those in other regions, one in every four is younger than 50 years of age, and there is a high prevalence of diabetes mellitus (DM), cigarette smoking and obesity[4-7]. Several risk score models have been utilised to predict adverse cardiovascular events among ACS patients, thus identifying a high-risk group that might benefit from aggressive therapeutic strategies. Such strategies include the use of anti-ischaemic and antithrombotic pharmacological agents and adopting an early invasive coronary revascularisation approach during index admission, to reduce the short- and long-term mortality and morbidity[8-11]. The GRACE (Global Registry of Acute Coronary Events) study developed a score system that predicts in-hospital and six-month mortality following an ACS episode[12-14]. Despite the geographic and regional variations in the clinical and demographic features of patients presenting with ACS and in the availability of medical and invasive therapeutic resources, the GRACE risk score (RS) has been validated in several regions in the world[15-19]. The First Jordanian Percutaneous Coronary Intervention Registry (JoPCR1) is the first study to assess the GRACE RS predictability of in-hospital and one-year mortality in a contemporary cohort of Middle Eastern patients who underwent percutaneous coronary intervention (PCI) for ACS.

Methods

Consecutive patients who underwent PCI for ACS or stable coronary disease (SC) in 12 tertiary care hospitals between January 2013 and February 2014 were enrolled in this prospective, observational registry. GRACE RS was calculated for each patient at admission by assigning the appropriate number for each of eight independent risk factors that account for 90% of prognostic information for hospital mortality (age, Killip class, systolic blood pressure [SBP], heart rate [HR], ST-segment deviation, cardiac arrest at presentation, serum creatinine and elevated cardiac biomarkers). The pre-discharge GRACE RS was calculated based on 10 variables (age, history of heart failure, history of myocardial infarction [MI], HR and SBP at admission, ST-segment depression, serum creatinine at admission, elevated cardiac biomarkers, lack of PCI during admission and in-hospital coronary artery bypass graft [CABG] surgery)[12,20]. The GRACE scores were calculated on admission and prior to hospital discharge for each patient admitted with ACS. Three risk severity categories were established using the cut-off points as determined by the GRACE study. The GRACE study RS tertiles on admission (corresponding to low, intermediate, and high-risk groups) were tested as a predictor of cardiac mortality during the index admission, and the pre-discharge RS was tested as a predictor of cardiac mortality at six and 12 months after discharge.

A case report form was used to record patient data prospectively during index hospitalisation, and at one, six and 12 months of follow-up. Data were collected during follow-up visits or through phone calls to the patient, household relative or primary care physician. Baseline data included clinical, laboratory, electrocardiographic, echocardiographic, and coronary angiographic features and PCI procedure details and outcomes.

All PCI procedures were performed according to current standard guidelines. The arterial access site, dual antiplatelet therapy, and type of stent were all left to the operator's discretion. ACS was classified as (1) acute ST-segment elevation MI (STEMI), defined by the presence of cardiac ischaemic chest pain, ST-segment elevation of ≥2 mm in at least two contiguous leads on the 12-lead electrocardiogram (EKG), and elevated cardiac biomarkers (troponin or creatinine kinase-myocardial band) greater than the upper limit of normal, or (2) non-ST-segment elevation ACS (NSTEACS). This included non-ST-segment elevation MI (NSTEMI), defined by the presence of cardiac ischaemic chest pain, ST-segment depression, inverted T-wave, or normal EKG and elevated cardiac biomarkers, and unstable angina (UA), defined by the presence of ischaemic cardiac pain, ST-segment depression, inverted T-wave or normal EKG and no elevation of cardiac biomarkers on admission and eight to 12 hours later.

The major outcome measure, cardiac death, was evaluated during admission, and after one, six and 12 months. All deaths were considered cardiac unless a definite non-cardiac cause could be established. The study was approved by the institutional review board of each participating hospital.

Statistical analysis

Data were described and analysed using the IBM SPSS Statistics, Version 20 (IBM Corp., Armonk, NY, USA). Data were described using means, standard deviations, or percentages

wherever appropriate. Cardiac mortality rates were compared between GRACE RS tertiles and analysed using the chi-square test. Receiver operating characteristic (ROC) curve analyses were used to examine the overall discriminatory power of GRACE RS to predict cardiac mortality. The overall performance of GRACE RS was assessed by computing the C-statistics. A p-value of less than 0.05 was considered statistically significant.

Results

The registry enrolled 2,426 patients, including 1,870 (77.1%) who had PCI for ACS and 556 (22.9%) who had PCI for stable coronary disease. The baseline clinical and angiographic characteristics and PCI procedure of the ACS patients upon admission are shown in **Table 1**. More than one third of patients were 55 years of age or younger, 43% had DM and 70% were overweight or obese. Multivessel coronary disease was present in about 40%, nearly all patients had stent-based PCI, and 98% of the stents used were drug-eluting. Of the 726 patients with STEMI, 398 (54.8%) had primary PCI, 68 (9.4%) had rescue PCI and 260 (35.8%) had elective PCI. Of the 328 patients who underwent rescue or elective PCI, 81 (24.7%) received thrombolytic therapy. The other 247 patients (75.3%) were initially treated at peripheral hospitals and then transferred to the tertiary care centres for further invasive therapy. The rate of primary PCI varied between the participating hospitals and ranged between 40% and 99% of STEMI patients in public and private hospitals, respectively. During hospitalisation, dual antiplatelet therapy (DAPT) was administered to >98.5% of the patients and glycoprotein IIb/IIIa inhibitors to 16.6% of the patients.

The GRACE risk tertiles on admission and prior to discharge are shown in **Table 2**, and are compared with the RS in the GRACE study. The scores during admission and pre-discharge in this study were lower than those in the GRACE study. The median GRACE RS on admission was 118 (25th and 75th percentiles were 94 and 142, respectively). Compared to the score of NSTEACS patients, the mean score for STEMI patients was significantly higher on admission (137.3±33.9 vs. 109.1±34.0; p<0.0001) and significantly lower prior to discharge (71.3±28.4 vs. 74.7±23.0; p=0.002).

Cardiac mortality rates during the index hospitalisation and at six and 12 months, according to the GRACE study low, intermediate and high-risk tertiles, are shown in **Table 3**. Patients in the high-risk tertile had a significantly higher risk of death than those in the low- and intermediate-risk tertiles during index hospitalisation. At six months, patients in the high- and intermediate-risk tertiles had a significantly higher risk of death than those in the low-risk tertile. Patients in the high-risk tertile had a significantly higher mortality rate at one year than patients in the intermediate- and low-risk tertiles.

Overall, the GRACE risk score had a high predictive power and demonstrated excellent discrimination for in-hospital mortality (C-statistic 0.84, 95% CI: 0.82-0.86; p<0.001) **(Figure 1)**. Similarly, the GRACE risk score had a high predictive power for predicting six-month and 12-month mortality (all C-statistics ≥0.8). Similar results were also observed in the STEMI and NSTEACS subgroups (all C-statistics ≥0.8). Of the 19 patients (0.78%) who had in-hospital mortality, the GRACE RS in 14 of them (73.7%) was in the high-risk tertile.

Table 1. Clinical characteristics of 1,870 consecutive patients who underwent PCI for ACS.

Feature		N (%)
Age in years (mean+SD)		57.9±10.1
Female gender		373 (19.9)
Hypertension		1,122 (60.0)
Hypercholesterolaemia		866 (46.3)
Diabetes mellitus		878 (47.0)
Current cigarette smoking		862 (46.1)
Chronic kidney disease		50 (2.7)
Previous cardiovascular disease		679 (36.3)
Previous myocardial infarction		192 (10.3)
Previous PCI		429 (22.9)
Previous CABG		59 (3.2)
ST-segment deviation		1,098 (58.7)
Elevated cardiac enzymes		965 (51.6)
Left ventricular EF <45%		248 (13.3)
ACS	STEMI	726 (38.8)
	NSTEMI	306 (16.4)
	UA	838 (44.8)
Coronary artery disease	Single-vessel disease	1,094 (58.5)
	Multivessel disease	746 (39.9)
	Left main coronary artery disease	30 (1.6)
Number of coronary arteries treated by PCI	Single vessel	1,347 (72.0)
	>2 vessels	523 (28.0)
In-hospital medications	Aspirin	1,848 (98.7)
	Clopidogrel	1,490 (79.7)
	Ticagrelor	356 (19.0)
	Heparin	1,815 (97.1)
	Tirofiban	310 (16.6)
	Thrombolytic agents	81 (4.3)
	Beta-blockers	1,478 (79.0)
	Renin-angiotensin blockers	1,132 (60.5)
	Statins	1,821 (97.4)
In-hospital complications	Death	19 (1.0)
	Heart failure	154 (8.2)
	Cardiogenic shock	14 (0.75)
	Ventricular tachyarrhythmias	21 (1.1)
	Stent thrombosis	9 (0.48)
	Major bleeding events	20 (1.1)
	Acute renal failure	6 (0.3)

ACS: acute coronary syndrome; CABG: coronary artery bypass graft surgery; EF: ejection fraction; NSTEACS: non-ST-segment elevation ACS; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina

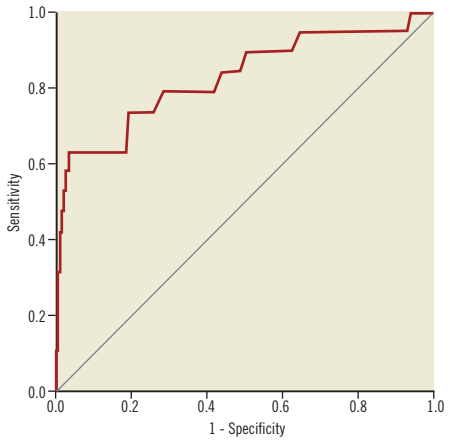

Figure 1. *Receiver operating characteristic (ROC) curve. Receiver operating characteristic (ROC) curve for predicting in-hospital mortality by the GRACE risk score in patients with ACS who underwent PCI (N=1,870, C-statistic 0.84, 95% CI: 0.82-0.86; p<0.001).*

Table 2. GRACE risk score tertiles on admission and prior to discharge in this study compared with GRACE study.

GRACE risk score		ACS patients (JoPCR1 study)	ACS patients (GRACE study)
During admission	Low tertile	<103	<109
	Intermediate tertile	103-133	109-140
	High tertile	>133	>140
Pre-discharge	Low tertile	<62	<89
	Intermediate tertile	62-83	89-118
	High tertile	>83	>118

ACS: acute coronary syndrome; NSTEACS: non-ST-segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction

Discussion

The main finding of the present study is that, in a contemporary Middle Eastern cohort of ACS patients who underwent PCI, the GRACE RS predicts in-hospital, six- and 12-month cardiac mortality. We used the original scores in the GRACE study as a potential predictor of mortality in our patients. The GRACE scores in our population were lower than those reported by the GRACE study. Score tertiles during admission were <103, 103-133, and >133, and pre-discharge tertiles were <60, 62-83, >83. This explains the finding in our study that 40% and 76% of our patients were in the GRACE low-risk groups, and 26% and 4.2% were in the GRACE high-risk groups, considering the scores during admission and pre-discharge, respectively. Potential explanations of this finding include the lower mean age of our patients, the fact that all patients underwent PCI, and the low incidence rate of the components used to calculate the GRACE RS, including heart failure, cardiac arrest, and renal dysfunction.

Table 3. In-hospital, 6- and 12-month cardiac mortality in patients with ACS according to the GRACE risk score tertiles.

GRACE risk score tertile	Cardiac mortality		
	In-hospital	6-month	12-month
Low-risk tertile	0.27%	1.07%	2.00%
Intermediate-risk tertile	0.47%	3.10%	5.68%
High-risk tertile	2.90%	3.13%	8.05%
p-value (high-risk tertiles vs. others)	<0.001	0.008	0.0002

During hospitalisation, the highest rate of death was observed in patients in the high GRACE RS tertile. Similarly, at one year, patients in the highest GRACE risk tertile had the highest rate of death compared with the death rate in the intermediate and low tertiles. The discriminatory capacity of the model, which was tested using the ROC curve and was ≥0.80 in all of the tests we ran, implies that the model offers a good calibration of the probability of in-hospital and 12-month cardiac mortality following PCI for ACS in this group of patients.

Risk scoring systems can help to select aggressive therapeutic strategies for the treatment of high-risk patients. The significant regional variations in outcomes observed among patients with ACS and the fact that geographic location is an independent predictor of mortality in such patients raise the concern that risk scores developed in specific geographic areas might not have the same predictive prognostic value when applied on a global level[21-23]. However, studies from different countries, including Spain, United Kingdom, Belgium, Canada, Pakistan and Portugal, have clearly demonstrated that the GRACE RS is predictive of in-hospital and post-discharge mortality in these regions. The predictive value of the GRACE RS has been validated for in-hospital, six-month, one-year, and five-year follow-up[13,24] in the entire ACS spectrum of patients. Our study provides the first evidence of the score's predictability of in-hospital and post-discharge mortality in Middle Eastern ACS patients who underwent PCI during index admission. It clearly demonstrated that the scores in the GRACE study (i.e., a score >140 on admission or >118 prior to discharge) were likely to be associated with a higher risk of death in hospital or up to one year after discharge, respectively. A similar study from this region[25] showed that the GRACE RS predicts in-hospital mortality, but prediction of the post-discharge events was not addressed.

Relying on clinical variables to predict outcome lacks sufficient precision due to the heterogeneous nature of the ACS population. Although certain clinical features, such as cardiogenic shock, heart failure and hypotension, can predict worse outcome among patients admitted with ACS, only a minority of patients will have these complications. Since most ACS patients are at intermediate risk, several multivariable prognostic score systems were developed to predict in-hospital and future events accurately. The GRACE RS (online calculator: http://www.outcomes-umassmed.org/GRACE/acs_risk.cfm) was derived from a large multinational registry of patients with ACS, based on independent predictors of

outcome. Based on direct comparisons with two other commonly used risk score models, namely the Thrombolysis In Myocardial Infarction (TIMI) and Platelet glycoprotein IIb/IIIa inhibitors in Unstable angina: Receptor Suppression Using Integrilin (PURSUIT) scores[26,27], the GRACE RS demonstrated superiority in accurate stratification of risk over others[19], most likely due to the fact that the GRACE RS was developed from a registry that involved less selected patients and therefore reflects practice in real-world settings. The TIMI RS, although simpler to use than the GRACE RS, does not incorporate important prognostic factors such as Killip class, HR and SBP[26]. Recently, the GRACE 2.0 RS has been introduced as an updated model derived from the GRACE registry. It has a better discriminatory power than the GRACE RS. The GRACE 2.0 RS was validated externally in the French registry (FAST-MI) and is used when serum creatinine and Killip class are not known (history of renal dysfunction and use of a diuretic replace these missing data, respectively). GRACE RS predicts the risk of short-term and long-term mortality, and death/MI, overall and in hospital survivors[28].

The GRACE RS estimates the risk of two endpoints (all-cause death and the composite measure of death or non-fatal MI)[27]. We limited this study to the mortality predictive value of the GRACE RS in a group of PCI patients. In a previous study we demonstrated that the TIMI risk score showed an excellent prognostic value in all ACS patients, regardless of the therapeutic strategy (PCI, CABG or medical treatment)[29]. Previous validation of the GRACE RS in our region assessed the in-hospital, but not the one-year, mortality[25].

The in-hospital mortality rate among our patients (0.74%) was lower than the 4.9% and 2.4% rates reported by the GRACE and Canadian GRACE RS studies, respectively. Likewise, the six-month cardiac mortality in our study (1.59%) was also lower than the 9.1% rate reported by the GRACE study[13,14,17], and the mortality rate at one year (1.94%) in our cohort was also lower than rates reported by several studies from other regions in the world (13.7% in STEMI, 12.0% in NSTEMI, and 4.8% in UA patients)[30], but similar to other Middle Eastern ACS studies[4,5,31]. Potential explanations for lower death rates in our region include the younger age of our patients, the high incidence of one-vessel coronary artery disease and PCI in the majority of patients, the high rate of utilising the catheterisation laboratory for PCI, and the low incidence of major life-threatening adverse events during index hospitalisation, such as heart failure, cardiogenic shock, major bleeding events and renal failure.

Limitations

A few limitations in our study warrant discussion. Inherent to similar observational registries, the study is subject to selection bias, collection of non-randomised data, and missing or incomplete information[32]. Participation was voluntary and the enrolment of consecutive patients was encouraged, but this was not verified, as is the case with other registries. ACS patients who died before or shortly after admission and those who did not undergo angiography were not represented in this study. The study evaluated a selected group of patients who underwent PCI. Hence, the results cannot be generalised to the whole ACS population, who, in addition to PCI, are also treated conservatively or by coronary artery bypass surgery. Furthermore, the participating hospitals were high-volume tertiary care centres; thus, the results may not represent the PCI practice and outcome in all areas in the country or region[33]. Despite these limitations, our study is unique in that it evaluated short- and long-term outcomes of ACS patients who underwent PCI in the Middle East, a region that is not well represented in cardiovascular interventional studies and registries.

Conclusion

In conclusion, this Middle Eastern registry of a contemporary cohort of patients admitted with ACS and who underwent PCI demonstrated that the GRACE RS was highly predictive for in-hospital, six- and 12-month cardiac mortality. Further studies are needed to evaluate the predictive value of the GRACE RS in all patients admitted with ACS, including those treated conservatively.

Impact on daily practice

Clinical practice guidelines advocate calculating one of the commonly used risk scores for patients admitted with ACS in order to identify high-risk groups which would benefit from an invasive strategy. The GRACE risk score was validated in several geographic regions in the world. In this study we demonstrated for the first time that the GRACE risk score was highly predictive for in-hospital, six- and 12-month cardiac mortality in a Middle Eastern contemporary cohort of patients admitted with ACS and undergoing PCI.

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Conflict of interest statement

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References

1. Alsheikh-Ali AA, Omar MI, Raal FJ, Rashed W, Hamoui O, Kane A, Alami M, Abreu P, Mashhoud WM. Cardiovascular risk factor burden in Africa and the Middle East: the Africa Middle East Cardiovascular Epidemiological (ACE) study. *PloS One.* 2014;9: e102830.

2. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;386:743-800.

3. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ; Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet.* 2002;360:1347-60.

4. Hammoudeh A, Alhaddad I. Triggers and the Onset of Acute Myocardial Infarction. *Cardiology in Review.* 2009;17:270-4.

5. Saleh A, Hammoudeh AJ, Hamam I, Khader YS, Alhaddad I, Nammas A, Tarawneh H, Tabbalat R, Harassis A, Bakri M, Alnaquib A, Izraiq M, Al-Mousa E. Prevalence and impact on prognosis of glucometabolic states in acute coronary syndrome in a middle eastern country: The GLucometabolic abnOrmalities in patients with acute coronaRY syndrome in Jordan (GLORY) study. *Int J Diabetes Dev Ctries.* 2012;32:37-43.

6. Zubaid M, Rashed WA, Al-Khaja N, Almahmeed W, Al-Lawati J, Sulaiman K, Al-Motarreb A, Amin H, Al-Suwaidi J, Al-Habib K. Clinical presentation and outcomes of acute coronary syndromes in the Gulf Registry of Acute Coronary Events (Gulf RACE). *Saudi Med J.* 2008;29:251-5.

7. Hammoudeh AJ, Al-Tarawneh H, Elharassis A, Haddad J, Mahadeen Z, Badran N, Izraiq M, Al-Mousa E. Prevalence of conventional risk factors in Jordanians with coronary heart disease: the Jordan Hyperlipidemia And Related Targets Study (JoHARTS). *Int J Cardiol.* 2006;110:179-83.

8. O'Donoghue ML, Vaidya A, Afsal R, Alfredsson J, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KA, Lagerqvist B, McCullough PA, Murphy SA, Spacek R, Swahn E, Windhausen F, Sabatine MS. An invasive or conservative strategy in patients with diabetes mellitus and non-ST-segment elevation acute coronary syndromes: a collaborative meta-analysis of randomized trials. *J Am Coll Cardiol.* 2012;60:106-11.

9. Katritsis DG, Siontis G, Kastrati A, van't Hof A, Neuman FJ, Siontis K, Ioannidis J. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. *Eur Heart J.* 2011;32:32-40.

10. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol.* 2006;48:1319-25.

11. Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E; TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)--Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndrome treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med.* 2001;344:1879-87.

12. Eagle KA, Lim MJ, Dubbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA; GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA.* 2004;291:2727-33.

13. Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG, Dabbous O, Fox KA, Gore JM. Six-month outcomes in a multinational registry of patients hospitalized with an ACS (The Global Registry of ACS [GRACE]). *Am J Cardiol.* 2004;93: 288-93.

14. Tang EW, Wong CK, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. *Am Heart J.* 2007;153:29-35.

15. Abu-Assi E, Garcia-Acuna JM, Pena-Gil C, Gonzalez-Juanatey JR. Validation of the GRACE risk score for predicting death within 6 months of follow-up in a contemporary cohort of patients with acute coronary syndrome. *Rev Esp Cardiol.* 2010;63:640-8.

16. Fox KA, Carruthers KF, Dunbar DA, Graham C, Manning JR, De Raedt H, Buysschaert I, Lambrechts D, Van de Werf F. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J.* 2010;31:2755-64.

17. Elbarouni B, Goodman SG, Yan RT, Welsh RC, Kornder JM, DeYoung JP, Wong GC, Rose B, Grondin FR, Gallo R, Tan M, Casanova A, Eagle KA, Yan AT. Validation of the Global Registry of Acute Coronary Events (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada. *Am Heart J.* 2009;158:392-9.

18. Shaikh MK, Hanif B, Shaikh K, Khan W, Parkash J. Validation of Grace risk score in predicting in-hospital mortality in patients with non-ST-segment myocardial infarction and unstable angina. *J Pak Med Assoc.* 2014;64:807-11.

19. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained

prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J.* 2005;26:865-72.

20. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med.* 20013;163:2345-53.

21. Yan AT, Jong P, Yan RT, Tan M, Fitchett D, Chow CM, Roe MT, Pieper KS, Langer A, Goodman SG; Canadian Acute Coronary Syndromes Registry Investigators. Clinical trial-derived risk model may not generalize to real-world patients with acute coronary syndrome. *Am Heart J.* 2004;148:1020-7.

22. Greco C, Luongo R. [Prognostic stratification in non-ST-elevation acute coronary syndromes: how and why]. [Article in Italian]. *G Ital Cardiol (Rome).* 2006;7:7S-12S.

23. Wong CK, White HD. Value of community-derived risk models for stratifying patients with non-ST elevation acute coronary syndromes. *Eur Heart J.* 2005;26:851-2.

24. Kozieradzka A, Kaminski KA, Maciorkowska D, Olszewska M, Dobrzycki S, Nowak K, Kralisz P, Prokopczuk P, Musial WJ. GRACE, TIMI, Zwolle and CADILLAC risk scores--do they predict 5-year outcomes after ST-elevation myocardial infarction treated invasively? *Int J Cardiol.* 2011;148:70-5.

25. Yusufali A, Zubaid M, Al-Zakwani I, Alsheikh-Ali AA, Al-Mallah MH, Al Suwaidi J, AlMahmeed W, Rashed W, Sulaiman K, Amin H. Validation of the GRACE Risk score for hospital mortality in patients with acute coronary syndrome in the Arab Middle East. *Angiology.* 2011;62:390-6.

26. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D. The TIMI risk score for unstable angina/non ST-elevation MI: a method for prognostication and therapeutic decision making. *JAMA.* 2000;284:835-42.

27. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with ACS without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation.* 2000;101:2557-67.

28. Fox KA, FitzGerald G, Puymirat E, Huang W, Carruthers K, Simon T, Coste P, Monsegu J, Steg PG, Danchin N, Anderson F. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open.* 2014;4:e004425.

29. Hammoudeh A, Saleh A, Hamam I, Alhaddad I, Bakri M, Nammas A, Alnaquib A, Izraiq M, Tarawneh H, Harassis A, Tabbalat R, Khader Y, Al-Mousa E. The prognostic implications of TIMI risk scores in Jordanian patients with acute coronary syndrome. Results from the Glucometabolic Abnormalities in Acute Coronary Syndrome in Jordan (GLORY) Study. *J Med J.* 2012;46:237-245.

30. Ndrepepa G, Mehilli J, Schulz S, Iijima R, Keta D, Byrne RA, Pache P, Seyfarth M, Schömig A, Kastrati A. Patterns of presentation and outcomes of patients with acute coronary syndromes. *Cardiology.* 2009;113:198-206.

31. Saleh A, Hammoudeh A, Tabbalat R, Alhaddad I, Al-Mousa E, Jarrah M, Izraiq M, Nammas A, Janabi H, Shakhatreh A, Khader Y. Incidence and prognosis of stent thrombosis following percutaneous coronary intervention in Middle Eastern patients: The First Jordanian Percutaneous Coronary Intervention Registry (JoPCR1). *Ann Saudi Med.* 2016;36:17-22.

32. Lenzen MJ, Boersma E, Bertrand ME, Maier W, Moris C, Piscione F, Sechtem U, Stahle E, Widimsky P, de Jaegere P, Scholte op Reimer WJ, Mercado N, Wijns W; European Society of Cardiology. Management and outcome of patients with established coronary artery disease: Euro Heart Survey on coronary revascularization. *Eur Heart J.* 2005;26:1169-79.

33. Wijns W, Kolh PH. Experience with revascularization procedures does matter: low volume means worse outcome. *Eur Heart J.* 2010;31:1954-7.

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Predictors of recurrent restenosis after second-generation drug-eluting stent implantation for in-stent restenosis of drug-eluting stents

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KEYWORDS

- calcified stenosis
- drug-eluting stent
- in-stent restenosis

Abstract

Aims: The aim of the study was to evaluate predictors of recurrent restenosis after second-generation drug-eluting stent (DES) implantation for in-stent restenosis (ISR) of DES.

Methods and results: We retrospectively investigated 228 consecutive patients undergoing second-generation DES implantation for ISR of DES. There were 285 lesions in total and the implanted stents were as follows: biolimus-eluting stent, 71; everolimus-eluting stent, 214. We performed eight-month follow-up on 241 lesions (84.6%). The primary angiographic endpoint was binary restenosis, which was defined as ≥50% stenosis at follow-up angiography. Of the 241 lesions, recurrent restenosis was documented in 54 lesions (22.4%), and target lesion revascularisation was performed in 39 lesions (16.2%). Multivariate analysis showed that small vessel (odds ratio [OR] 2.21; 95% confidence interval [CI]: 1.12 to 4.40; p=0.02) and non-focal type restenosis (OR 2.78; 95% CI: 1.36 to 5.78; p=0.0048) were independent predictors of recurrent restenosis. The type of second-generation DES, whether a biolimus-eluting stent or an everolimus-eluting stent, did not affect the angiographic outcomes (OR 0.80; 95% CI: 0.37-1.78; p=0.58).

Conclusions: Small vessel and non-focal type restenosis are predictors of recurrent restenosis after second-generation DES implantation for ISR of DES.

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Abbreviations

BES biolimus-eluting stent
DES drug-eluting stent
EES everolimus-eluting stent
ISR in-stent restenosis

Introduction

Drug-eluting stents (DES) have substantially reduced the revascularisation rate in *de novo* lesions, and outcomes have been further improved with the advent of second-generation DES. In-stent restenosis (ISR) remains a significant clinical issue after DES implantation. The treatment outcome of patients with ISR lesions is worse than that of patients with *de novo* lesions.

It has been reported that the rate of target lesion revascularisation is about 15% and that of target vessel revascularisation about 22% one year after treatment of ISR of DES[1-5], and second-generation DES are superior to first-generation DES in the treatment of ISR of DES[6,7]. We sought to evaluate predictors of recurrent restenosis after second-generation DES implantation for ISR of DES.

Methods

ETHICS

The study was carried out in accordance with the provisions of the Declaration of Helsinki and the guidelines for epidemiological studies issued by the Ministry of Health, Labour, and Welfare of Japan, and has been approved by the institutional review board of Kurashiki Central Hospital. All patients provided informed consent for both the procedure and subsequent data collection and analysis for research purposes.

PATIENT POPULATION

We retrospectively investigated 228 consecutive patients undergoing second-generation DES implantation for ISR of DES between January 2010 and November 2012 (285 lesions: biolimus-eluting stent [BES], 71; everolimus-eluting stent [EES], 214). We performed eight-month follow-up angiography on 241 lesions (84.6%). The 241 lesions were classified into two groups according to the presence or absence of recurrent restenosis. Fifty-four lesions had recurrent restenosis. We compared patient and lesion characteristics between the above-mentioned two groups.

PROCEDURES

We performed predilatation on all ISR lesions. Two types of second-generation DES, BES (Nobori®; Terumo, Tokyo, Japan) and EES (XIENCE V® and XIENCE PRIME®; Abbott Vascular, Santa Clara, CA, USA), were used. Available BES were 8 to 28 mm in length and 2.5 to 3.5 mm in diameter. Available EES were 8 to 38 mm in length and 2.5 to 3.5 mm in diameter. The choice of stent type was at the operator's discretion. All patients were pretreated with aspirin (100 mg daily) and clopidogrel (75 mg daily). Aspirin treatment was maintained lifelong. Clopidogrel treatment was recommended for at least eight months.

ANGIOGRAPHIC ANALYSIS

Coronary angiography was performed serially at baseline (before and after procedure) and at eight-month follow-up. Quantitative coronary angiography (QCA) analysis was performed with QCA-CMS (Medis medical imaging systems, Leiden, The Netherlands). All angiograms were analysed in a random sequence by two experienced observers who were blinded to the clinical characteristics of the patients. Coronary angiograms in multiple views were obtained after intracoronary nitrate injection. Reference diameter, minimal lumen diameter, percentage diameter stenosis, and lesion length were measured before and after procedure, and at eight-month follow-up.

DEFINITIONS

Binary restenosis was defined as ≥50% stenosis inside the stent or within margins 5 mm proximal or distal to the stent at follow-up angiography. ISR was classified according to the Mehran classification[8], and this study defined non-focal type as type ID, patterns II, III, and IV. Target lesion revascularisation was defined as repeat percutaneous coronary intervention or aortocoronary bypass surgery due to angiographic restenosis (>50%) associated with symptoms or objective signs of ischaemia. A bifurcation lesion was defined as a lesion in a branch whose vessel size was >2.0 mm.

STATISTICAL ANALYSIS

Data are expressed as mean±standard deviation for continuous variables. We compared the differences between patients with and without recurrent restenosis using the t-test for continuous data and the χ^2 test for categorical data. Stepwise multivariable logistic regression analysis was applied to individuate the variables independently associated with recurrent restenosis. Multivariable analysis was selected if the variables were shown to affect dependent variables in a univariate analysis or if they were empirically known to have predictive values as follows: non-focal type restenosis, small vessel (reference diameter ≤2.5 mm), dialysis, bifurcation, acute coronary syndrome, chronic total occlusion, and diabetes mellitus. P-values of less than 0.05 were considered to be statistically significant. JMP 9 (SAS Institute Inc., Cary, NC, USA) was used for all statistical calculations.

Results

BASELINE AND PROCEDURAL DATA

Table 1 shows baseline characteristics of the 228 patients including those with hypertension, 182 (63.9%); diabetes mellitus, 121 (42.5%); dyslipidaemia, 146 (51.2%); and dialysis, 41 (17.9%). The rates of the following two factors were significantly higher in the BES group: bifurcation lesion (45.1% vs. 17.3%, p<0.001); reference diameter (3.30±0.59 mm vs. 2.97±0.50 mm, p<0.001). The rate of 2.5 mm stent use was significantly higher in the EES group (19.7% vs. 38.8%, p=0.004).

Figure 1 shows the lesion sites of ISR as follows: left main trunk, 35 (12.3%); left anterior descending, 79 (27.7%); left

Table 1. Baseline characteristics.

Lesion, number	Total (285)	BES (71)	EES (214)	*p*-value
Age, yrs	69.3±11.2	69.3±12.7	69.3±10.7	0.91
Men	234 (82.1)	60 (84.5)	174 (81.2)	0.60
Diabetes mellitus	121 (42.5)	34 (47.9)	87 (40.6)	0.33
Hypertension	182 (63.9)	49 (69.0)	133 (62.1)	0.32
Dyslipidaemia	146 (51.2)	38 (53.5)	108 (50.5)	0.68
Current smoker	11 (3.86)	2 (2.82)	9 (4.20)	0.74
Dialysis	41 (14.3)	10 (14.1)	31 (14.5)	1.00
Acute coronary syndrome	45 (16.0)	10 (14.5)	35 (16.8)	0.71
Bifurcation lesion	69 (24.2)	32 (45.1)	37 (17.3)	<0.001
Reference diameter, mm	3.06±0.54	3.30±0.59	2.97±0.50	<0.001
Lesion length, mm	18.4±15.8	16.6±16.6	19.0±15.5	0.28
Non-focal lesion	132 (46.3)	28 (39.4)	104 (48.6)	0.22
Chronic total occlusion	32 (11.2)	9 (12.7)	23 (10.7)	0.67
2.5 mm stent	97 (34)	14 (19.7)	83 (38.8)	0.004

Data are shown as n (%) unless otherwise indicated.

circumflex artery, 34 (11.9%); right coronary artery, 133 (46.7%); and graft, 4 (1.4%). The right coronary artery accounted for the major portion of the ISR sites.

Figure 2 shows the previously deployed stent as follows: sirolimus-eluting stent, 164 (57.5%); paclitaxel-eluting stent, 51 (17.9%); zotarolimus-eluting stent, 13 (4.6%); BES, 22 (7.7%); and EES, 35 (12.3%). Sirolimus-eluting stents accounted for the major portion of the ISR sites. In treating ISR of EES, BES were more frequently deployed than EES.

Figure 3 shows the angiographic patterns of ISR as follows: focal type (55.8%) and non-focal type (30.5%). Focal body type IC was observed most frequently in both BES and EES.

FOLLOW-UP AND RECURRENT RESTENOSIS

We performed eight-month follow-up angiography on 241 (84.6%) of the 285 lesions. Of the 241 lesions, recurrent restenosis was documented in 54 (22.4%): type IB, 6 (11.1%); type IC, 23 (42.6%); pattern II, 19 (35.2%); pattern III, 2 (3.7%); and pattern IV, 4 (7.4%), and angiographically driven target lesion revascularisation was performed in 39 lesions (16.2%).

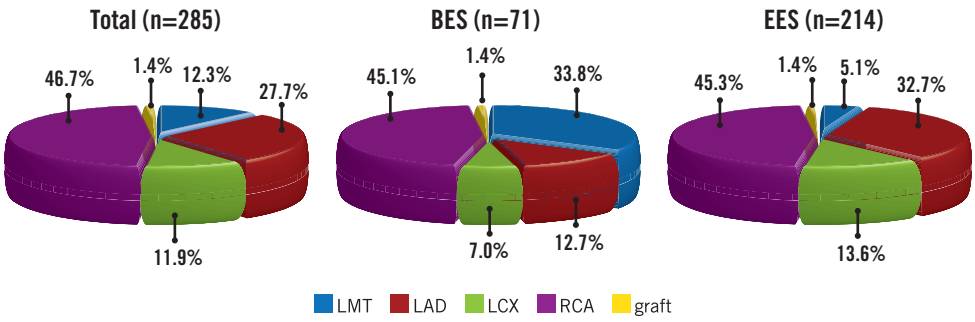

Figure 1. *Lesion sites of in-stent restenosis. The right coronary artery accounted for the largest portion of the in-stent restenosis sites. BES: biolimus-eluting stent; EES: everolimus-eluting stent; LAD: left anterior descending; LCX: left circumflex artery; LMT: left main trunk; RCA: right coronary artery*

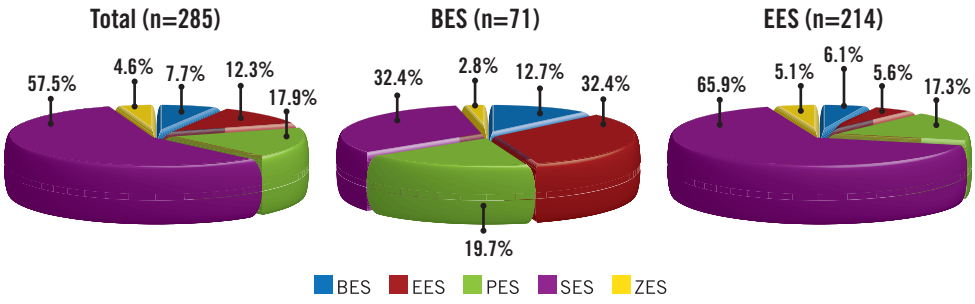

Figure 2. *Stent types of in-stent restenosis. Sirolimus-eluting stents accounted for the largest portion of the in-stent restenosis sites. In treating in-stent restenosis of everolimus-eluting stents, biolimus-eluting stents were more frequently deployed than everolimus-eluting stents. BES: biolimus-eluting stent; EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent*

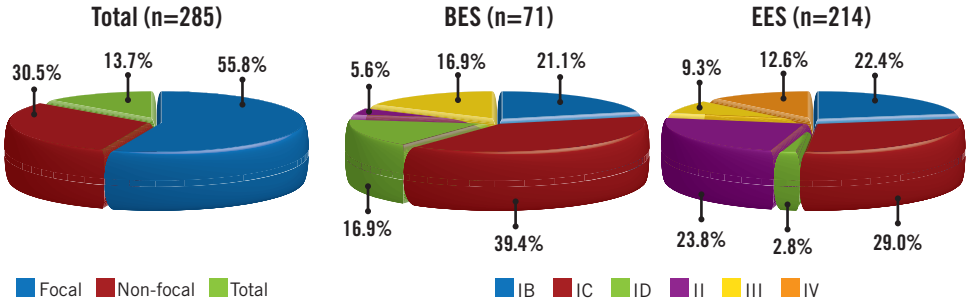

Figure 3. *Angiographic patterns of in-stent restenosis. The angiographic patterns are based on the Mehran classifications. Focal body type IC was observed most frequently in both biolimus-eluting and everolimus-eluting stents. BES: biolimus-eluting stent; EES: everolimus-eluting stent*

UNIVARIATE ANALYSIS

As shown in **Table 2**, the 241 lesions undergoing follow-up angiography were classified as recurrent restenosis (54 lesions) and non-recurrent restenosis (187 lesions). There were no significant differences in baseline characteristics such as hypertension, current smoker, dialysis, diabetes mellitus, and acute coronary syndrome between the two groups. The rates of the following three factors were significantly higher in the recurrent restenosis group: dyslipidaemia (68.5% vs. 48.2%, p=0.01); non-focal type restenosis (61.1% vs. 41.7%, p=0.01); and 2.5 mm stent (46.3% vs. 31.0%, p=0.048).

MULTIVARIATE ANALYSIS

As shown in **Table 3**, small vessel (odds ratio [OR] 2.21; 95% confidence interval [CI]: 1.12 to 4.40; p=0.02) and non-focal type restenosis (OR 2.78; 95% CI: 1.36-5.78; p<0.05) were independent predictors of recurrent restenosis. The type of second-generation DES, whether BES or EES, may make no difference to the angiographic outcomes (OR 0.80; 95% CI: 0.37-1.78; p=0.58). However, this result should be interpreted with caution because the available lengths of BES and EES were different.

Table 2. Univariate analysis.

	Recurrent restenosis		
Lesion, number	**Yes (187)**	**No (54)**	***p*-value**
Age, yrs	69.9±10.6	67.0±9.77	0.06
Men	149 (79.7)	45 (80.5)	0.69
Diabetes mellitus	77 (41.2)	23 (42.6)	0.88
Hypertension	137 (73.2)	38 (70.4)	0.73
Dyslipidaemia	128 (68.5)	26 (48.2)	0.01
Current smoker	5 (2.67)	2 (3.70)	0.20
Dialysis	22 (11.8)	11 (20.4)	0.12
Acute coronary syndrome	32 (17.1)	7 (13.0)	0.54
Bifurcation lesion	43 (23.0)	18 (33.3)	0.15
Reference diameter, mm	3.07±0.52	2.98±0.59	0.27
Non-focal lesion	78 (41.7)	33 (61.1)	0.01
Chronic total occlusion	18 (9.63)	6 (11.1)	0.80
2.5 mm stent	58 (31.0)	25 (46.3)	0.048
Data are shown as n (%) unless otherwise indicated.			

Table 3. Multivariate analysis.

	Odds ratio	95% confidence interval	*p*-value
Non-focal type restenosis	2.78	1.36-5.78	0.0048
Small vessel (stent length ≤2.5 mm)	2.21	1.12-4.40	0.02
Dialysis	2.20	0.90-5.20	0.08
Bifurcation	1.86	0.89-3.82	0.09
Acute coronary syndrome	1.91	0.75-5.40	0.18
Chronic total occlusion	1.95	0.66-6.40	0.23
Everolimus-eluting stent	0.80	0.37-1.78	0.58
Diabetes mellitus	1.14	0.60-2.22	0.69

Discussion

Our results suggest that small vessel and non-focal type restenosis have a major impact on the risk of recurrent restenosis after second-generation DES implantation for ISR of DES. The type of second-generation DES, whether BES or EES, did not affect the angiographic outcomes. The ISR rate in *de novo* lesions has substantially decreased by using second-generation DES compared with first-generation DES. Byrne et al showed that the incidence of recurrent restenosis when using first-generation DES in the treatment of ISR of DES was 24.0%[9], whereas that in the present study using second-generation DES was 22.4%, and the rate of target lesion revascularisation was 16.2%. Thus, the efficacy of DES implantation for ISR of DES may not be notably different between first- and second-generation DES. The prognosis of ISR is reported to be worse with DES than with BMS due to drug-specific factors such as hypersensitivity, inflammation, and neoatherosclerosis[10].

In the present study, small vessel and non-focal type restenosis were independent predictors of recurrent restenosis, as described in the previous report on first-generation DES implantation for ISR of DES[11]. Patients with small vessels had several clinical

characteristics such as a higher prevalence of diabetes mellitus, multivessel disease, and chronic occlusions, which are often associated with a poorer outcome after DES implantation. Stent overlap in a long lesion can easily cause inflammation and uneven drug distribution. An occluded lesion may result in stent malexpansion due to organised thrombus. Because the struts of EES are thinner than those of BES, using EES seems to be more suitable for treating ISR lesions, especially for those with small vessels. Our study was unable to confirm that there were no significant differences between EES and BES because of the small numbers involved and the differences in the available stent lengths.

Recently, drug-coated balloons (DCB) have emerged as a potential alternative to the current treatment of ISR[12]. Although both DES and DCB are recommended for the treatment of ISR of DES, the RIBS IV study, a recent randomised controlled study based on relatively simple angiographic scenarios, demonstrated that EES implantation provided long-term clinical and angiographic results superior to DCB angioplasty[13], whereas Habara et al reported the inferiority of DES implantation to DCB angioplasty in the treatment of non-focal type DES restenosis[14]. The strategy selection according to the lesion characteristics may be important.

Limitations

First, this is a single-centre, small-scale, highly selective and retrospective study. However, this study is valuable because we included all consecutive patients undergoing second-generation DES implantation for ISR of DES, and serial clinical and angiographic outcomes with a high follow-up rate were obtained. Second, intravascular ultrasound was not used in any patient at the time of DES implantation. Finally, the available lengths of BES and EES were different. Hence, the results may be biased.

Conclusion

Small vessel and non-focal type restenosis are predictors of recurrent restenosis after second-generation DES implantation for ISR of DES.

Impact on daily practice

More attention should be paid to small vessel and non-focal type restenosis when performing second-generation DES implantation for ISR of DES to reduce the incidence of recurrent restenosis.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Kastrati A, Mehilli J, von Beckerath N, Dibra A, Hausleiter J, Pache J, Schühlen H, Schmitt C, Dirschinger J, Schömig A; ISAR-DESIRE Study Investigators. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA.* 2005;293:165-71.

2. Koizumi T, Fitzgerald PJ, Honda Y, Ellis SG, Kent K, Martin SL, Brown CL, Masud AR, Patterson JB, Greenberg J, Friedman M, Uchida T, Stone GW. Vascular responses to the multiple overlapped paclitaxel-eluting stents for the treatment of bare-metal in-stent restenotic lesions: angiographic and intravascular ultrasound analysis from the TAXUS-V ISR trial. *Cardiovasc Revasc Med.* 2010;11:140-8.

3. Steinberg DH, Gaglia MA Jr, Pinto Slottow TL, Roy P, Bonello L, De Labriolle A, Lemesle G, Torguson R, Kineshige K, Xue Z, Suddath WO, Kent KM, Satler LF, Pichard AD, Lindsay J, Waksman R. Outcome differences with the use of drug-eluting stents for the treatment of in-stent restenosis of bare-metal stents versus drug-eluting stents. *Am J Cardiol.* 2009;103:491-5.

4. Mehilli J, Byrne RA, Tiroch K, Pinieck S, Schulz S, Kufner S, Massberg S, Laugwitz KL, Schömig A, Kastrati A; ISAR-DESIRE 2 Investigators. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J Am Coll Cardiol.* 2010;55:2710-6.

5. Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, Werner GS, Antoni D, Kleber FX, Bocksch W, Leschke M, Ackermann H, Boxberger M, Speck U, Degenhardt R, Scheller B. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation.* 2009;119:2986-94.

6. Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J.* 2006;151:1260-4.

7. Yamashita K, Ochiai M, Yakushiji T, Ebara S, Okabe T, Yamamoto MH, Saito S, Hoshimoto K, Isomura N, Araki H, Obara C. Repeat drug-eluting stent implantation for in-stent restenosis: first- or second-generation stent. *J Invasive Cardiol.* 2012;24:574-8.

8. Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, Pichard AD, Kent KM, Stone GW, Leon MB. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation.* 1999;100:1872-8.

9. Byrne RA, Neumann FJ, Mehilli J, Pinieck S, Wolff B, Tiroch K, Schulz S, Fusaro M, Ott I, Ibrahim T, Hausleiter J, Valina C, Pache J, Laugwitz KL, Massberg S, Kastrati A; ISAR-DESIRE 3 investigators. 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;381:461-7.

10. Ge H, Zhang Q, Zhou W, He Q, Han ZH, He B. Efficacy and safety of drug-eluting stent implantation for the treatment of in-stent restenosis occurring within bare-metal stent and drug-eluting stent. *J Zhejiang Univ Sci B.* 2010;11:553-60.

11. Habara S, Mitsudo K, Goto T, Kadota K, Fujii S, Yamamoto H, Kato H, Takenaka S, Fuku Y, Hosogi S, Hirono A, Yamamoto K,

Tanaka H, Hasegawa D, Nakamura Y, Tasaka H, Otsuru S, Okamoto Y, Yamada C, Miyamoto M, Inoue K. The impact of lesion length and vessel size on outcomes after sirolimus-eluting stent implantation for in-stent restenosis. *Heart.* 2008;94:1162-5.

12. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 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: 2541-619.

13. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, García del Blanco B, García-Touchard A, López-Minguéz JR, Benedicto A, Masotti M, Zueco J, Iñiguez A, Velázquez M, Moreno R, Mainar V, Domínguez A, Pomar F, Melgares R, Rivero F, Jiménez-Quevedo P, Gonzalo N, Fernández C, Macaya C; RIBS IV Study Investigators (under auspices of Interventional Cardiology Working Group of Spanish Society of Cardiology). A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Randomized Clinical Trial. *J Am Coll Cardiol.* 2015;66: 23-33.

14. Habara S, Kadota K, Kanazawa T, Ichinohe T, Kubo S, Hyodo Y, Otsuru S, Hasegawa D, Tada T, Tanaka H, Fuku Y, Goto T, Mitsudo K. Paclitaxel-coated balloon catheter compared with drug-eluting stent for drug-eluting stent restenosis in routine clinical practice. *EuroIntervention.* 2016;11:1098-105.

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Long-term prognostic significance of periprocedural myonecrosis in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention

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KEYWORDS

- biochemical markers
- death
- myocardial infarction
- stable angina

Abstract

Aims: The aim of this study was to ascertain the relationship between periprocedural myonecrosis (PPMN) and long-term mortality in patients with stable coronary artery disease (CAD) undergoing elective percutaneous coronary intervention (PCI).

Methods and results: A retrospective cohort study of consecutive patients undergoing elective PCI for stable CAD at a major Australian tertiary centre was undertaken. Cardiac troponin I levels were measured 12-24 hours post procedure in all patients. Those with a troponin I elevation >5x upper reference limit (URL) were diagnosed with PPMN as per the Third Universal Definition of Myocardial Infarction. The primary endpoint was long-term all-cause mortality. Of the 682 patients included in our study, 233 (34%) were diagnosed with PPMN. At a mean follow-up of 5.3±1.3 years, there were 34 (14.6%) deaths in patients with PPMN and 43 (9.6%) deaths in those without PPMN (p=0.04). PPMN was not an independent predictor of long-term mortality (OR 1.52, 95% CI: 0.95-2.43, p=0.08).

Conclusions: Periprocedural myonecrosis, defined by the Third Universal Definition of Myocardial Infarction, does not appear to have prognostic implications for patients with stable CAD undergoing elective PCI.

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Abbreviations

CAD	coronary artery disease
CK	creatine kinase
NDI	National Death Index
PCI	percutaneous coronary intervention
PPMI	periprocedural myocardial infarction
PPMN	periprocedural myonecrosis
SCAI	Society of Cardiovascular Angiography and Interventions
ULN	upper limit of normal
URL	upper reference limit

Introduction

The clinical significance of myonecrosis, measured by cardiac troponin, in the context of percutaneous coronary intervention (PCI) is a matter of ongoing debate. The lack of substantial scientific evidence in this domain is apparent from the ever-changing definitions of periprocedural myocardial infarction and the uncertainty regarding its prognostic relevance[1-4].

Myonecrosis due to PCI is common and occurs in up to 40% of cases, depending on the definition and biomarker used[5]. In the Third Universal Definition of Myocardial Infarction (MI), the cut-off cardiac troponin level to diagnose myonecrosis increased from 3 to 5 times the upper reference limit (URL)[3,4]. In contrast to previous definitions, troponin elevation needs to be associated with clinical, electrocardiographic, angiographic or cardiac imaging-related evidence of ischaemia to be classified as a periprocedural MI, or type 4a MI. However, the occurrence of post-PCI chest pain without troponin elevation and troponin elevation without chest pain, angiographic complications or other signs of ischaemia is well documented[6-9]. The Society of Cardiovascular Angiography and Interventions (SCAI) has proposed an alternative definition of "clinically significant myocardial infarction" requiring troponin levels of ≥70x upper limit of normal (ULN) or ≥35x ULN with electrocardiographic evidence of infarction.

The association between adverse prognosis and periprocedural biomarker elevation has been established when creatine kinase (CK) or its MB fraction is used[10-13]. The Universal Definition of MI preferentially advocates the use of troponin though the arbitrarily chosen threshold has uncertain prognostic significance. Consequently, a range of post-PCI troponin elevation cut-offs has been postulated[14-16].

The aim of our study was to evaluate the effect of periprocedural myonecrosis (PPMN), defined by the Third Universal Definition of MI as cardiac troponin elevation >5x URL, on long-term mortality in patients with stable coronary artery disease (CAD) undergoing elective PCI.

Methods

Consecutive patients who underwent elective PCI for stable CAD at Austin Health, Melbourne, Australia, between May 2007 and January 2011 were included in our study. Austin Health is a large tertiary teaching hospital located in Melbourne, Australia, which services a population of approximately 1.25 million people.

Patients who underwent PCI for acute coronary syndrome were excluded. All patients had cardiac troponin I levels measured 12-24 hours post PCI. The troponin I assay used was the Access AccuTnI (Beckman Coulter, Chaska, MN, USA), with an URL value of 0.04 µg/L. This URL is equivalent to our laboratory's ULN level. Patients with a troponin level >0.2 µg/L (>5x URL) were classified as having PPMN in accordance with the Third Universal Definition of MI troponin threshold. Patients with a troponin level >0.2 µg/L and either clinical, angiographic, electrocardiographic or imaging-related evidence of ischaemia were diagnosed with a periprocedural MI. The treating interventional cardiologist was responsible for adjudicating whether a patient suffered a periprocedural MI after analysing the available evidence.

Baseline demographics, and clinical, angiographic, and procedural characteristics of consecutive patients undergoing PCI were prospectively recorded on case report forms using standardised definitions for all fields[17]. The study protocol was approved by the Human Ethics Committee at Austin Health[18].

In-hospital outcomes and complications were recorded at the time of discharge. Follow-up was conducted at 30 days and 12 months by telephone, using a standardised questionnaire[18]. All adverse events were verified by reviewing the patients' medical records. Long-term mortality data, including date of death, were obtained by linkage to the Australian National Death Index (NDI). The Australian NDI is a database housed at the Australian Institute of Health and Welfare, Canberra, which contains records of all deaths occurring in Australia since 1980.

The primary endpoint was all-cause long-term mortality. Other clinical outcomes assessed included 30-day and 12-month mortality and spontaneous MI. Spontaneous MI was defined as: cardiac troponin elevation; and/or a significant ST-segment change, development of new Q-waves in ≥2 contiguous electrocardiographic leads, or new left bundle branch block pattern in the context of new clinical symptoms. Additionally, we analysed in-hospital mortality and bleeding. In-hospital bleeding was defined as bleeding requiring a transfusion and/or prolonged hospital stay due to bleeding and/or a drop in haemoglobin >3g/dL[17].

Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD), and categorical data expressed as counts and percentages. Continuous variables were compared using Student's t-tests or ANOVA, and categorical variables using Fisher's exact or Pearson's chi-square tests. All calculated p-values were two-sided and p-values <0.05 were considered statistically significant. Cumulative incidence of mortality was estimated by the Kaplan-Meier method and the log-rank test was used to evaluate differences between groups with and without PPMN. Logistic regression modelling was used to identify univariate and multivariate predictors of PPMN. Twelve univariate variables with a p-value ≤0.10 were included in multivariate backward regression models. Cox proportional hazard modelling was used to identify univariate and multivariate predictors of long-term mortality. Fourteen univariate

variables with a p-value ≤0.10 were included in multivariate models. All statistical analysis was performed using SPSS, Version 21 (IBM Corp., Armonk, NY, USA).

Results

Of 682 consecutive patients with stable CAD who underwent elective PCI in our study, 233 (34%) experienced PPMN but only 14 (2%) sustained a periprocedural MI according to the Third Universal Definition of MI. For comparison, if the Second Universal (>3x URL) or SCAI (≥70x ULN or ≥35x with new clinical or electrocardiographic evidence of ischaemia) definitions had been used, 302 (44%) and 25 (4%) patients, respectively, would have received a diagnosis of periprocedural MI.

Baseline clinical characteristics **(Table 1)** reveal that patients with PPMN had higher post-procedural troponin levels (1.59±5.18 vs. 0.07±0.05 µg/L, p<0.01). Furthermore, they were more likely to have a history of congestive heart failure (7.7% vs. 3.1%, p<0.01) and be undergoing staged PCI (18.1% vs. 11.1%, p=0.01). Patients with PPMN had higher rates of multi-lesion PCI (25.8% vs. 13.6%, p<0.01), required longer stent lengths (23.2±15.7 mm vs. 19.0±13.1 mm, p<0.01) and had lesions with greater angiographic complexity as suggested by higher rates of type B2/C lesions (48.3% vs. 39.1%, p=0.02) **(Table 2)**. Glycoprotein IIb/IIIa use was more common in patients with PPMN, most likely due to its use as a bail-out strategy (9.0% vs. 4.5%, p=0.02).

Table 1. Clinical characteristics.

	No PPMN (n=449)	PPMN (n=233)	*p*-value
Troponin level (µg/L)	0.07±0.05	1.59±5.18	<0.01
Age (years)	64.8±10.8	65.6±11.0	0.37
Height (cm)	170.5±9.9	169.2±10.5	0.13
Weight (kg)	83.1±17.6	82.4±15.2	0.74
Gender (female), n (%)	94 (20.9)	61 (26.1)	0.13
Current smoker, n (%)	43 (9.6)	24 (10.3)	0.76
Chronic lung disease, n (%)	29 (6.5)	24 (10.3)	0.08
Diabetes mellitus, n (%)	120 (26.7)	73 (31.3)	0.21
Hypertension, n (%)	370 (82.4)	193 (82.8)	0.89
Hypercholesterolaemia, n (%)	419 (93.3)	212 (91.0)	0.27
Previous MI, n (%)	188 (41.9)	109 (46.8)	0.22
Family history of CAD, n (%)	188 (41.9)	104 (44.6)	0.49
Congestive heart failure, n (%)	14 (3.1)	18 (7.7)	<0.01
PVD, n (%)	31 (6.9)	18 (7.7)	0.70
CVA, n (%)	21 (4.7)	17 (7.3)	0.17
Previous PCI, n (%)	173 (38.5)	100 (42.9)	0.27
Previous CABG, n (%)	63 (14.0)	21 (9.0)	0.06
Recent CHF (<2 weeks), n (%)	7 (1.6)	3 (1.3)	0.78
Atrial fibrillation, n (%)	22 (4.9)	9 (3.9)	0.67
Positive stress test, n (%)	194 (43.2)	99 (42.5)	0.38
Staged PCI, n (%)	50 (11.1)	42 (18.1)	0.01
eGFR <60 ml/min/1.73 m^2	82 (18.3)	46 (19.7)	0.64
Fasting glucose (mmol/L)	6.1±1.6	6.0±2.0	0.82
Total cholesterol (mmol/L)	3.7±1.0	3.7±1.0	0.99
LDL-cholesterol (mmol/L)	2.1±0.9	2.2±0.9	0.81
HDL-cholesterol (mmol/L)	0.9±0.3	0.9±0.3	0.69
Triglycerides (mmol/L)	1.4±0.8	1.3±0.8	0.27

CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CHF: congestive heart failure; CVA: cerebrovascular accident; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction; PCI: percutaneous coronary intervention; PPMN: post-procedural myonecrosis; PVD: peripheral vascular disease

Table 2. Angiographic and procedural characteristics.

	No PPMN (n=449)	PPMN (n=233)	*p*-value
Multivessel CAD, n (%)	279 (62.3)	162 (69.5)	0.06
Multi-lesion PCI, n (%)	61 (13.6)	60 (25.8)	<0.01
Left main PCI, n (%)	12 (2.7)	2 (0.9)	0.11
Ostial lesion, n (%)	37 (8.3)	11 (4.7)	0.09
Bifurcation lesion, n (%)	67 (14.9)	44 (18.8)	0.19
Chronic total occlusion, n (%)	46 (10.2)	19 (8.2)	0.38
Type B2/C lesion, n (%)	175 (39.1)	112 (48.3)	0.02
PCI to *de novo* lesion, n (%)	398 (88.6)	211 (90.6)	0.67
GP IIb/IIIa use, n (%)	20 (4.5)	21 (9.0)	0.02
Total stent length (mm)	19.0±13.1	23.2±15.7	<0.01

CAD: coronary artery disease; GP IIb/IIIa: glycoprotein IIb/IIIa inhibitor; PCI: percutaneous coronary intervention; PPMN: post-procedural myonecrosis

PCI angiographic success rates were equivalent between groups (97.0% vs. 97.1%, p=0.94). Patients with PPMN had higher rates of acute closure, coronary dissection and no reflow but the differences were not statistically significant as the numbers were small **(Table 3)**. **Table 4** shows medical therapy at 30 days and 12 months.

Table 3. Acute procedural outcomes.

	No PPMN (n=449)	PPMN (n=233)	*p*-value
Successful PCI, n (%)	436 (97.1)	226 (97.0)	0.94
Acute closure, n (%)	0 (0)	2 (0.9)	0.05
Coronary dissection, n (%)	22 (4.9)	17 (7.3)	0.21
Coronary perforation, n (%)	2 (0.4)	1 (0.4)	0.97
No reflow, n (%)	4 (0.9)	7 (3.0)	0.05
Emergency PCI, n (%)	0 (0)	2 (0.9)	0.05
Stent thrombosis, n (%)	0 (0)	1 (0.4)	0.17
Unplanned CABG, n (%)	0 (0)	0 (0)	–
Post-PCI arrhythmia, n (%)	8 (1.8)	4 (1.7)	0.95
Post-PCI stroke, n (%)	0 (0)	0 (0)	–
Post-PCI CHF, n (%)	1 (0.2)	1 (0.4)	0.64
In-hospital bleeding, n (%)	1 (0.2)	0 (0.0)	0.47

CABG: coronary artery bypass graft surgery; CHF: congestive heart failure; PCI: percutaneous coronary intervention; PPMN: post-procedural myonecrosis

Table 4. Medication history at 30 days and 12 months.

		No PPMN (n=449)	PPMN (n=233)	*p*-value
30 days	Aspirin,%	98.8	99.0	0.81
	Clopidogrel,%	96.7	95.7	0.53
	Prasugrel,%	1.20	4.20	0.2
	Statin,%	93.5	94.6	0.61
	Beta-blocker,%	68.1	70.2	0.61
	ACE inhibitor,%	47.9	52.3	0.32
	ARB,%	24.2	26.6	0.52
	Warfarin,%	5.01	3.90	0.55
12 months	Aspirin,%	93.6	93.7	0.98
	Clopidogrel,%	73.1	77.3	0.28
	Prasugrel,%	1.80	2.90	0.44
	Statin,%	93.6	93.7	0.98
	Beta-blocker,%	60.5	62.3	0.70
	ACE inhibitor,%	45.7	48.9	0.49
	ARB,%	28.1	25.0	0.45
	Warfarin,%	6.30	5.60	0.74

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; PPMN: post-procedural myonecrosis

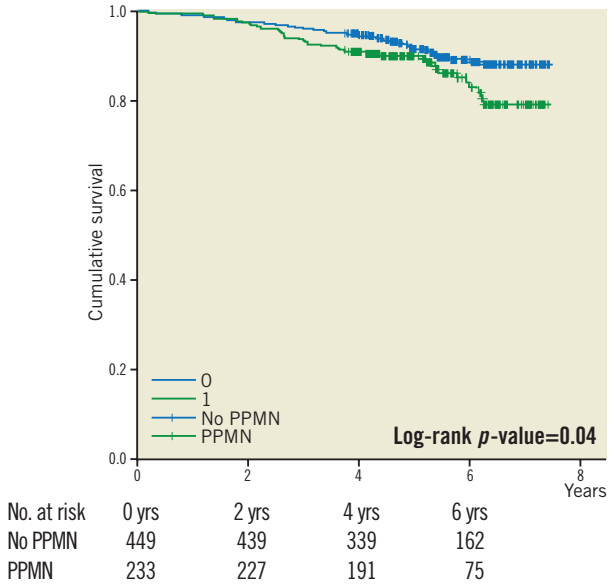

Figure 1. *Kaplan-Meier survival curve for periprocedural myonecrosis (PPMN), defined by the Third Universal Definition of MI (troponin level >5x URL).*

Multivariate logistic regression showed stent length (hazard ratio [HR] 1.02, 95% confidence interval [CI]: 1.01-1.03), congestive heart failure (HR 2.58, 95% CI: 1.22-5.47), multivessel CAD (HR 1.47, 95% CI: 1.02-2.10), transient no-reflow (HR 4.76, 95% CI: 1.16-2.10), and glycoprotein IIb/IIIa inhibitor use (HR 2.01, 95% CI: 1.03-3.92) to be independent predictors of PPMN.

Table 5 shows short, medium, and long-term outcomes. At 30 days, there were no deaths and only two patients experienced spontaneous myocardial infarctions, both in the PPMN group. At 12 months, there were four (0.9%) deaths in the no PPMN group and one (0.4%) in the PPMN group (p=0.5) with equivalent rates of MI (1.6% vs. 1.7%, p=0.88). At a mean follow-up of 5.3±1.3 years, mortality was higher in the PPMN group with 34 (14.6%) deaths compared to 43 (9.6%) deaths in those without PPMN (p=0.04). The Kaplan-Meier survival curve in **Figure 1** shows that patients with PPMN had worse long-term outcomes.

Multivariate analysis using a Cox proportional hazards model showed PPMN was not an independent predictor of long-term mortality (odds ratio [OR] 1.52, 95% CI: 0.95-2.43, p=0.08) **(Table 6)**. Periprocedural MI defined by SCAI (troponin rise ≥70x ULN or ≥35x ULN with new clinical or electrocardiographic evidence of ischaemia) or the Second Universal Definition of MI (troponin rise >3x URL) was also not associated with worse prognosis by Kaplan-Meier analysis **(Figure 2, Figure 3)**.

Table 5. Short, medium-term and long-term clinical outcomes.

		No PPMN (n=449)	PPMN (n=233)	*p*-value
Long-term mortality*, n (%)		43 (9.6)	34 (14.6)	0.04
30 days	Mortality, n (%)	0 (0)	0 (0)	–
	MI, n (%)	0 (0)	2 (0.9)	0.15
12 months	Mortality, n (%)	4 (0.9)	9 (3.9)	0.20
	MI, n (%)	7 (1.6)	4 (1.7)	0.88

*Mean (±standard deviation) follow-up times for the No PPMN and the PPMN groups were 5.4±1.3 and 5.2±1.4 years, respectively ($p=0.11$). MI: myocardial infarction; PPMN: post-procedural myocardial necrosis

Discussion

In this single-centre observational study, we assessed the long-term prognostic implication of periprocedural myonecrosis defined by troponin I elevation in patients with stable coronary

Table 6. Cox proportional hazards model for long-term mortality.

	No PPMN (n=449)	PPMN (n=233)	*p*-value
PPMN	1.52	0.95 - 2.43	0.08
Age (per year)	1.08	1.05 - 1.11	<0.01
Staged PCI	1.82	1.03 - 3.21	0.04
Previous CABG	2.05	1.18 - 3.58	0.01
Chronic lung disease	2.21	1.13 - 4.30	0.02
Peripheral vascular disease	2.91	1.58 - 5.38	<0.01
eGFR <60 ml/min/1.73 m^2	1.64	0.99 - 2.70	0.05
Congestive heart failure	2.10	0.96 - 4.59	0.06
Diabetes mellitus	1.33	0.81 - 2.02	0.26
Single-vessel CAD	0.73	0.38 - 1.40	0.34
Previous MI	1.20	0.70 - 1.90	0.59
Previous stroke	1.13	0.53 - 2.42	0.76

CAD: coronary artery disease; CABG: coronary artery bypass graft surgery; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; PCI: percutaneous coronary intervention; PPMN: post-procedural myonecrosis

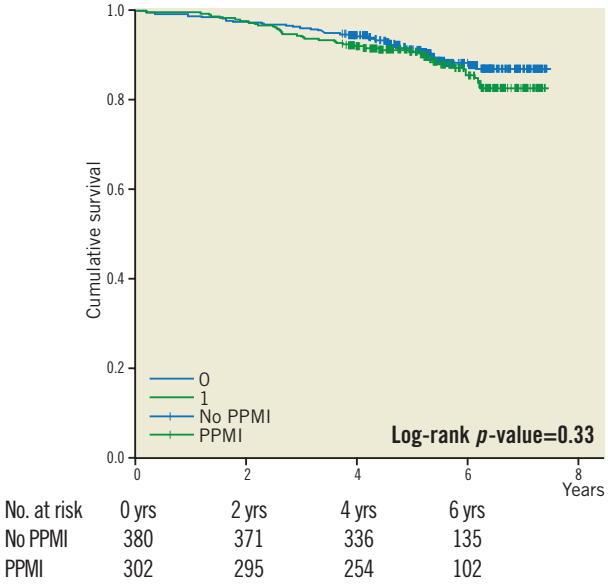

Figure 2. *Kaplan-Meier survival curve for periprocedural MI, defined by the Second Universal Definition of MI (troponin level >3x URL).*

artery disease undergoing elective PCI. Several findings have particular clinical importance. Firstly, the rate of periprocedural myonecrosis and MI varies widely depending on the definition used. Secondly, independent predictors of PPMN include a combination of patient-specific characteristics (congestive heart failure, multivessel CAD, chronic lung disease) and procedural factors (length of stent required, use of GP IIb/IIIa inhibitors, presence of transient no-reflow). Finally, PPMN was not an independent predictor of long-term mortality.

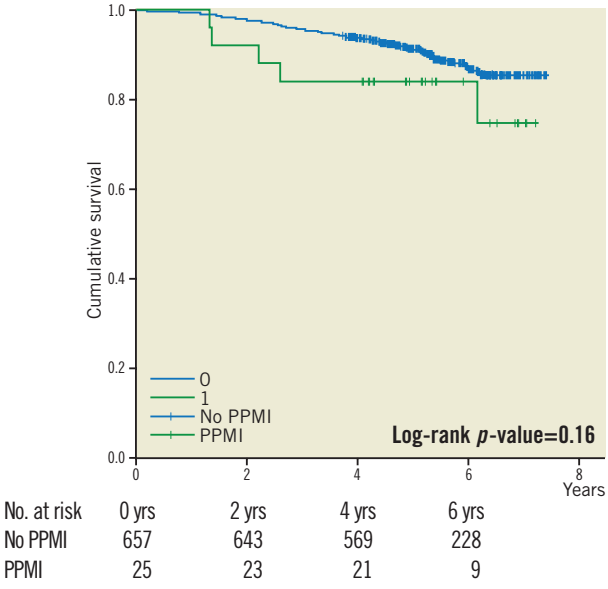

Figure 3. *Kaplan-Meier survival curve for periprocedural MI, defined by the SCAI (troponin level ≥70x ULN or ≥35x ULN with new clinical or electrocardiographic evidence of ischaemia).*

Diagnosing a periprocedural MI in clinical practice is complicated by the varying definitions proposed in international guidelines over the past decade[1-4]. Previously, cardiac biomarker elevation alone was required to diagnose a periprocedural MI[2,4]. However, in the widely used Third Universal Definition of MI, a significant biomarker elevation alone post PCI is no longer an "infarction" but merely myonecrosis[3]. In an attempt to link diagnosis to prognosis, the SCAI proposed a "new definition of a clinically relevant MI after revascularisation"[1]. In this latest attempt to define a periprocedural MI, a considerably higher troponin cut-off has been postulated (≥70x ULN alone or ≥35x ULN with new clinical or electrocardiographic evidence of ischaemia). Our study highlights the clinical difficulties associated with interpreting cardiac biomarkers after elective PCI in the context of differing definitions – periprocedural MI could have been diagnosed in 2% or 44% of our patients. Given the significant implications for the patient, the interventional cardiologist and the healthcare system, the pursuit of a uniform definition for periprocedural MI that has prognostic relevance should continue.

The association between periprocedural MI and mortality, defined by creatine kinase (CK) or CK-MB alone is robust[10-13,19-22]. When defined by cardiac troponin, this association is less certain[1]. Given the greater sensitivity of cardiac troponin, the rate of periprocedural MI diagnosed has increased[16,23]. The diagnostic criteria, however, may be too sensitive to have prognostic implication[5,15]. Aside from SCAI, a number of research groups have proposed differing cut-offs for prognostically significant post-PCI troponin elevations[14-16]. In our study a troponin elevation >5x URL was associated with an unadjusted higher mortality rate while elevations >3x URL or ≥70x ULN were not. However, when adjusting for other confounding variables, PPMN defined by the Third Universal Definition of MI was not an independent predictor of long-term mortality.

The main strength of our study is its long-term mean follow-up of 5.3±1.3 years. To our knowledge, this is the longest study assessing the prognostic value of PPMN diagnosed with cardiac troponin by the Third Universal Definition of MI in patients undergoing elective PCI. Previous studies with shorter follow-up have also failed to find an association between periprocedural myocardial myonecrosis, defined by varying criteria, and mortality[16,20,23,24]. These negative findings have not been unanimous. Prasad et al showed that any troponin elevation post PCI, in the context of normal baseline levels, was associated with increased mortality at two years[25].

It is plausible that PPMN is an epiphenomenon in patients with stable CAD undergoing elective PCI. The extent of atherosclerotic burden has been associated with PPMN and is also an independent predictor of mortality[26-31]. Thus, PPMN may be a marker of advanced atherosclerosis rather than a prognostic factor in its own right. Our findings support this proposition, as longer stent length and multivessel CAD, both variables that suggest advanced atherosclerosis, were independent predictors of PPMN but PPMN itself did not predict long-term mortality. However, distal

microembolisation is also important in the aetiology of PPMN: this is more likely to occur in patients with advanced atherosclerosis who require multi-lesion PCI and longer stent lengths.

As previously stated, the Third Universal Definition of MI requires clinical, angiographic, electrocardiographic or imaging-related evidence of ischaemia along with a troponin elevation >5x URL. However, angiographic complications are not always associated with significant biomarker elevations and biomarker elevations can occur without angiographic complications[6-9]. In our study, only 2% of patients experienced an MI by this definition although a higher number had troponin elevations ≥70x ULN, consistent with a periprocedural MI by the SCAI definition[1]. It is possible that subtle angiographic complications, such as loss of very small side branches, were not recognised. Furthermore, microinfarcts are known to be difficult to identify even with cardiac magnetic resonance imaging[15]. This may account for our relatively low rate of "myocardial infarction" but our high rate of "myonecrosis". An advantage of our study is the inclusion of consecutive patients who had post-PCI troponin measured. Other studies only analysed selected patients who had biomarkers assessed as a result of clinical suspicion of periprocedural complications[24]. This allowed us to undertake an unbiased analysis of the link between PPMN and long-term mortality.

Limitations

A significant limitation of our study is the absence of pre-procedural cardiac troponin levels. Jeremias et al have shown that up to 6% of patients with stable CAD undergoing elective PCI have elevated pre-PCI troponin levels[32]. Furthermore, pre-intervention rather than post-intervention troponin elevation may have greater prognostic significance[23,32]. In our study, patients with PPMN had higher rates of congestive heart failure and were more likely to be undergoing staged PCI. It is conceivable that these patients could have had elevated troponin levels at baseline. In attempting to correct for confounding factors, we found congestive heart failure was an independent predictor of PPMN while staged PCI was not. This highlights the importance of pre-procedural troponin levels in the diagnosis of periprocedural MI[3,33-35]. A further limitation of our study is the potential underestimation of patients classified as having a periprocedural MI by the SCAI criteria as we may not have captured true peak troponin levels. Lastly, our study's single-centre retrospective design has inherent drawbacks. Although we have attempted to account for confounding variables in our multivariate analyses, unmeasured and unaccounted factors may exist. Thus, these results should be considered as hypothesis-generating rather than conclusive.

Conclusion

The incidence of periprocedural myonecrosis and/or MI varies widely depending on the definition utilised. Periprocedural myonecrosis, defined by the Third Universal Definition of MI, does not appear to have prognostic implications for patients with stable CAD undergoing elective PCI.

Impact on daily practice

Periprocedural troponin elevations are common in patients undergoing elective PCI for stable CAD. Our study, which has the longest reported follow-up, suggests that periprocedural myonecrosis may not have prognostic implication in patients with stable CAD. Given the prognostic uncertainty of isolated post-PCI troponin elevation, at present it should only be interpreted in the context of ischaemia, as per the Third Universal Definition of MI.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, Reilly JP, Zoghbi G, Holper E, Stone GW. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol.* 2013;62:1563-70.

2. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB 3rd, Morrison DA, O'Neil WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation.* 2006;113:e166-286.

3. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *J Am Coll Cardiol.* 2012;60:1581-98.

4. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J.* 2007;28:2525-38.

5. Prasad A, Herrmann J. Myocardial infarction due to percutaneous coronary intervention. *N Engl J Med.* 2011;364:453-64.

6. Blankenship JC, Islam MA, Wood GC, Iliadis EA. Angiographic adverse events during percutaneous coronary

intervention fail to predict creatine kinase-MB elevation. *Catheter Cardiovasc Interv.* 2004;63:31-41.

7. Jeremias A, Kutscher S, Haude M, Heinen D, Holtmann G, Senf W, Erbel R. Nonischemic chest pain induced by coronary interventions: a prospective study comparing coronary angioplasty and stent implantation. *Circulation.* 1998;98:2656-8.

8. Kini AS, Lee P, Mitre CA, Duffy ME, Sharma SK. Postprocedure chest pain after coronary stenting: implications on clinical restenosis. *J Am Coll Cardiol.* 2003;41:33-8.

9. Muschart X, Slimani A, Jamart J, Chenu P, Dangoisse V, Gabriel L, Guedes A, Marchandise B, Schroder E. The different mechanisms of periprocedural myocardial infarction and their impact on in-hospital outcome. *J Invasive Cardiol.* 2012;24:655-60.

10. Abdelmeguid AE, Topol EJ, Whitlow PL, Sapp SK, Ellis SG. Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions. *Circulation.* 1996;94:1528-36.

11. Bonaca MP, Wiviott SD, Braunwald E, Murphy SA, Ruff CT, Antman EM, Morrow DA. American College of Cardiology/American Heart Association/European Society of Cardiology/World Heart Federation universal definition of myocardial infarction classification system and the risk of cardiovascular death: observations from the TRITON-TIMI 38 trial (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38). *Circulation.* 2012;125:577-83.

12. Ellis SG, Chew D, Chan A, Whitlow PL, Schneider JP, Topol EJ. Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. *Circulation.* 2002;106:1205-10.

13. Stone GW, Mehran R, Dangas G, Lansky AJ, Kornowski R, Leon MB. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. *Circulation.* 2001;104:642-7.

14. Herrmann J, Lennon RJ, Jaffe AS, Holmes DR Jr, Rihal CS, Prasad A. Defining the optimal cardiac troponin T threshold for predicting death caused by periprocedural myocardial infarction after percutaneous coronary intervention. *Circ Cardiovasc Interv.* 2014;7:533-42.

15. Lim CC, van Gaal WJ, Testa L, Cuculi F, Arnold JR, Karamitsos T, Francis JM, Petersen SE, Digby JE, Westaby S, Antoniades C, Kharbanda RK, Burrell LM, Neubauer S, Banning AP. With the "universal definition," measurement of creatine kinase-myocardial band rather than troponin allows more accurate diagnosis of periprocedural necrosis and infarction after coronary intervention. *J Am Coll Cardiol.* 2011;57:653-61.

16. Novack V, Pencina M, Cohen DJ, Kleiman NS, Yen CH, Saucedo JF, Berger PB, Cutlip DE. Troponin criteria for myocardial infarction after percutaneous coronary intervention. *Arch Intern Med.* 2012;172:502-8.

17. Yan BP, Ajani AE, Duffy SJ, New G, Horrigan M, Szto G, Walton A, Eccleston D, Lefkovits J, Black A, Sebastian M, Brennan AL, Reid CM, Clark DJ. Use of drug-eluting stents in Victorian public hospitals. *Med J Aust.* 2006;185:363-7.

18. Ajani AE, Szto G, Duffy SJ, Eccleston D, Clark DJ, Lefkovits J, Chew DP, Warren R, Black A, New G, Walton A, Lew R, Shaw J, Horrigan M, Sebastian M, Yan BP, Brennan A, Meehan A, Reid C, Krum H; Melbourne Interventional Group investigators. The foundation and launch of the Melbourne Interventional Group: a collaborative interventional cardiology project. *Heart Lung Circ.* 2006;15:44-7.

19. Brener SJ, Ellis SG, Schneider J, Topol EJ. Frequency and long-term impact of myonecrosis after coronary stenting. *Eur Heart J.* 2002;23:869-76.

20. Kini AS, Lee P, Marmur JD, Agarwal A, Duffy ME, Kim MC, Sharma SK. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. *Am J Cardiol.* 2004;93:18-23.

21. Lindsey JB, Kennedy KF, Stolker JM, Gilchrist IC, Mukherjee D, Marso SP, Pencina MJ, Kleiman NS, Cohen DJ. Prognostic implications of creatine kinase-MB elevation after percutaneous coronary intervention: results from the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry. *Circ Cardiovasc Interv.* 2011;4:474-80.

22. Park DW, Kim YH, Yun SC, Ahn JM, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Frequency, causes, predictors, and clinical significance of peri-procedural myocardial infarction following percutaneous coronary intervention. *Eur Heart J.* 2013;34:1662-9.

23. Prasad A, Rihal CS, Lennon RJ, Singh M, Jaffe AS, Holmes DR Jr. Significance of periprocedural myonecrosis on outcomes after percutaneous coronary intervention: an analysis of preintervention and postintervention troponin T levels in 5487 patients. *Circ Cardiovasc Interv.* 2008;1:10-9.

24. Idris H, Lo S, Shugman IM, Saad Y, Hopkins AP, Mussap C, Leung D, Thomas L, Juergens CP, French JK. Varying definitions for periprocedural myocardial infarction alter event rates and prognostic implications. *J Am Heart Assoc.* 2014;3:e001086.

25. Prasad A, Singh M, Lerman A, Lennon RJ, Holmes DR Jr, Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. *J Am Coll Cardiol.* 2006;48:1765-70.

26. Garg S, Sarno G, Girasis C, Vranckx P, de Vries T, Swart M, Bressers M, Garcia-Garcia HM, van Es GA, Raber L, Campo G, Valgimigli M, Dawkins KD, Windecker S, Serruys PW. A patient-level pooled analysis assessing the impact of the SYNTAX (synergy between percutaneous coronary intervention with taxus and cardiac surgery) score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. *JACC Cardiovasc Interv.* 2011;4:645-53.

27. Kanaparti PK, Brown DL. Relation between coronary atherosclerotic plaque burden and cardiac enzyme elevation following percutaneous coronary intervention. *Am J Cardiol.* 2000;86:619-22.

28. Lee T, Yonetsu T, Koura K, Hishikari K, Murai T, Iwai T, Takagi T, Iesaka Y, Fujiwara H, Isobe M, Kakuta T. Impact of coronary plaque morphology assessed by optical coherence tomography on cardiac troponin elevation in patients with elective stent implantation. *Circ Cardiovasc Interv.* 2011;4:378-86.

29. Mehran R, Dangas G, Mintz GS, Lansky AJ, Pichard AD, Satler LF, Kent KM, Stone GW, Leon MB. Atherosclerotic plaque burden and CK-MB enzyme elevation after coronary interventions: intravascular ultrasound study of 2256 patients. *Circulation.* 2000;101:604-10.

30. Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Dangas G, Lazar D, Sanchez R, Fahy M, Xu K, Stone GW. Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) trial. *J Am Coll Cardiol.* 2011;57:2389-97.

31. van Gaal WJ, Ponnuthurai FA, Selvanayagam J, Testa L, Porto I, Neubauer S, Banning AP. The Syntax score predicts peri-procedural myocardial necrosis during percutaneous coronary intervention. *Int J Cardiol.* 2009;135:60-5.

32. Jeremias A, Kleiman NS, Nassif D, Hsieh WH, Pencina M, Maresh K, Parikh M, Cutlip DE, Waksman R, Goldberg S, Berger PB, Cohen DJ; Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) Registry Investigators. Prevalence and prognostic significance of preprocedural cardiac troponin elevation among patients with stable coronary artery disease undergoing percutaneous coronary intervention: results from the evaluation of drug eluting stents and ischemic events registry. *Circulation.* 2008;118:632-8.

33. Gustavsson CG, Hansen O, Frennby B. Troponin must be measured before and after PCI to diagnose procedure-related myocardial injury. *Scand Cardiovasc J.* 2004;38:75-9.

34. Jaffe AS. Chasing troponin: how low can you go if you can see the rise? *J Am Coll Cardiol.* 2006;48:1763-4.

35. Miller WL, Garratt KN, Burritt MF, Lennon RJ, Reeder GS, Jaffe AS. Baseline troponin level: key to understanding the importance of post-PCI troponin elevations. *Eur Heart J.* 2006;27:1061-9.

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Modified jailed balloon technique for coronary artery bifurcation lesions

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KEYWORDS

- coronary bifurcation lesion
- jailed balloon technique
- stent

Abstract

Coronary bifurcation lesions are one of the most challenging lesions in interventional cardiology in terms of procedural success rate as well as long-term cardiac events. PCI of bifurcation lesions continues to use main vessel (MV) stenting with the proximal optimisation technique (POT) and provisional side branch (SB) stenting as the preferred approach. A jailed SB balloon can restore the SB flow after SB occlusion. In this case report, we introduce a modified jailed balloon technique for coronary bifurcation lesions and illustrate its use using a case description. This involves placing the main vessel (MV) stent in position and a jailed balloon in the SB, inflating the SB balloon with normal pressure, subsequently inflating the MV stent at high pressure, removing the balloons and performing POT using a non-compliant balloon. The modified jailed balloon technique can shift the carina to the MV, keep the SB open, and is safe and feasible for true coronary bifurcation lesions.

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Introduction

Coronary bifurcation lesions are technically challenging, and implantation of a drug-eluting stent is associated with unfavourable long-term angiographic and clinical results. Risk stratification based on coronary anatomy from the recent DEFINITION study showed the benefit of a simpler stenting approach for simple bifurcation lesions[1]. Provisional stenting using a jailed side branch (SB) wire is the most extensively accepted simple technique and is effective for the vast majority of bifurcation lesions[2]. As a jailed wire is unable to prevent SB closure after stenting the main vessel (MV) for all lesions, the recently proposed jailed balloon technique has created a great deal of interest[3]. Similar to the jailed wire approach, the jailed balloon technique requires a small balloon to be positioned in the SB before stenting the MV. Unfortunately, the jailed balloon technique is limited in that: 1) predilating the SB is still required, which is associated with a high incidence of SB dissection; 2) it is unable to prevent SB closure in some difficult cases; and 3) it is very difficult to remove the jailed balloon in very calcified and complex settings. A schematic description of the modified jailed balloon technique is introduced in **Figure 1**, followed by a case description **(Figure 2)**.

Discussion

Percutaneous treatment of coronary bifurcation disease remains technically challenging. The optimal treatment strategy for coronary bifurcation lesions remains to be defined. Provisional stenting using a jailed wire in the SB has been widely accepted as the gold standard in the majority of simple bifurcation lesions[1,2], but is associated with the risk of SB closure after MV stent implantation. SB closure puts patients at high risk, as a significant increase of myocardial biomarkers suggests the presence of myocardial necrosis. Furthermore, the rescue procedure to restore the flow in the SB is more complex and is sometimes impossible. Currently, our understanding of SB closure after stenting the MV is the shift induced by either carina or plaque, and stent struts are usually seen in the ostium of the SB. As a result, a jailed balloon technique has been proposed by several interventionalists[3-5]. However, a jailed balloon technique is not perfect in terms of completely avoiding SB closure. In some cases it is very difficult to remove the balloon from the SB. Most importantly, removing the jailed balloon itself can cause the SB dissection. Dr H.F. Wang described a similar technique at the China Interventional Therapeutic Congress, held in Beijing in 2011. They simply opened the stent with low pressure and after removing the SB balloon, the stent balloon was used to post-dilate the stent. This perhaps pushed the carina back to the SB to obtain perfect matching between the stent and the MV, as simply delivering the stent with a single balloon inflation is almost impossible. Taken together, we introduce our modified jailed balloon technique in this schematic description.

First of all, the MV stent diameter is usually defined according to the diameter of the distal MV but in our case the stent size was chosen according to the proximal LAD trunk. As a result, the stent was well-apposed to the LAD identified by IVUS.

Next, the jailed SB balloon was inflated so as to push the carina from the SB to the MV. Then the MV stent was opened with high pressure to maintain the carina position, minimising the risk of carina or plaque shift and thereby avoiding SB compromise.

Thirdly, POT was used to achieve full apposition of the MV stent just in the proximal MV, which led to minimal pinching of the SB. At this point, a jailed SB wire was still kept in the SB, a way to prevent the further risk of acute closure by the POT approach.

Finally, the performance of final kissing balloon inflation was dependent on the residual stenosis of the ostial SB. In other words, less compromising of the SB does not require additional kissing inflation, as shown in our case. Of course, another option would be FFR-guided kissing inflation for the SB.

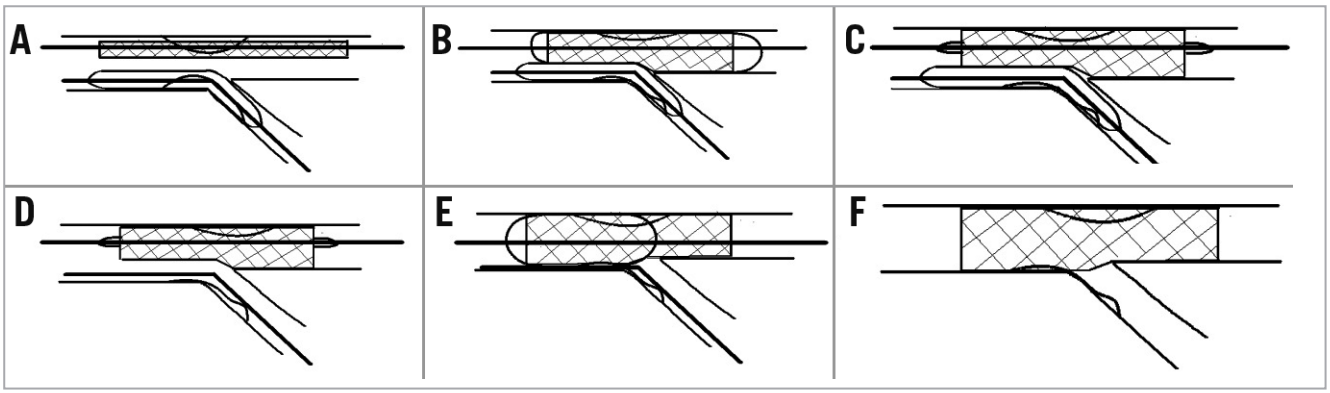

Figure 1. *Schematic description of modified jailed balloon technique. Two wires are positioned in the SB and MV, respectively. The SB balloon/vessel ratio is 1:1, the SB balloon protrudes into the MV by 0.5-1 mm, the SB balloon is inflated with normal pressure (A), and subsequently the MV stent is inflated (at a ratio of 1:1) at high pressure (B). Then, the SB balloon is kept in the SB when the MV stent is deflated (C). Next, the SB balloon is removed and the SB wire is left in position (D). Post-dilation using a non-compliant balloon (E) is performed for the proximal MV stent. Finally, kissing balloon inflation may be used when an angiographically significant ostial SB lesion remains after MV stenting (F).*

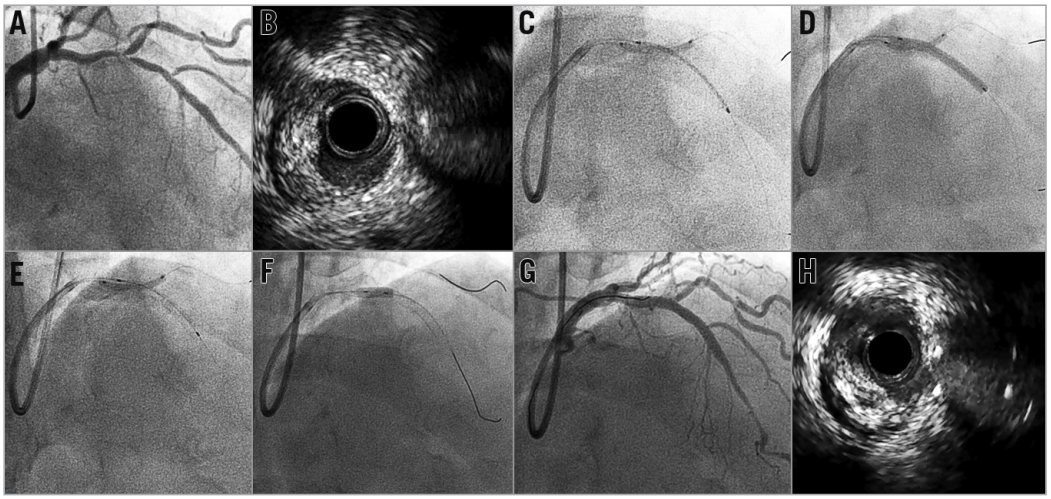

Figure 2. *Case report. The patient was a 56-year-old gentleman, who had had diabetes for four years and who had been complaining of stable angina for three months. Baseline coronary angiography (A) showed true coronary bifurcation lesions involving the left anterior descending artery (LAD) and first diagonal. Intravascular ultrasound (IVUS) confirmed the bifurcation lesions, with minimal lumen area 1.9 mm² in the LAD and 2.6 mm² in the diagonal (B), respectively. A balloon and a stent were simultaneously positioned in the SB and MV, and the SB balloon inflated with normal pressure (C). The SB balloon was kept inflated and the MV stent inflated with high pressure (D). The stent balloon was deflated first and then the SB balloon was deflated (E). After removing the SB balloon, the proximal optimisation technique (POT) was performed using a non-compliant balloon (F). The ostial SB was minimally compromised (G). IVUS found no dissection (H), and the minimal lumen area was 8.8 mm² in the LAD and 3.4 mm² in the SB. Final kissing inflation was not used for this patient.*

Conclusion

In general, our modified jailed balloon technique is safe and feasible for true coronary bifurcation lesions. Further study is required to confirm our preliminary experiences.

Impact on daily practice

Provisional stenting using a jailed wire in the SB has been widely accepted, but associated with the risk of SB closure after MV stent implantation. The rescue procedure to restore the flow in the SB is more complex and sometimes impossible. The modified jailed balloon technique is a safe and easy way to prevent SB closure after MV stent implantation for true coronary bifurcation lesions.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Chen SL, Sheiban I, Xu B, Jepson N, Paiboon C, Zhang JJ, Ye F, Sansoto T, Kwan TW, Lee M, Han YL, Lv SZ, Wen SY, Zhang Q, Wang HC, Jiang TM, Wang Y, Chen LL, Tian NL, Cao F, Qiu CG, Zhang YJ, Leon MB. Impact of the complexity of bifurcation lesions treated with drug-eluting stents: the DEFINITION study (Definitions and impact of complEx biFurcation lesIons on clinical outcomes after percutaNeous coronary IntervenTIOn using drug-eluting steNts). *JACC Cardiovasc Interv.* 2014;7:1266-76.

2. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR Jr, Spanos V, Louvard Y, Desmedt B, Di Mario C, Leon MB. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation.* 2004;109:1244-9.

3. Burzotta F, Trani C, Sianos G. Jailed balloon protection: a new technique to avoid acute side-branch occlusion during provisional stenting of bifurcated lesions. Bench test report and first clinical experience. *EuroIntervention.* 2010;5:809-13.

4. Hildick-Smith D, Lassen JF, Albiero R, Lefèvre T, Darremont O, Pan M, Ferenc M, Stankovic G, Louvard Y; European Bifurcation Club. Consensus from the 5th European Bifurcation Club meeting. *EuroIntervention.* 2010;6:34-8.

5. Catakoglu AB, Aytekin V. The Highway Technique: a new stenting technique to treat coronary bifurcation lesions. *EuroIntervention.* 2010;5:821-5.

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The effect of CD34-capturing coronary stents with abluminal sirolimus coating on endothelial coverage

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KEYWORDS

- drug-eluting stent
- in-stent restenosis
- stent thrombosis

Abstract

Aims: Drug-eluting stents (DES) reduce neointimal hyperplasia by inhibition of vascular smooth muscle cell proliferation, concomitantly inhibiting stent endothelialisation and increasing the risk for stent thrombosis. The present study compares a contemporary DES to an endothelial progenitor cell-capturing DES (COMBO stent), with regard to intimal hyperplasia and endothelial coverage.

Methods and results: Twelve New Zealand white rabbits were subjected to bilateral iliac artery stent placement. Each animal received both an everolimus-eluting stent (EES) and a COMBO stent. Four weeks after implantation, optical coherence tomography (OCT) was performed in six animals and tissue was harvested from the other six animals. Endothelial stent coverage assessed by scanning electron microscopy was significantly higher in COMBO stents than in EES (96.6±3.5% vs. 78.5±16.8%; $p<0.05$). Neointimal hyperplasia by OCT differed significantly (EES: 0.227±0.025 mm^2 vs. COMBO: 0.188±0.044 mm^2; $p<0.05$), but not by histology (EES: 0.823±0.200 mm^2 vs. COMBO: 0.891±0.312 mm^2; p=NS). No differences were observed in late loss between EES and COMBO stents (0.29±0.19 mm^2 vs. 0.29±0.16 mm^2; p=NS).

Conclusions: Endothelialisation is significantly improved in the COMBO stent with equal inhibition of intimal hyperplasia, which may reduce thrombotic events after DES implantation and allow earlier discontinuation of dual antiplatelet therapy.

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Abbreviations

BAR	balloon-to-artery ratio
BMS	bare metal stent
DES	drug-eluting stent
EC	endothelial cell
EES	everolimus-eluting stent
EPC	endothelial progenitor cell
H&E	haematoxylin and eosin
IV	intravenous
IM	intramuscular
LL	late loss
NIH	neointimal hyperplasia
NS	not significant
OCT	optical coherence tomography
PES	paclitaxel-eluting stent
sEM	scanning electron microscopy
SES	sirolimus-eluting stent
VSMC	vascular smooth muscle cell

Introduction

Cardiovascular disease remains the leading cause of death in the world with rising numbers especially in non-Western countries[1]. The most frequent treatment for coronary artery disease (CAD) is to restore coronary blood flow by percutaneous coronary intervention (PCI).

Though superior to solo balloon angioplasty[2], coronary stent implantation has two complications: in-stent restenosis and stent thrombosis[3]. In-stent restenosis is driven by the inflammatory response that occurs upon inflation of the balloon catheter to restore the lumen and the accompanying endothelial damage. This triggers vascular smooth muscle cell (VSMC) proliferation, leading to neointimal hyperplasia (NIH) and subsequent luminal narrowing. The advent of drug-eluting stents (DES) that reduce VSMC proliferation has largely solved this problem[4,5]. However, by non-selectively inhibiting endothelial cell proliferation as well, the risk for in-stent thrombosis is increased.

In particular, early stent endothelialisation reduces thrombotic complications and decreases neointima formation[6,7]. Endothelial progenitor cell (EPC) capturing stents use anti-CD34 antibody coatings to facilitate colonisation of circulating EPCs onto the stent struts. In comparison to bare metal stents (BMS) or DES, they have been shown to improve stent endothelialisation and decrease stent thrombosis in both *in vitro* and *in vivo* studies[8-11]. However, compared to DES, neointima formation and the need for target vessel revascularisation were significantly higher due to the lack of antiproliferative coatings.

It is for these reasons that the COMBO™ Dual Therapy Stent (OrbusNeich, Hong Kong) combines a luminal anti-CD34 antibody coating to improve luminal stent endothelialisation with abluminal antiproliferative drug elution from a bioresorbable polymer matrix to inhibit VSMC proliferation and intimal hyperplasia. The REMEDEE trial has shown the non-inferiority of the COMBO stent compared to paclitaxel-eluting stents (PES) with regard to angiographic in-stent late lumen loss[12] .

However, PES belong to the first-generation DES, which nowadays have been largely replaced by safer and more effective second-generation DES[13,14]. Yet, histological data regarding stent endothelialisation in combination with clinical standard optical coherence tomography (OCT) have not been reported so far. The aim of the current study was to compare these stent types in rabbits, using both histology and OCT to assess endothelial cell coverage and intimal hyperplasia.

Methods

EXPERIMENTAL DESIGN

Twelve female New Zealand white rabbits (Charles River, Chatillon-sur-Chalaronne, France; 3.5-4.0 kg) were subjected to iliac artery stenting. Two different types of stent were implanted in the left and right iliac arteries in an alternating fashion (switching sides). The COMBO stent combines a sirolimus-eluting bioresorbable coating on the abluminal side with an anti-CD34 antibody coating on the luminal side. The XIENCE PRIME® stent (Abbott Vascular, Santa Clara, CA, USA) has a conformal, everolimus-eluting permanent polymer coating with omnidirectional release of the drug.

Data acquisition and measurements were performed by a blinded observer. All animal experiments were approved by the Ethical Committee on Animal Experimentation of the University Medical Center Utrecht (Utrecht, The Netherlands) and conform to the "Guide for the care and use of laboratory animals".

ANAESTHESIA

The rabbits were fasted overnight prior to surgery. From the day before implantation until termination at 28 days, rabbits received 10 mg/kg aspirin (Aspro; Bayer, Mijdrecht, The Netherlands) daily, dissolved in 400 mL freshly prepared drinking water after closely monitoring the average water intake per day. Subcutaneous meloxicam (1 mg/kg) was given before surgery as analgesia.

Acepromazine and methadone (both 1.5 mg/kg) were injected intramuscularly for premedication. Etomidate (1.5-2 mg/kg) was injected via the ear vein, after which rabbits were intubated and ventilated with a mixture of oxygen/air (1:2) and 1.5% isofluorane. Sufentanil (1 µg/kg/hr) was continuously administered intravenously.

STENT IMPLANTATION

Heparin (150 IU/kg IV) was injected prior to cannulation of the left carotid artery. A 4 Fr sheath was inserted through which a 3 Fr Fogarty balloon (Edwards Lifesciences, Irvine, CA, USA) was inserted. After inflation, the balloon was retracted through both iliac arteries twice for approximately 4 cm to induce endothelial denudation. Afterwards, the stents (3.0×15.0 mm) were implanted in the iliac artery. Nominal pressure was applied to inflate the balloon to a diameter of 3.0 mm, followed by a second angiogram.

QUANTITATIVE ANGIOGRAPHY

Angiograms of the iliac arteries were obtained before and after stent implantation and at termination. Luminal diameters were measured using ImageJ. Calibration was performed on the guiding catheter in the same image. The balloon-to-artery ratio (BAR) was

defined as the luminal diameter after stenting/luminal diameter before stenting. Late loss was defined as the difference between the angiographic diameter directly after stenting and the angiographic diameter at 28 days of follow-up.

OPTICAL COHERENCE TOMOGRAPHY (OCT)

To avoid detection of iatrogenic endothelial damage in the scanning electron microscopy (sEM), OCT was performed in six of the 12 rabbits. Four weeks after implantation, the rabbits were heparinised with 150 IU/kg prior to cannulation of the right carotid artery. A 6.5 Fr SheathLess Eaucath multipurpose guiding catheter (ASAHI Intecc, Aichi, Japan) was inserted and selectively placed in the iliac artery. A C7 Dragonfly™ Duo imaging catheter (St. Jude Medical, St. Paul, MN, USA) was positioned with the proximal and distal markers on both sides of the stent. Pure contrast agent was injected through the guiding catheter for temporary removal of signal-distorting blood flow from the iliac artery. A manually triggered pullback was performed using the OCT ILUMIEN™ OPTIS™ OCT system (St. Jude Medical). Image analysis was performed using dedicated software (Curad B.V., Amsterdam, The Netherlands)[15], including automated contour detection algorithms. For each cross-sectional frame (n=10/mm; n=150/stent), the lumen contour and the stent contour were automatically delineated and manually corrected where needed. Neointima formation was defined as the difference between stent area and luminal area, expressed both as mm^2 and as a percentage of the total stent area (i.e., two separate outcome measurements). All 150 cross-sectional frames were used to calculate the average neointimal area and neointimal area as a percentage of total stent area. These were then used to calculate the mean and standard deviation for each group (EES or COMBO). Stent struts were classified into three categories: embedded, if buried in the vessel wall; protruding, if protruding in the lumen but still in contact with the vessel wall; and malapposed, if protruding and not in contact with the vessel wall. For the latter, the distance between stent strut and luminal contour was automatically measured and classified malapposed if greater than its strut thickness (EES: 88 µm; COMBO: 104 µm).

TISSUE PREPARATION, HISTOLOGICAL ANALYSIS AND SCANNING ELECTRON MICROSCOPY

The remaining six rabbits were also sacrificed after 28 days. After heparinisation (1,000 IU/kg IV), catheters were placed in the aorta and caval vein under general anaesthesia as described above. An angiogram was performed to visualise the stents and surrounding arteries. After sacrifice, the aorta was perfused with Ringer's lactate to remove blood cells from the stents, followed by pressure fixation with 4% formalin. Subsequently, the stents and adjacent arteries were dissected. The stent was cut axially so that one part comprised one third of the stent and the other part comprised two thirds of the stent.

The larger part was used for morphometric and inflammation analyses. After an additional formalin fixation for at least 72 hours, the stents were embedded in methyl methacrylate for histological analysis. Sections were cut with a diamond-coated saw at three levels. A haematoxylin and eosin (H&E) staining was performed for morphometric analysis. Luminal contours and internal elastic laminae (IEL) were traced manually using pictures made at a 20x magnification using ImageJ. The amount of neointima was calculated by subtracting the luminal area from the IEL area. Inflammation was evaluated as previously described[16]. At 40x magnification, each stent strut in a tissue section was scored for inflammation as follows: 0= no inflammatory cells surrounding the strut; 1= very light, non-circumferential cellular infiltrate surrounding the strut; 2= localised moderate to dense cellular aggregate surrounding the strut non-circumferentially with or without slight expansion into the neointima not in direct contact with the strut; 3= circumferential dense cellular infiltrate of the strut with extensive expansion into the neointima not in direct contact with the stent strut. The scores of the individual stent struts were averaged per tissue section and tissue sections were averaged per stent. The averages of all the stents in one group (EES or COMBO) were used to calculate the means and standard deviations.

The smaller part was cut longitudinally and used for sEM. Stents were fixed in a 1.5% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.2). A secondary fixation using 1% osmium tetroxide in 0.1 M cacodylate buffer was performed, followed by dehydration. Liquid was removed from the samples using critical point drying. The samples were sprayed with platinum and analysed using sEM (Phenom Desktop SEM; Phenom-World BV, Eindhoven, The Netherlands). Of each single stent, eight to 12 images at 360x magnification were made. Stent strut contours could easily be visualised as slightly elevated areas in the image. In each image, the covered area of the stent strut contour was measured as well as the total area of the stent strut contour, using ImageJ. The covered area was then expressed as a percentage of the total stent strut area. In each animal, the individual scores (i.e., percentages) of these eight to 12 images were averaged per rabbit. These averages were then used to calculate the mean and standard deviation for each group (EES or COMBO).

Statistical analysis

Values are presented as mean±standard deviation (SD). Data distribution was evaluated for normality using the Shapiro-Wilk test. All data were normally distributed and a paired-samples t-test was performed to test for significant differences ($p<0.05$). Statistical analyses were performed using SPSS software, Version 21 (IBM Corp., Armonk, NY, USA).

Results

QUANTITATIVE ANGIOGRAPHY

Angiograms were taken before, directly after stent implantation and at 28-day follow-up **(Figure 1)**. No differences in vessel diameters, BAR or late loss at four-week follow-up were observed **(Table 1)**.

STENT ENDOTHELIALISATION

Figure 2A-Figure 2D show overview images of the EES and COMBO stent by sEM. Four weeks after stent implantation,

Table 1. Angiography measurements at baseline and 28-day follow-up.

Stent	Before stent placement, diameter (mm)	After stent placement, diameter (mm)	B:A ratio	Follow-up diameter (mm)	Late loss
EES (n=12)	2.14±0.23	2.99±0.18	1.42±0.19	2.70±0.20	0.29±0.19
COMBO (n=12)	2.15±0.21	2.91±0.18	1.37±0.16	2.62±0.16	0.29±0.16

Values are represented as mean±standard deviation (SD). No significant differences were observed between the two groups. B:A ratio: balloon-to-artery ratio

the COMBO stent showed visually improved strut coverage at intermediate (**Figure 2A-Figure 2D**, upper right panels) and higher magnification (**Figure 2A-Figure 2D**, lower right panels). Quantification of strut coverage confirmed a lower endothelial coverage in the EES and a significantly improved endothelial coverage in the COMBO stent (78.5±16.8% vs. 96.6±3.5%; p=0.038, **Figure 2E**).

NEOINTIMAL HYPERPLASIA AND INFLAMMATION

Four weeks after stent implantation, intravascular OCT was performed in six of the 12 animals. All images per stent were semi-automatically analysed and luminal and stent areas were quantified **(Figure 3A, Figure 3B)**. Absolute neointimal area by OCT analysis was significantly higher in EES compared to COMBO stents (0.227±0.025 mm^2 vs. 0.188±0.044 mm^2; p=0.013; **Figure 3C**), but did not differ when expressed as a percentage of the total stent area (EES: 3.78±0.45% vs. COMBO: 3.49±0.95%; p=NS; **Figure 3D**). The percentage of protruding stent struts as a measure of the vascular healing response did not differ significantly between the two stent types (EES: 35.1±14.7% vs. COMBO: 29.7±17.1%; p=NS; **Figure 3E**).

Neointimal hyperplasia was also assessed in H&E stained tissue sections **(Figure 4A, Figure 4B)**. In contrast to OCT, no significant differences were observed with respect to neointima formation between EES and COMBO stents (0.823±0.200 mm^2 vs. 0.891±0.312 mm^2; p=NS; **Figure 4C**). This may be due to the higher accuracy of histology or the lower number of analysed sections compared to OCT.

Finally, H&E stained tissue sections were evaluated for inflammation **(Figure 4D, Figure 4E)**. In the majority of stent struts, cellular infiltrate was absent or only minimally present. Hence, average inflammatory scores did not differ significantly between EES and COMBO stents (0.530±0.380 vs. 0.435±0.295; p=NS; **Figure 4F**).

Discussion

The significant reduction of in-stent restenosis in DES that we have witnessed so far has come at the expense of reduced endothelialisation and the corresponding higher risk for stent thrombosis[8-11]. To overcome these drawbacks, different approaches have been shown to be promising. Amongst these are using a sole abluminal antiproliferative drug coating[17], seeding stents with human trophoblastic endovascular progenitor cells[18] and using anti-CD34 for endothelial progenitor cell (EPC) capturing[7]. It is this latter approach that is investigated in the current study, comparing an abluminal sirolimus-eluting stent with luminal anti-CD34 coating (COMBO stent) to a second-generation everolimus-eluting stent (EES) with respect to endothelial cell coverage and neointimal hyperplasia. At 28 days, the COMBO stent showed significantly improved endothelial coverage by sEM compared to the EES.

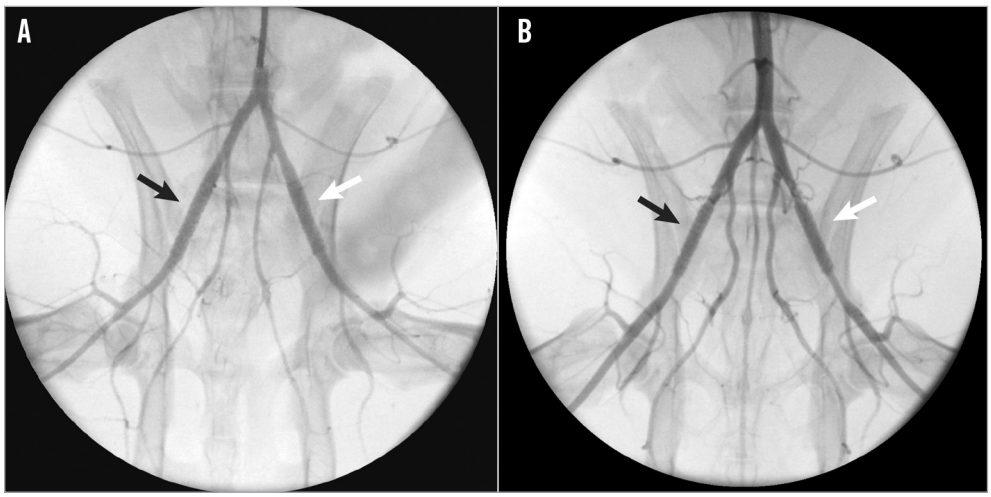

Figure 1. *Angiographic images. Angiograms obtained directly after implantation (A) and after 28 days of follow-up (B). Stent location is indicated by arrows, black for the everolimus-eluting stent and white for the COMBO stent.*

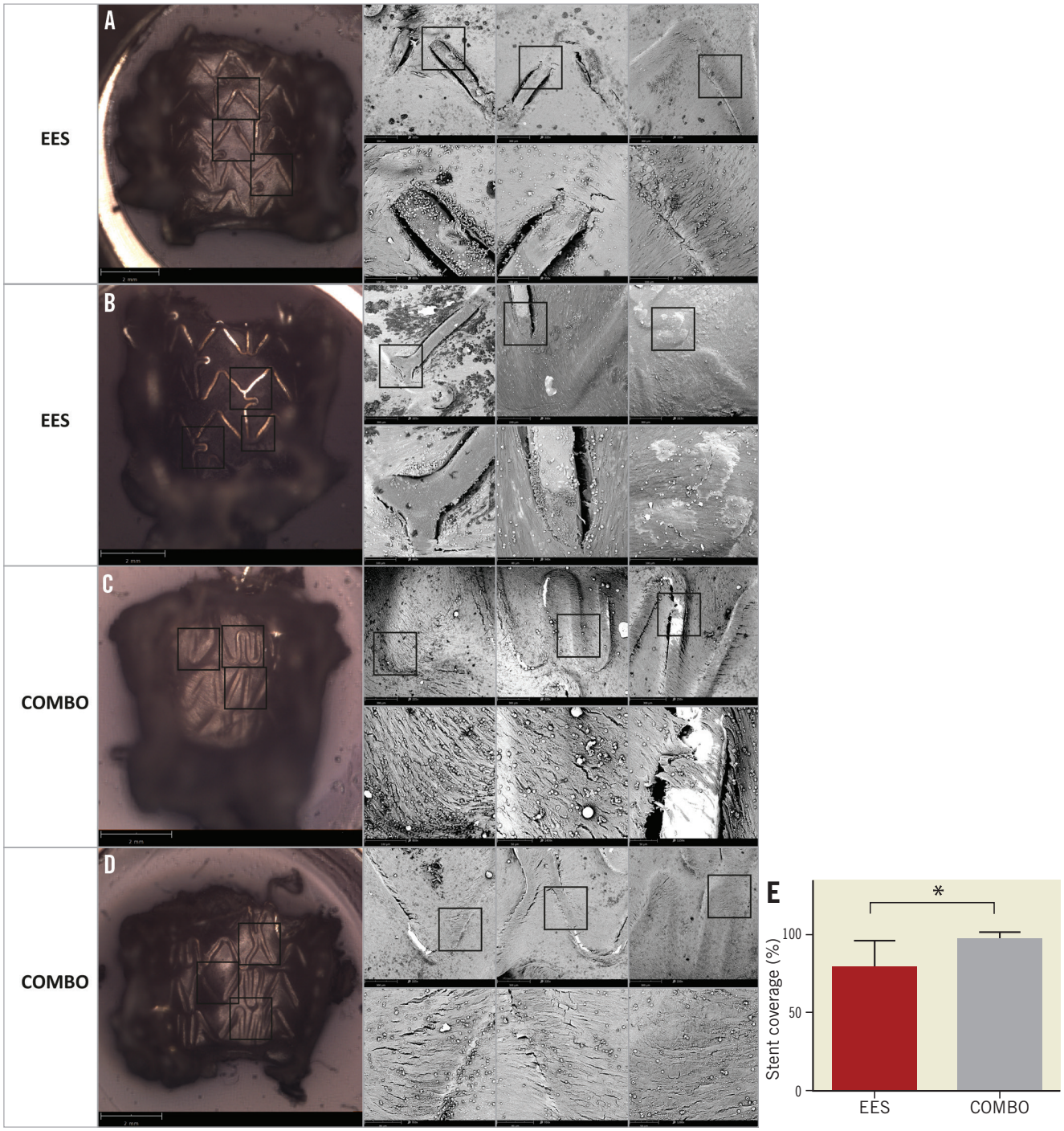

Figure 2. *Assessment of stent endothelialisation using scanning electron microscopy (sEM). Scanning electron microscopy imaging of the luminal surface of the everolimus-eluting stent (EES) (A, B) and the COMBO stent (C, D); intermediate (upper right panels) and high magnification (lower right panels). At high magnification, the COMBO stent showed confluent stent coverage, whereas the EES struts were not completely endothelialised. Quantification of stent strut coverage showed a significantly improved endothelialisation of the COMBO stent compared to the EES (E). *: p<0.05*

DES are known to interfere with endothelial cell proliferation and function, leading to delayed strut endothelialisation. Strut coverage in our study was decreased in the EES to a comparable degree to that previously reported[19]. In contrast, the COMBO stent showed almost complete endothelial coverage. This finding indicates that the anti-CD34 coating accelerates stent coverage, even in the presence of an antiproliferative component, similar to stents without antiproliferative coatings[20]. As stent endothelialisation is a major determinant of stent thrombosis[5], the COMBO stent might therefore reduce stent-related thrombotic events.

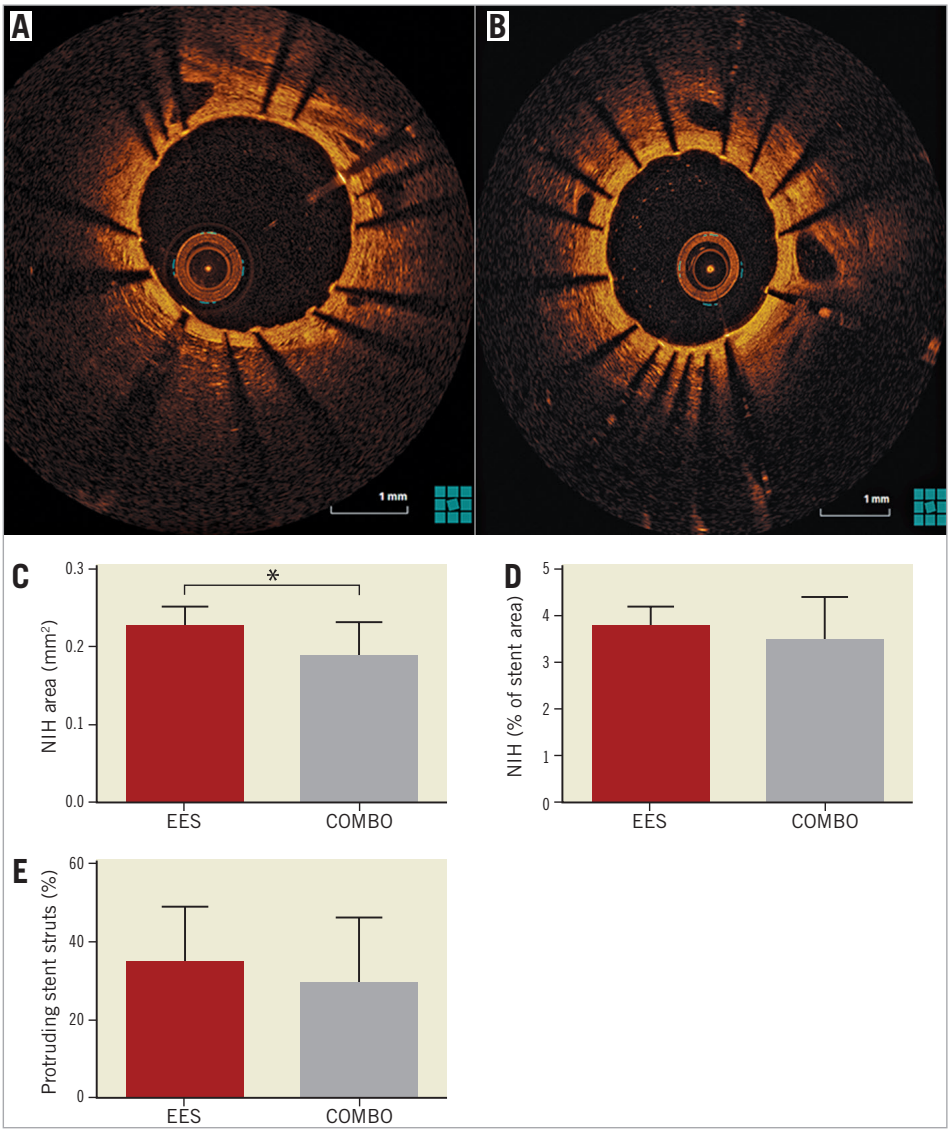

Figure 3. *Assessment of neointima formation by optical coherence tomography (OCT). Representative optical coherence tomography images of the everolimus-eluting stent (EES) (A) and the COMBO stent (B). The difference between stent and lumen contour represents neointima formation, which was significantly decreased in the COMBO stent (C). Neointima formation expressed as a percentage of the total stent area did not differ between both stent types (D). Classification of stent struts as being buried in the vessel wall (embedded) or protruding into the lumen (protruding) was not different between both groups (E). *: p<0.05*

In our previous findings with the anti-CD34 capturing stents (without a drug-eluting component) in comparison with BMS we found superior endothelial coverage with the anti-CD34 stent at seven days (82.21% vs. 77.92%)[21]. Our current results with the COMBO stent (96.6% endothelial coverage at 28 days) are largely in line with the earlier findings, suggesting that the abluminal elution of the antiproliferative drug has no negative effect on stent endothelialisation.

Neointima formation was significantly higher in EES compared to COMBO stents when measured by OCT, whereas histologic measurements did not show significant differences. In histological sections, the internal elastic membrane (IEM) can be easily detected and very accurately traced. In OCT as the clinical standard, the stent strut contour is semi-automatically detected using the endoluminal stent strut reflections. This method excludes the abluminal part of the stent struts and corresponding neointimal area. In situations with very low amounts of neointima as present in the current study, OCT is therefore less accurate than histology. However, the differences between both techniques are very small and therefore clinically not significant.

Previous studies have shown similar underestimation of neointima formation in OCT compared to histology[22]. Moreover, our current results are in line with previous experiments, comparing

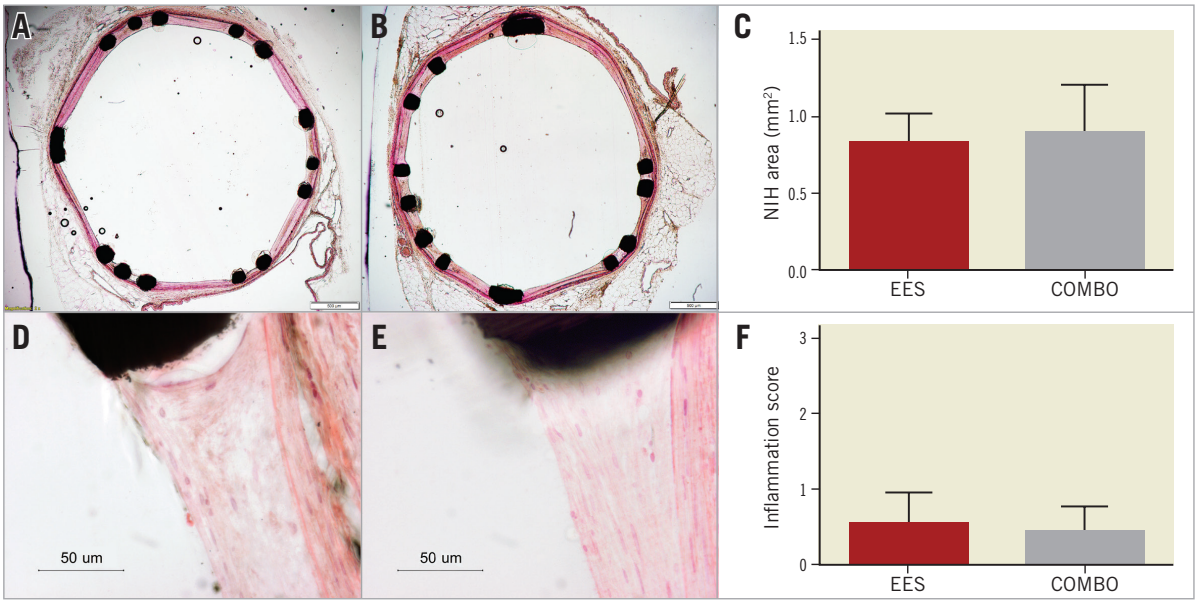

Figure 4. *Neointima formation assessment by HE-stained tissue sections. Representative images of tissue sections of the everolimus-eluting stent (A) and the COMBO stent (B). The difference between internal elastic membrane (IEL) and lumen area represents neointima formation, which did not differ between the two groups (C). Representative high magnification images of both everolimus-eluting (D) and COMBO stent (E) with minor inflammatory cell deposition near the stent strut. Quantification of inflammation on a 0–3 scale confirmed no differences between the two groups (F).*

different DES types with BMS. While BMS showed significantly more neointima formation compared to any DES, there was no difference between DES types[19,23]. The comparable neointimal areas found with EES compared to the COMBO stent suggest that the effect of the improved endothelialisation on VSMC mobilisation is relatively small in comparison with the inhibitory action of the antiproliferative drug. Inflammatory cell deposition was also not affected by accelerated endothelialisation.

Limitations

Because two thirds of each stent was used for morphometric analysis (H&E), we were unable to describe the effect of the COMBO stents on endothelialisation in the middle part of the stent. In comparison to most of the contemporary preclinical studies that assessed the entire stent for endothelialisation[10,18,23], the assessment of only one third of the stent limits its translation to stent re-endothelialisation in the middle part of the stent. In addition, though the COMBO stent can be expected to reduce neointima formation both by accelerated endothelialisation[24] and by the elution of an antiproliferative drug, our current study was not designed to discriminate between the relative effects of these mechanisms. Moreover, since sEM and histology data on one side and OCT data on the other side were not assessed in the same rabbits, the present study does not allow direct comparison of stent coverage and neointima formation. Comparisons and associations between OCT and microscopy (i.e., histology or sEM) should therefore be interpreted with caution.

Conclusion

In summary, when compared to the EES, the COMBO stent shows improved endothelialisation and equal inhibition of neointimal hyperplasia in rabbits at 28 days post PCI. Large-scale clinical trials are warranted to show how the accelerated endothelialisation in the COMBO stent translates into clinical benefits in terms of reduced stent thrombosis and neo-atherosclerosis as well as the ability to reduce the duration of antiplatelet therapies after PCI.

Impact on daily practice

This study shows that, compared to the everolimus-eluting stent, the COMBO stent shows improved endothelialisation and equal inhibition of neointimal hyperplasia in rabbits at 28 days post PCI. As stent endothelialisation is an important determinant of stent thrombosis, this finding increases the evidence for preferred use of endothelial cell-capturing DES in patients with an increased risk for stent thrombosis or with contraindications for dual antiplatelet therapy.

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Conflict of interest statement

E. Ligtenberg and S. Rowland are employees of OrbusNeich Medical. The other authors have no other relevant affiliations or financial involvement with any organisation or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

1. WHO. The top ten causes of death, 2000-2012. 2012. Available at: http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed April 11, 2015.

2. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med.* 1994;331:496-501.

3. Khan W, Farah S, Domb AJ. Drug eluting stents: developments and current status. *J Control Release.* 2012;161:703-12.

4. Nakazawa G, Finn AV, Virmani R. Vascular pathology of drug-eluting stents. *Herz.* 2007;32:274-80.

5. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.

6. Aoki J, Serruys PW, van Beusekom H, Ong AT, McFadden EP, Sianos G, van der Giessen WJ, Regar E, de Feyter PJ, Davis HR, Rowland S, Kutryk MJ. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry. *J Am Coll Cardiol.* 2005;45:1574-9.

7. Rotmans JI, Heyligers JM, Verhagen HJ, Velema E, Nagtegaal MM, de Kleijn DP, de Groot FG, Stroes ES, Pasterkamp G. In vivo cell seeding with anti-CD34 antibodies successfully accelerates endothelialization but stimulates intimal hyperplasia in porcine arteriovenous expanded polytetrafluoroethylene grafts. *Circulation.* 2005;112:12-8.

8. Beijk MA, Klomp M, Verouden NJ, van Geloven N, Koch KT, Henriques JP, Baan J, Vis MM, Scheunhage E, Piek JJ, Tijssen JG, de Winter RJ. Genous endothelial progenitor cell capturing stent vs. the Taxus Liberte stent in patients with de novo coronary lesions with a high-risk of coronary restenosis: a randomized, single-centre, pilot study. *Eur Heart J.* 2010;31:1055-64.

9. Damman P, Klomp M, Silber S, Beijk MA, Ribeiro EE, Suryapranata H, Wójcik J, Sim KH, Tijssen JG, de Winter RJ; e-Healing investigators. Duration of dual antiplatelet therapy and outcomes after coronary stenting with the Genous™ bio-engineered R stent™ in patients from the e-HEALING registry. *Catheter Cardiovasc Interv.* 2012;79:243-52.

10. Nakazawa G, Granada JF, Alviar CL, Tellez A, Kaluza GL, Guilhermier MY, Parker S, Rowland SM, Kolodgie FD, Leon MB, Virmani R. Anti-CD34 antibodies immobilized on the surface of sirolimus-eluting stents enhance stent endothelialization. *JACC Cardiovasc Interv.* 2010;3:68-75.

11. van Beusekom HM, Ertaş G, Sorop O, Serruys PW, van der Giessen WJ. The Genous™ endothelial progenitor cell capture stent accelerates stent re-endothelialization but does not affect intimal hyperplasia in porcine coronary arteries. *Catheter Cardiovasc Interv.* 2012;79:231-42.

12. Haude M, Lee SW, Worthley SG, Silber S, Verheye S, Erbs S, Rosli MA, Botelho R, Meredith I, Sim KH, Stella PR, Tan HC, Whitbourn R, Thambar S, Abizaid A, Koh TH, Den Heijer P, Parise H, Cristea E, Maehara A, Mehran R. The REMEDEE trial: a randomized comparison of a combination sirolimus-eluting endothelial progenitor cell capture stent with a paclitaxel-eluting stent. *JACC Cardiovasc Interv.* 2013;6:334-43.

13. Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goedhart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet.* 2010;375:201-9.

14. Mahmoudi M, Delhaye C, Wakabayashi K, Ben-Dor I, Gonzalez MA, Maluenda G, Gaglia MA Jr, Torguson R, Xue Z, Suddath WO, Satler LF, Kent KM, Pichard AD, Waksman R. Outcomes after unrestricted use of everolimus-eluting stent compared to paclitaxel- and sirolimus-eluting stents. *Am J Cardiol.* 2011;107:1757-62.

15. Belkacemi A, Agostoni P, Nathoe HM, Voskuil M, Shao C, Van Belle E, Wildbergh T, Politi L, Doevendans PA, Sangiorgi GM, Stella PR. First results of the DEB-AMI (drug eluting balloon in acute ST-segment elevation myocardial infarction) trial: a multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in primary percutaneous coronary intervention with 6-month angiographic, intravascular, functional, and clinical outcomes. *J Am Coll Cardiol.* 2012;59:2327-37.

16. Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. *J Am Coll Cardiol.* 1998;31:224-30.

17. Zhang H, Deng W, Wang X, Wang S, Ge J, Toft E. Solely abluminal drug release from coronary stents could possibly improve reendothelialization. *Catheter Cardiovasc Interv.* 2013 Dec 10. [Epub ahead of print]

18. Raina T, Iqbal J, Arnold N, Moore H, Aflatoonian B, Walsh J, Whitehouse S, AI-Lamee K, Francis S, Gunn J. Coronary stents seeded with human trophoblastic endovascular progenitor cells show accelerated strut coverage without excessive neointimal proliferation in a porcine model. *EuroIntervention.* 2014;10:709-16.

19. Steigerwald K, Ballke S, Quee SC, Byrne RA, Vorpahl M, Vogeser M, Kolodgie F, Virmani R, Joner M. Vascular healing in drug-eluting stents: differential drug-associated response of limus-eluting stents in a preclinical model of stent implantation. *EuroIntervention.* 2012;8:752-9.

20. Soucy NV, Feyging JM, Tunstall R, Casey MA, Pennington DE, Huibregtse BA, Barry JJ. Strut tissue coverage and endothelial cell coverage: a comparison between bare metal stent platforms and platinum chromium stents with and without everolimus-eluting coating. *EuroIntervention.* 2010;6:630-7.

21. Tersteeg C, Hoefer IE, Ligtenberg E, Rowland S, Mak-Nienhuis EM, Balang V, Jansen MS, Velema E, de Groot PG, Roest M, Pasterkamp G. Fibronectin/fibrinogen/tropoelastin on a stent to promote CD34+ cell growth does not reduce neointima formation. *Interventional Cardiology.* 2013;5:359-67.

22. Murata A, Wallace-Bradley D, Tellez A, Alviar C, Aboodi M, Sheehy A, Coleman L, Perkins L, Nakazawa G, Mintz G, Kaluza GL, Virmani R, Granada JF. Accuracy of optical coherence tomography in the evaluation of neointimal coverage after stent implantation. *JACC Cardiovasc Imaging.* 2010;3:76-84.

23. Granada JF, Inami S, Aboodi MS, Tellez A, Milewski K, Wallace-Bradley D, Parker S, Rowland S, Nakazawa G, Vorpahl M, Kolodgie FD, Kaluza GL, Leon MB, Virmani R. Development of a novel prohealing stent designed to deliver sirolimus from a biodegradable abluminal matrix. *Circ Cardiovasc Interv.* 2010;3:257-66.

24. Kipshidze N, Dangas G, Tsapenko M, Moses J, Leon MB, Kutryk M, Serruys P. Role of the endothelium in modulating neointimal formation: vasculoprotective approaches to attenuate restenosis after percutaneous coronary interventions. *J Am Coll Cardiol.* 2004;44:733-9.

Serial observation of a calcified nodule by optical coherence tomography

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This paper also includes supplementary data published online at: www.asiaintervention.org

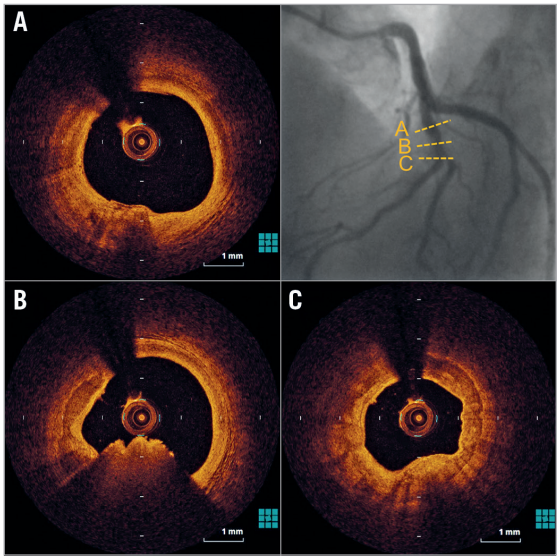

Figure 1.

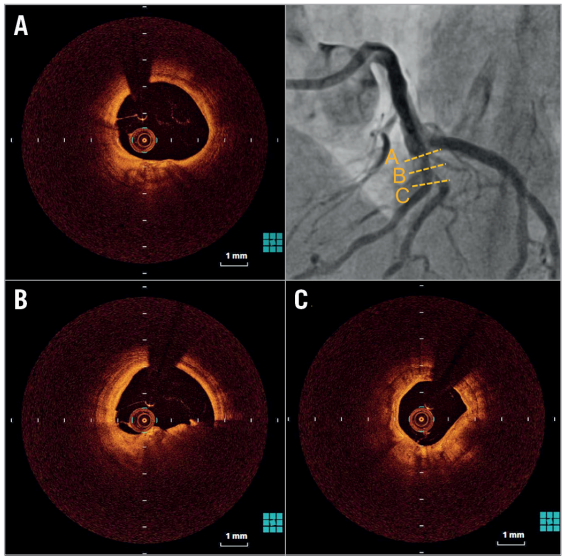

Figure 2.

The three most common underlying mechanisms of acute coronary syndrome (ACS) are believed to be plaque rupture, plaque erosion and, least common, a calcified nodule. Although treatment of ACS mainly consists of catheter-based reperfusion using a coronary stent, it remains under discussion whether deployment of a coronary stent is necessary for a culprit calcified nodule, particularly when coronary flow is preserved.

A 75-year-old man with ST-elevation myocardial infarction (STEMI) was referred to our hospital. He had a history of hypertension and dyslipidaemia. Emergency coronary angiography revealed a moderately stenotic lesion in the mid left anterior descending coronary artery (LAD) with a filling defect **(Moving image 1)**. Protrusion of calcium with an overlying thrombus was observed by optical coherence tomography (OCT), but neither plaque rupture nor erosion was detected **(Figure 1, Moving image 2)**. The diagnosis of STEMI caused by a calcified nodule was made. We avoided coronary stent deployment and initiated dual antiplatelet therapy (DAPT) because the coronary flow was preserved. Follow-up CAG three months later showed mild stenosis in the mid LAD **(Moving image 3)** and OCT revealed a residual thrombus at the same site **(Figure 2, Moving image 4)**. We then decided to treat the lesion with a coronary stent **(Moving image 5)**, since the thrombus had persisted, despite three months of DAPT.

Calcified nodules are characterised by disruptive nodular calcifications protruding into the lumen and known to be the cause of coronary thrombosis. Because the pathophysiological process of a calcified nodule is different from that of plaque rupture or erosion, tailored treatment is required when this morphology is observed at a culprit lesion. In our case, we initially tried to treat this calcified nodule with DAPT, but, as a result, avoiding stent implantation failed to obtain the satisfactory morphological outcome and we finally implanted a coronary stent. However, it is controversial whether this decision was correct because there is no evidence concerning the treatment of calcified lesions with persistent thrombus resistant to DAPT.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Supplementary data

The legends of the **Moving images** can be found in the online version of this article.

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Chest pain with a blue hand: simultaneous coronary and left subclavian artery thrombosis

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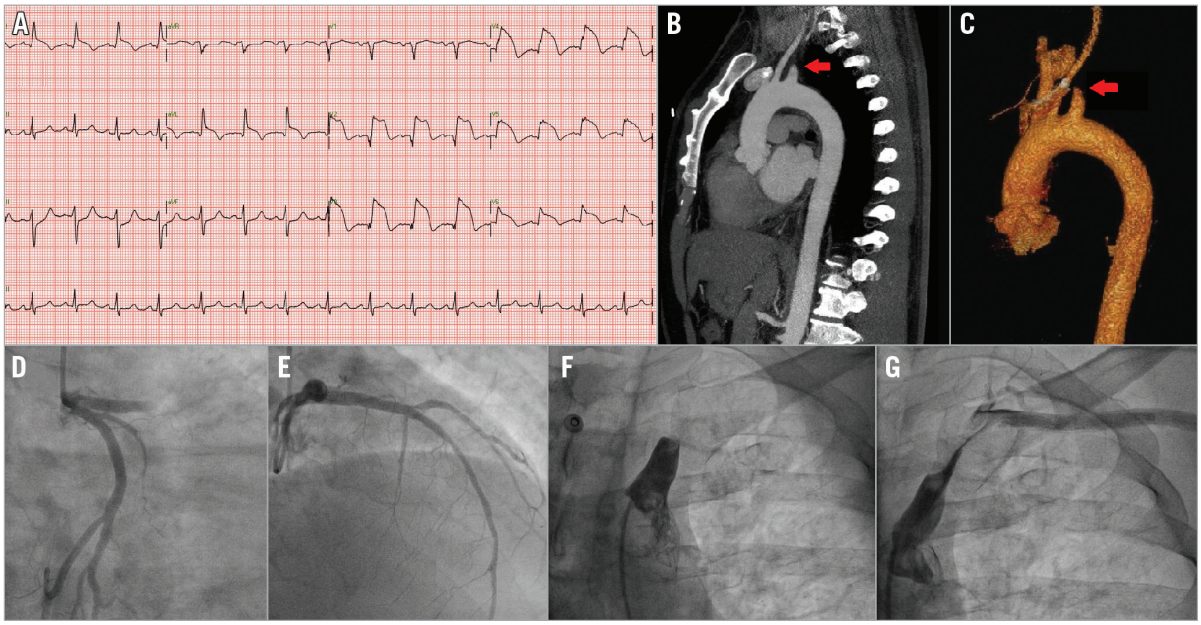
This paper also includes supplementary data published online at: www.asiaintervention.org



Simultaneous dual territory ischaemia is uncommon but, if misdiagnosed, can lead to delay in appropriate treatment. A middle-aged hypertensive male presented with acute chest pain and simultaneous left hand discolouration and coldness. Electrocardiography showed anterolateral ST-elevation **(Panel A)**. Left upper limb examination revealed absent pulses, systolic blood pressure 50 mmHg less than the right and a cyanosed hand. An urgent CT aortogram excluded aortic dissection and revealed acute proximal left subclavian artery (LSA) occlusion **(Panel B, Panel C)**. Successful primary PCI was performed to the proximal left anterior descending artery **(Panel D, Panel E, Moving image 1, Moving image 2)**. LSA angiography confirmed proximal thrombosis **(Panel F, Moving image 3)**, and aspiration thrombectomy achieved partial re-canalisation **(Panel G, Moving image 4)**. Limb ischaemia steadily improved and surgery was deferred. Echocardiography and cardiac MRI did not reveal intracardiac thrombus. The patient was discharged on warfarin and dual antiplatelet therapy. Six weeks later, an ultrasound scan showed LSA patency with 50% residual stenosis.

Acute upper limb ischaemia with STEMI necessitates urgent exclusion of aortic dissection, which mandates completely different management. Subclavian artery thrombosis causing simultaneous acute myocardial infarction is uncommon and previously reported only in patients after coronary bypass grafting with the internal mammary artery. In our case, simultaneous dual vessel embolism or simultaneous plaque rupture, although rare, could explain the double occlusion. More likely, the patient had suffered an acute STEMI leading to rapid intracardiac clot formation and embolisation to the LSA. Early cardioembolism following MI is a recognised phenomenon and must be considered in patients presenting with simultaneous acute MI and non-coronary ischaemia.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Supplementary data

Moving image 1. Coronary angiography showing acute occlusion of the proximal LAD.

Moving image 2. Coronary angiography after percutaneous coronary intervention and stenting of the LAD.

Moving image 3. Angiography showing acute occlusion of the proximal left subclavian artery (LSA).

Moving image 4. Angiography after aspiration thrombectomy of the LSA.

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How should I treat a post-CABG patient who presents with myocardial infarction within two months of surgery?

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Invited experts: Leonardus van der Pijl[2], MD; Pieter Kappetein[2], MD, PhD; Marie-Claude Morice[3]*, MD, FESC, FACC*
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This paper also includes supplementary data published online at: www.asiaintervention.org

CASE SUMMARY

BACKGROUND: A 78-year-old diabetic male with chronic stable angina. He had undergone CABG about three months previously. Recently he developed severe retrosternal chest pain of four hours duration with subsequent angina and dyspnoea on minimal exertion.

INVESTIGATION: electrocardiography, echocardiography, coronary angiography.

DIAGNOSIS: Post-CABG myocardial infarction, predominantly due to tight stenosis of the SVG to RCA.

MANAGEMENT: PCI vs. repeat CABG, and PCI to native vessels vs. PCI to graft vessels was discussed by the Heart Team. PCI to the SVG to RCA was carried out.

KEYWORDS: embolic protection device, graft vessel PCI, myocardial infarction, post-CABG, SVG stenosis

PRESENTATION OF THE CASE

A 78-year-old diabetic male with chronic stable angina had undergone a coronary arterial angiogram four months before. He was diagnosed as having triple-vessel disease and had undergone CABG about three months previously. One arterial (left internal mammary artery [LIMA] to left anterior descending [LAD]) and three venous grafts (to the diagonal, obtuse marginal [OM] and right coronary artery [RCA]) were used for CABG. He had no other comorbid conditions. About 15 days before, he developed severe retrosternal chest pain at rest lasting for four hours and since then was having angina and dyspnoea on minimal exertion. His electrocardiogram showed new Q-waves with T-wave inversion in the inferior leads, and echocardiography showed new regional wall motion abnormality (RWMA) in the inferior wall of the left ventricle. We then carried out a coronary arterial angiogram of the native and graft vessels **(Figure 1-Figure 6, Moving image 1-Moving image 4)** which showed a proximal LAD 95-99% lesion, proximal RCA 100%, proximal OM1 50% lesion, proximal to mid saphenous vein graft (SVG) to RCA long segment lesion 95% (TIMI 2 flow), variable degrees of stenosis of the other graft-native vessel anastomotic points.

Should we go for repeat revascularisation or keep the patient only on medical management?

If revascularisation is planned, considering the type of lesion, should we plan for redo CABG or PCI?

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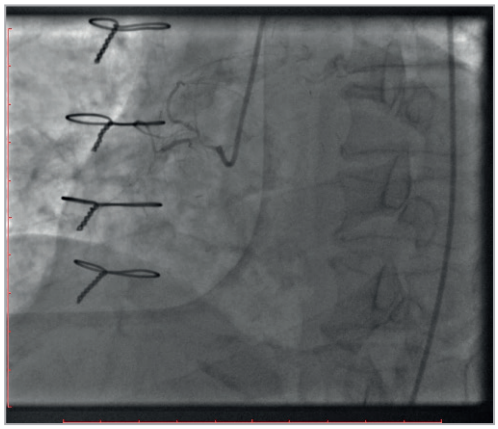

Figure 1. *Left anterior oblique (LAO) view of the RCA.*

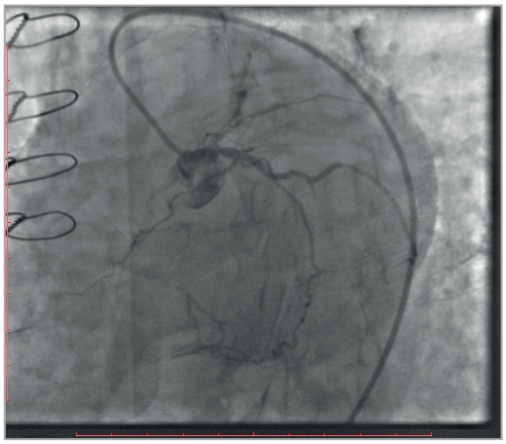

Figure 2. *LAO view of the left coronary arteries.*

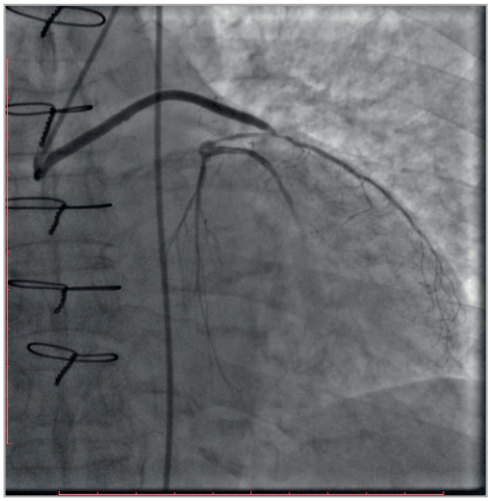

Figure 3. *LAO caudal view of the venous graft to diagonal.*

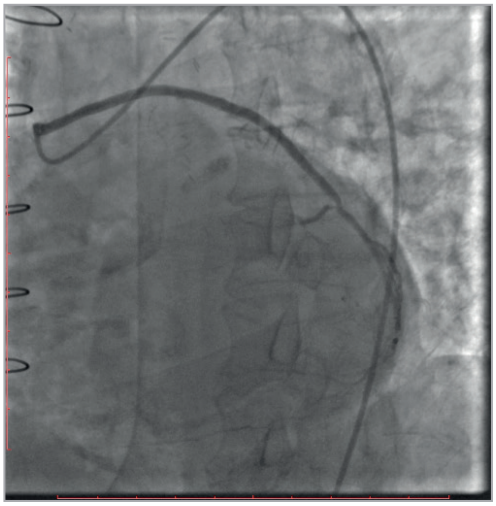

Figure 4. *LAO caudal view of the venous graft to obtuse marginal (OM).*

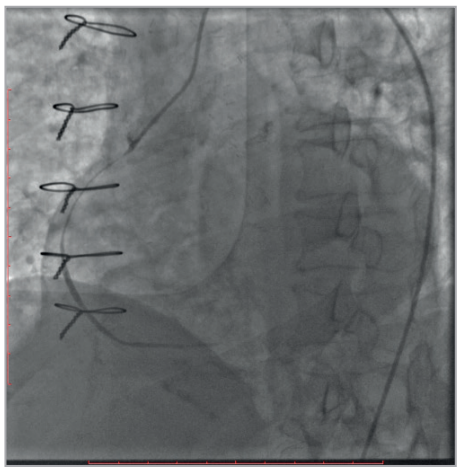

Figure 5. *LAO view of the SVG to RCA.*

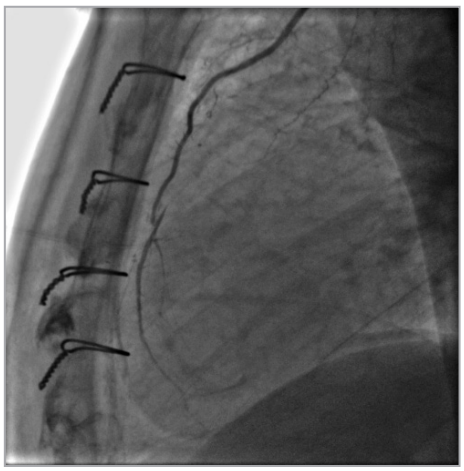

Figure 6. *Lateral view of the LIMA to LAD.*

If we plan for PCI, should we even attempt native vessel PCI of the RCA in this patient or should we directly plan for PCI to the SVG to RCA?

Should we also attempt PCI of the other grafts which are showing variable degrees of stenosis at the graft-native vessel anastomosis points?

AsiaIntervention 2016;2:143-148

How would I treat?

THE INVITED EXPERTS' OPINION

Leonardus van der Pijl[2], MD; Pieter Kappetein[2]*, MD, PhD

2. Department of Cardio-thoracic surgery, Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

The following case is compelling, as well as challenging. A 78-year-old male who had undergone coronary artery bypass grafting (CABG) three months earlier presented at the author's department with recurrent angina and dyspnoea on minimal exertion. Discussing potential clinical management plans, the author faced several clinical scenarios.

The option of repeat revascularisation or medical management should be discussed in a Heart Team meeting with an interventional cardiologist and a cardiac surgeon[1,2]. This patient was also discussed by our Heart Team. The information that is needed before a decision can be taken comprises an ECG, echocardiogram, and the coronary angiogram (CAG) from before the CABG took place. Furthermore, a postoperative CAG with visualisation of the anastomoses in different directions is critical. The description of the current ECG and echocardiogram suggests that an inferior myocardial infarction (MI) has already occurred. The echocardiogram showed regional wall motion abnormality (RWMA). Using non-invasive cardiac imaging we would investigate the presence of any viable myocardium[2-4]. In case this is present, repeat revascularisation would be the first choice of treatment in a symptomatic patient. First choice of treatment: based on the angiogram, it seems there are technical errors at three anastomotic sites. The left internal mammy artery (LIMA) to the left anterior descending (LAD) and the venous graft to the obtuse marginal seem to have a significant stenosis at the graft-native vessel anastomosis. The fact that the LIMA to the LAD is compromised and the proximal part of the vessel occluded provides a strong argument for a redo CABG[2], bearing in mind the higher risk that comes with reoperation[2,5]. The anastomosis of the venous graft on the diagonal branch was performed on a diseased section of the coronary vessel and should be made more distally. In case of myocardial viability in the inferior wall, a new bypass to the right descending posterior should be performed.

Second choice of treatment: it does not seem to be useful to revascularise only the RCA but the target for PCI of the RCA is the native vessel, while the stenotic SVG and the anastomosis should be avoided due to concerns over embolisation or perforation[2]. If possible, the length of the occlusion needs to be established on the preoperative CAG images before trying to accomplish patency of the chronic totally occluded (CTO) right coronary artery.

Third choice of treatment: PCI of the anastomosis of the LIMA-LAD, of the anastomosis of the venous graft on the diagonal and of the anastomosis of the venous graft on the obtuse marginal.

Early graft failure is an important complication after CABG. Although it is not routinely used, flow measurement of the grafts can be a valuable instrument for intraoperative quality assessment of bypass grafts[1,6].

Conflict of interest statement

The authors have no conflicts of interest to declare.

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How would I treat?

THE INVITED EXPERT'S OPINION

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3. Department of Interventional Cardiology, Institut Cardiovasculaire Paris Sud, Massy, France

The patient is a 78-year-old male with diabetes and multivessel coronary disease who had undergone quadruple bypass surgery three months before (LIMA to LAD, and three venous grafts to the distal RCA, a diagonal and a marginal branch, respectively). The patient had a four-hour episode of chest pain with new Q-waves in the inferior leads and kinetic abnormalities revealed by echocardiography and he has experienced incapacitating angina ever since.

The fact that the patient has severe persistent angina is a valid indication for revascularisation even though there is no certainty as to the existence of peri-necrotic ischaemia around the inferior infarcted territory or in other territories. The location of ischaemia is unknown.

The extent of coronary disease is as follows: the native right coronary artery is occluded from its origin with a very long lesion which seems to be a potentially poor indication for revascularisation; the LAD is occluded from one centimetre beyond its origin and the circumflex artery is patent. Lesions are present in three of the four grafts: tight anastomotic lesion of the LIMA graft to the LAD, tight anastomotic lesion of the venous graft to the diagonal branch, patent venous graft to the marginal, very tight and long (>30 mm) ostial lesion of the venous graft to the RCA with slow distal run-off.

The most obvious lesion is in the venous graft to the RCA. Nevertheless, I have some doubts as to whether this lesion is the cause of angina and the inferior MI is not transmural.

In this particular case, I would implement the following strategy: angioplasty of the LIMA/LAD anastomosis with DES implantation and angioplasty of the anastomosis of the venous graft to the diagonal branch with implantation of a short DES. Should the patient's symptoms improve and given his age, I would not carry out any further revascularisation. Should his incapacitating angina persist, I would perform an angioplasty of the venous graft to the RCA. This, albeit feasible, would require long-segment stenting in a venous graft, which has been shown to be associated with poor outcomes in diabetic patients.

This patient is clearly in a very active phase of his coronary artery disease as evidenced by the presence of lesions in the anastomoses of most of his grafts. As a consequence, additional restenosis is quite likely to occur.

Conflict of interest statement

The author has no conflicts of interest to declare.

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AsiaIntervention 2016;2:143-148

How did I treat?

ACTUAL TREATMENT AND MANAGEMENT OF THE CASE

The patient presented with recent onset chest pain with an electrocardiogram showing new Q-waves in the inferior leads and an echocardiogram showing new RWMA in the inferior wall of the left ventricle. His coronary artery angiogram shows severe stenosis of the SVG to RCA with TIMI 2 flow. There were also variable degrees of stenosis at the native vessel and graft vessel anastomosis points, but TIMI 3 flow was maintained in these vessels. Hence, in the light of the clinical features, electrocardiogram and echocardiogram features, we came to the conclusion that the lesion in the SVG to RCA was the culprit lesion.

After discussion with the Heart Team, which included the cardiologists and cardiothoracic surgeons, it was decided to go for revascularisation rather than medical management only, as it was a case of recent acute coronary syndrome resulting in left ventricular dysfunction.

As shown in previous studies, the mortality and morbidity rate of redo CABG is quite high as compared to PCI[7]. Since this patient is a 78-year-old male and the other vessels had TIMI 3 flow, we were of the opinion to perform PCI to revascularise the RCA territory.

There are anomalous results regarding graft vessel PCI. Previous studies have shown that PCI to the native vessel should be preferred over graft vessel PCI[8]. However, in our case the whole of the RCA was diseased with a long chronic total occlusion (CTO) segment. Hence, we decided not to try native vessel PCI of the RCA as the chances of success were less and there was an increased risk of contrast-induced nephropathy as he was an elderly diabetic patient.

We went ahead with the plan to carry out PCI to the SVG to RCA using a distal embolic protection device (filter device) and two overlapping drug-eluting stents. We achieved a good result with TIMI 3 flow rate **(Figure 7-Figure 9, Moving image 5-Moving image 7)**.

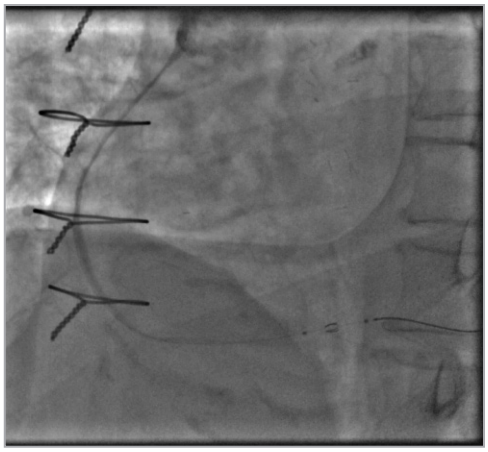

Figure 7. *LAO view showing distal embolic protection device (filter) placement.*

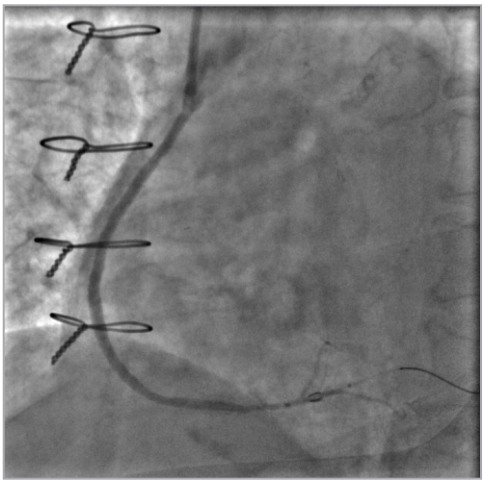

Figure 8. *LAO view of the SVG to RCA after stenting.*

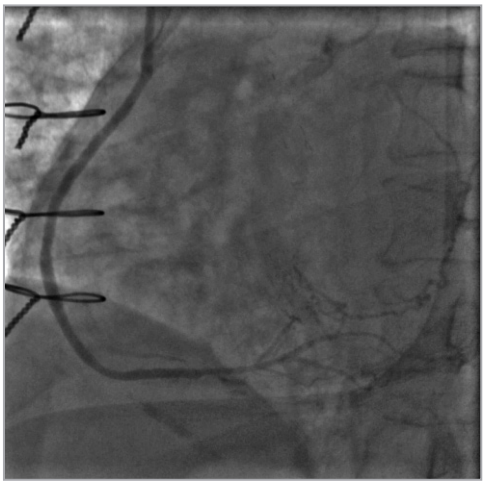

Figure 9. *Final LAO view after stenting and retrieval of the filter.*

Since the other graft vessel-anastomotic sites were showing variable degrees of stenosis, we did not do anything since TIMI 3 flow was present. We planned to keep the patient on optimal medical management and to have a thallium stress test carried out if the patient becomes symptomatic in future.

Conflict of interest statement

The author has no conflicts of interest to declare.

References

1. Head SJ, Borgermann J, Osnabrugge RL, Kieser TM, Falk V, Taggert DP, Puskas JD, Gummert JF, Kappetein AP. Coronary artery bypass grafting: Part 2--optimizing outcomes and future prospects. *Eur Heart J.* 2013;34:2873-86.

2. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention.* 2015;10:1024-94.

3. Health Quality Ontario. Magnetic resonance imaging (MRI) for the assessment of myocardial viability; an evidence-based analysis. *Ont Health Technol Assess Ser.* 2010;10:1-45.

4. Al Sayari S, Kopp S, Bremerich J. Stress cardiac MR imaging: the role of stress functional assessment and perfusion imaging in the evaluation of ischemic heart disease. *Radiol Clin North Am.* 2015;53:355-67.

5. Sbaik JF 3rd, Blackstone EH, Houghtalling PL, Walts PA, Lyttle BW. Is reoperation still a risk factor in coronary artery bypass surgery? *Ann Thorac Surg.* 2005;80:1719-27.

6. Walker PF, Daniel WT, Moss E, Thourani VH, Kilgo P, Liberman HA, Devireddy C, Guyton RA, Puskas JD, Halkos ME. The accuracy of transit time flow measurement in predicting graft patency after coronary artery bypass grafting. *Innovations (Phila).* 2013;8:416-9.

7. Morrison DA, Sethi G, Sacks J, Henderson WG, Grover F, Sedlis S, Esposito R; Investigators of the Department of Veterans Affairs Cooperative Study #385, Angina With Extremely Serious Operative Mortality Evaluation. Percutaneous coronary intervention versus repeat bypass surgery for patients with medically refractory myocardial ischemia: AWESOME randomized trial and registry experience with post-CABG patients. *J Am Coll Cardiol.* 2002;40:1951-4.

8. Brilakis ES, Rao SV, Banerjee S, Goldman S, Shunk KA, Holmes DR Jr, Honeycutt E, Roe MT. Percutaneous coronary intervention in native arteries versus bypass grafts in prior coronary artery bypass grafting patients: a report from the National Cardiovascular Data Registry. *JACC Cardiovasc Interv.* 2011;4:844-50.

Supplementary data

Moving image 1. LAO caudal view of venous graft to diagonal.

Moving image 2. LAO caudal view of venous graft to obtuse marginal (OM).

Moving image 3. LAO view of SVG to RCA.

Moving image 4. Lateral view of LIMA to LAD.

Moving image 5. LAO view showing distal embolic protection device (filter) placement.

Moving image 6. LAO view of SVG to RCA after stenting.

Moving image 7. Final LAO view after stenting and retrieval of the filter.

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