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AsiaIntervention

40 YEARS OF ANGIOPLASTY

CORONARY INTERVENTIONS

INTERVENTIONS FOR VALVULAR DISEASE AND HEART FAILURE

EDITORIAL

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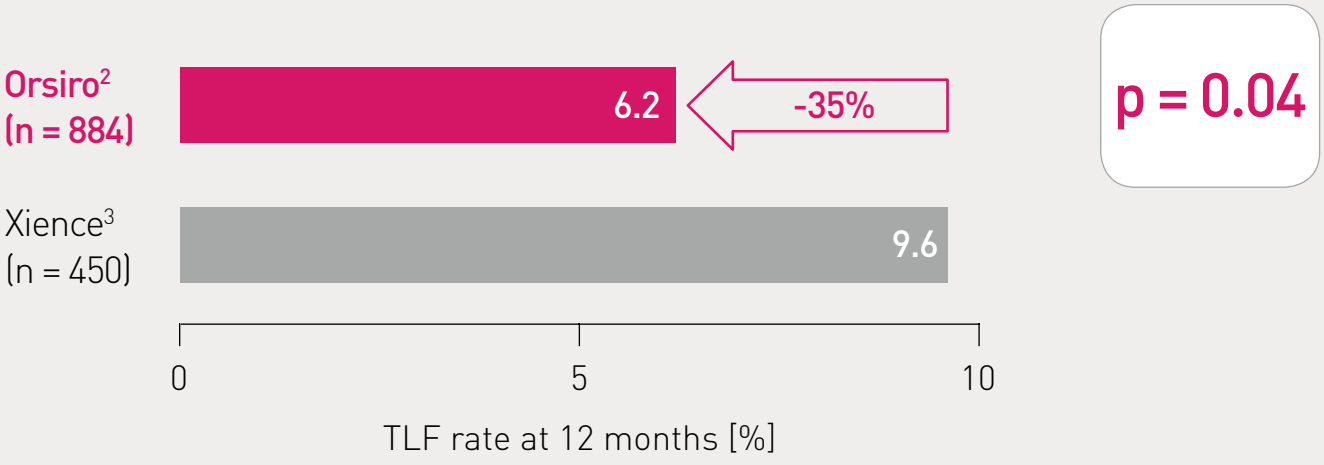

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AsiaIntervention Journal is an international, English language, peer-reviewed journal whose aim is to create a forum of high quality research and education in the field of percutaneous and surgical cardiovascular interventions.
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AsiaIntervention: marking the beginning of a new era in scientific publications in Asia

Huay Cheem Tan, *President APSIC and Chief Editor, AsiaIntervention*

As President of the Asian-Pacific Society of Interventional Cardiology (APSIC) and one of the Chief Editors of this journal, it is a great pleasure to introduce this latest edition of AsiaIntervention. Our young journal is growing rapidly and with this new edition we are entering a watershed period, where the rigorous development of our first issues is beginning to bear fruit in terms of the influence and recognition we receive from you our readers throughout Asia and internationally as well.

From the beginning, our goal has been to provide a showcase of the very best clinical and academic work coming out of Asia, work which we believe has an impact on the way we practice. It is thus only natural that APSIC has chosen AsiaIntervention as the official journal of our society, and we are not alone. AsiaIntervention has also been selected by the International Cardiology Foundation of India (ICFI) as its official journal, further underlining the representative nature of our work throughout the region.

When the APSIC was founded almost twenty-five years ago, we were convinced that for our region to continue to be a source of innovation in cardiovascular care it needed a dynamic forum in which we "could share knowledge and expertise in the field of catheter-based therapies". In addition, we committed ourselves to develop "joint academic research and education programmes". APSIC has grown since these early days, but remains true to its initial commitment, taking its place as a driving force representing the diversity of our membership and the clinical, academic and research work in Asia.

The match between the goals of APSIC and AsiaIntervention is clear. This journal – our journal – came into existence out of the belief that no adequate academic and clinical publication existed that was specifically "by and for" the Asia-Pacific interventional cardiology community. Convinced that by working together we can better advance the quality of cardiovascular care, AsiaIntervention has striven to be an open forum for all. There is no better proof of the diversity of our approach than a look at our editorial board which includes internationally respected Chief Editors coming from China, India, Japan, Korea and Singapore and who have given both of their time and credibility to further foster the reputation of our journal. Our Senior Consulting Editor, Patrick W. Serruys, and Consulting Editors, Christoph Naber and Richard Ng, offer us the depth of their experience and international outreach.

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Active presence at AICT – AsiaIntervention session

It is little wonder that we are confident that the coming year will offer increased visibility and growth for AsiaIntervention, and this will be seen in several substantive ways.

It is not by accident that this issue of the journal is being published at the same time as the 13th Asian Interventional Cardiovascular Therapeutics (AICT) Congress taking place this year in Melbourne, Australia. AICT is the official scientific meeting of APSIC and, as our Society's official journal, it is only natural that AsiaIntervention be an active presence during this gathering. Similar to EuroPCR, AICT has gained a reputation for its educational use of stimulating live cases on a broad range of topics. Participants will be coming from throughout Asia and the world, participating in the interactive environment and presenting their best cases.

There are many joint sessions showcasing the collaboration with other societies and meetings and, this year, similar to EuroIntervention and its relationship to EuroPCR and the EAPCI, we are offering a dedicated AsiaIntervention session which will further spotlight the work and commitment of our journal. This dedicated AsiaIntervention session will bring together the best of our recently published articles, showcasing their quality and that of the journal. These articles, chosen by the editorial board for their scientific merit, clinical impact and rigorous methodology, will be presented during the session and followed by an open discussion.

Make this journal your own – a call for submissions

Today, AsiaIntervention publishes articles of merit often coming from Singapore, China, India and Japan, but through our presence in Melbourne we want to encourage all of you – wherever you are located - to submit as well. AsiaIntervention and APSIC are platforms for your work, and we only exist if we can have the full and active participation of interventionalists from all over the Asian-Pacific region. By highlighting the quality and clinical impact of what we publish, we also want to underline an important fact – we need your submissions!

Entering our third year, we have applied for and expect PubMed listing shortly. When that recognition is obtained, submissions will increase and we urge you not to wait, but become fully part of our family now and submit today. As President of our Society, as an editor of AsiaIntervention, but more importantly, as a working clinical interventional cardiologist, I cannot emphasise enough how critically important your participation is for us.

While the challenges are complex in creating a scientific journal of note, we know that by bringing together the talent from all parts of our region we will – and are indeed – succeeding. Our society and our official journal have been created to facilitate the exchange of clinical knowledge, education and research. It is up to all of us to ensure that we are fully representative of the dynamic and far-reaching work that our region offers. The reward of having our own internationally recognised journal reflecting our own medical cultures is enormous, for us, and also for our patients.

The links we are creating today, between the different associations, meetings and organisations, the relations we have with the international scientific community, all of this adds to the strength and inherent value of APSIC and AsiaIntervention. Together, we remain committed more than ever before to the quality of our content and the excellence and breadth of our participation, dedicated, as always, to capturing the whole range of the vibrant medical academic, research and clinical culture of Asia. We look forward to your continued – and increasing – participation, as readers, as authors, but most of all as clinicians who want to offer the best interventional cardiovascular care to our patients wherever they may live.

AsiaIntervention 2017;3:95-96

40 YEARS OF ANGIOPLASTY

The evolution of percutaneous coronary intervention in Asia: in celebration of the 40th anniversary of percutaneous transluminal coronary angioplasty

Runlin Gao, *Chief Editor, AsiaIntervention*

Forty years ago, in September 1977, Dr Andreas Grüntzig heralded the era of interventional cardiology by successfully performing the first percutaneous transluminal coronary angioplasty (PTCA) in Zurich, Switzerland[1]. Through live demonstration courses, he went on to train cardiologists from around the world, leading to the rapid introduction of PTCA into clinical practice in the rest of Europe, the United States and beyond.

In October 1981, Dr Nobuyoshi from Kokura Memorial Hospital, Japan, performed the first PTCA in Japan and in Asia[2]. Unfortunately, the procedure failed and the patient underwent emergency cardiac bypass surgery. Dr Nobuyoshi's next two cases met the same fate. To refine his skills further, he visited several famous hospitals in the United States and learned from prominent masters, including Drs Myler, Simpson, Dorros, and Hotzler, carefully noting every precise detail of the procedure. In 1982, Dr Nobuyoshi performed his fourth PTCA case at Kokura Memorial Hospital with a successful outcome[2]. Thereafter, his caseload reached 93 during 1983, and 40 weekly in 1984, when he held the first live demonstration course in Japan with about 300 attendees. This live demonstration has been held yearly since, being instrumental in the rapid expansion of PTCA use in Japan during the 1980s, and its uptake in several Asian countries.

PTCA was first performed almost simultaneously to the first Japanese case in Taiwan, China, in 1981, in Korea and Malaysia in 1983, in Singapore and India in 1984, and in Hong Kong and mainland China in 1985. However, expansion of PTCA use was relatively slower in many Asian countries. In mainland China, for instance, during the first decade after its introduction in 1985, PTCA could only be performed at a few centres and by a few cardiologists. By the end of 1996, a total of only 6,200 percutaneous coronary intervention (PCI) cases had been performed at 51 hospitals. However, along with economic growth and extensive training, the last 10-15 years have witnessed an explosive growth in annual numbers of PCI, reaching a total of 666,495 cases performed at over 2,000 hospitals nationwide in 2016. During the same period, PCI use also expanded rapidly in most developing countries in Asia. According to a rough case count, approximately one million PCI were performed in 2016 in Asia, which is close to the figure for Europe or North America. Asia therefore has become a non-negligible force within the global PCI community.

Although PCI uptake was slower overall in Asia than in North America or Europe, interventional cardiologists in Asia have made remarkable contributions to PCI. In Japan, the skill and patience of interventionalists along with their development of specialised techniques and devices have translated into the highest success rates in the treatment of chronic total occlusion (CTO) lesions. Various antegrade approaches combined with retrograde CTO techniques developed by Japanese scholars[3] have increased the success rate of CTO treatment to 80%-90%; their adoption around the world has improved overall treatment outcomes for CTO lesions. Japan remains the worldwide leader in CTO treatment and, in recent years, Chinese interventional cardiologists have achieved great progress in the battle to conquer CTO lesions.

For their pioneering work, thanks are due to our Korean colleagues, who accumulated clinical experience on left main coronary artery stenting and shared it with the rest of the world via live

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demonstrations and international meetings. Korean investigators also led the early real-world registry and randomised trial comparing stenting vs. CABG to treat left main coronary artery disease[4,5], which provided important evidence to inform revascularisation strategy choice for left main coronary artery disease. Clinical practice and research on left main coronary artery stenting have also progressed in China in recent years[6,7].

Soon after Dr Kiemeneij first performed PCI via the transradial approach[8], the technique was introduced into Japan[9], China[10], and many other countries and regions in Asia. PCI via the transradial approach has many advantages compared to the femoral approach: patients can ambulate earlier, feel more comfortable, and experience significantly decreased rates of vascular and bleeding complications. Use of the transradial approach has rapidly spread in Asia where it is used in the highest proportions in the world. Currently, more than 90% of PCI in China are performed via the transradial approach.

The research and development on bioresorbable scaffolds (BRS) was flourishing worldwide until the Absorb BVS (Abbott Vascular, Santa Clara, CA, USA) was withdrawn from the global market; however, research and development on a second-generation BRS continues in China and India. First-in-man studies presented at TCT 2016 documented the safety and efficacy of the Firesorb bioresorbable sirolimus target eluting scaffold (MicroPort, Shanghai, China) and the MeRes bioresorbable scaffold (Meril Life Sciences, Vapi, India) with a strut thickness of 100-120 μm. The multicentre randomised trial of Firesorb has been launched in China. Asia is therefore in a leading position worldwide in terms of research and development of second-generation BRS.

The four decades since Dr Grüntzig ushered in the era of interventional cardiology have witnessed tremendous progress in revascularisation therapy of coronary artery disease. Although cardiologists in Asia initially lagged in assimilation of this new approach compared to those in the western world, PCI use and research on coronary intervention have grown in quantity and quality in recent years in the region, rendering Asia a powerhouse in interventional cardiology that is bound for continued growth and innovation.

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Role of professional medical writing in high-quality publications

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Whilst central and western Europe have witnessed declines in absolute numbers of cardiovascular deaths between 1990 and 2013, regions such as South and East Asia have witnessed the largest increases[1]. Despite these observations, Asian countries remain under-represented in cardiovascular research and scientific output. The reasons for this are complex and multifactorial, but there can be little doubt that, moving forward, the Asian region is a crucial element in the effort to understand and treat cardiovascular disease better, and AsiaIntervention will continue to work tirelessly to promote the region globally.

Proudly, we have witnessed a steady influx of submissions since our first issue in January 2015. Our founding vision remains to be the premier English-language peer-reviewed interventional journal that showcases the rapid expansion of technological advances and innovations in interventional cardiology. Without a doubt, the rapid population growth and formidable economic development across the Asia-Pacific region will see our journal become an increasingly important vehicle to share such scientific data, and it remains critical that this information be disseminated in an accurate, clear and unbiased fashion.

Our region is unique in many ways. With its cultural and linguistic diversity, primary communication often takes place in local and regional languages. At best, English may be a second or even third language for patients, staff, physicians, and scientists. Whatever the competing opinions, the current reality is that most international scientific communication still takes place in English. This seems to play a major role in limiting scientific engagement between Asia and the rest of the world. This is a huge loss for scientific communities on both sides of the language barrier.

It is widely recognised that numerous papers submitted are rejected by biomedical journals due to poor content organisation and writing style. Grammatical and simple spelling errors too frequently remain the bane of editors' and reviewers' lives. Writing a scientific paper can be arduous and requires a special skill set that not all of us possess to the same degree. An example of how to craft a manuscript is apparent by looking at one of the many thousands of published papers by our very own Senior Consulting Editor Patrick W. Serruys. These clearly demonstrate the art of medical writing to engage the target audience and provide the greatest scientific clarity and impact.

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In a globalised world with increasing information sharing and understanding of cultural diversities, high-calibre scientific discussion should not be limited by language. Scientific researchers should not be expected to be fluent in English, particularly because there are numerous high-quality professional medical writing services that can assist authors with expressing their content in a coherent, concise and effective manner and assist in the preparation and submission of articles to biomedical journals.

Such services can include simply aligning language style and grammar, to careful review of regulatory, quality-control, and clinical data documents. It should also be noted that English translation and writing services are routinely used and made available at top research institutions in Europe and the USA. Professional medical writing support is associated with more complete reporting of clinical trial results and increased adherence to Consolidated Standards of Reporting Trials (CONSORT). Authors globally, and particularly in industry-sponsored studies, have increasingly adopted the support of professional medical writing over the past decade[2,3]. The international Good Publication Practice guideline (GPP3) has recognised that professional medical writers have an important role in assisting authors with the development of publications, particularly where authors have limited time and knowledge of publication ethics and reporting guidelines[4]. It is hoped that the English-speaking scientific community will not penalise non-English-speaking scientists for utilising similar services to improve the quality of their contributions responsibly. Nonetheless, it should go without saying that the standards for scientific research and publication will remain unchanged at the highest levels regardless of language, culture, or creed.

The wealth of scientific data across Asia and the Pacific Rim provides a critical and unique opportunity for cardiovascular research. First, with Asians accounting for the greatest population numbers, it is crucial to have a better understanding of treatments in diverse ethnic groups. Second, with large, ethnically heterogeneous and high-density populations, the Asian region is naturally very attractive as a location for large clinical trials. These populations have tremendous socio-economic diversity with pockets of treatment-naïve populations in under-resourced regions among those with access to comprehensive medical care. Third, in addition to potentially quicker patient recruitment, Asia's cost-effectiveness also provides an attractive advantage for the sponsors of such trials[5].

Reflecting the increase in commitment and research funding, the international community has also witnessed rising engagement from Asian scientific communities. In fact, China has surpassed the USA with the largest science and technology workforce globally[6]. Although medical research articles emerging from Asia have increased accordingly, they are dwarfed in comparison by the number of articles emerging from Europe and the USA. This has been accompanied by slow growth in the number of highly cited research articles and patent applications. Clearly, there is still a large gap between Asian scientists and their American and European colleagues.

Part of the gap that exists in the scientific community arises from the diversity within Asia, with its vast array of ethnicities, nations, cultures, histories, and languages. Despite the current geopolitical waves roiling our world, we believe that language should not remain a primary barrier to publishing vital, high-quality research that has the potential to improve lives across the globe. We encourage clinicians and scientists in Asia and around the world to continue to pursue high-quality cardiovascular research, and to engage professional medical writing services as necessary to allow fluid communication across global scientific communities. Equally, we look forward to continued discussions, collaborations, and shared progress in the fight against cardiovascular disease and hold true the privileged and powerful position of our journal.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Dengue fever, thrombocytopaenia and management issues in post-coronary stenting patients

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Severe thrombocytopaenia is a rare finding, particularly in patients with coronary artery disease. Percutaneous coronary intervention (PCI) is best avoided in such patients because of the increased risk of bleeding complications that may result due to the mandatory use of periprocedural anticoagulation and post-procedural antiplatelet therapy. This concern is reinforced by data which has revealed an inverse relation between in-hospital death, major adverse cardiac events and major bleeding rates in PCI patients and platelet counts[1].

However, when faced with such a rare situation, there are no definite guidelines on how to address such tough calls. One such situation is where dengue fever along with thrombocytopaenia complicates periprocedural or post-procedural PCI settings.

The dengue virus is a single-stranded RNA arbovirus of the Flaviviridae family and is transmitted by the bite of the female mosquito of the genus Aedes (most commonly Aedes aegypti). Dengue fever has a wide clinical spectrum ranging from a mild self-limiting febrile illness (classic dengue) to life-threatening dengue haemorrhagic fever and dengue shock syndrome (DHF/DSS) which has ravaged mankind for centuries. Currently, the disease is endemic in all continents (especially tropical and subtropical countries) except Europe[2]. From a clinical point of view, it is not possible to distinguish those patients who will progress to the haemorrhagic form of the disease from those with the self-limiting illness. It is estimated that there are currently 50-100 million cases of dengue every year worldwide, including more than 500,000 reported cases of DHF/DSS[3]. In recent times, India has seen a major spurt in dengue, causing widespread panic, and this has stretched the medical services to their fragile limits.

One of the most dreaded features of dengue is thrombocytopaenia (TCP) which is usually seen between the 4th and 7th days of the illness, during the phase of defervescence when the fever is subsiding. The platelet counts may decline to alarmingly low levels. This is mentioned in the WHO guidelines of 2009 as a potential indicator of clinical severity[4]. In adults, a platelet count of 5,000/mm^3 and packed cell volume >50 are significantly associated with bleeding manifestations. Various mechanisms have been proposed in the pathogenesis of thrombocytopaenia in dengue, namely:

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– Bone marrow suppression by the virus. In the early phase of the disease marrow hypocellularity and retardation of megakaryocyte maturation have been documented[5].

– Increased platelet destruction is seen, which may be a part of an ongoing consumptive coagulopathy, secondary to complement system activation[6] or peripheral sequestration[7].

– Besides platelets counts, the functional disruption of these cells is seen[8]. Platelet function resumes its normal conditions two to three weeks after the initial convalescence period.

Also during the febrile period, variable reductions are observed in the different coagulation factors, such as fibrinogen, factor V, factor VIII, factor IX and factor X, besides antithrombin and alpha 2-antiplasmin. These changes explain the prolongation in prothrombin time and activated partial thromboplastin time. Elevations in the concentrations of fibrinogen/fibrin degradation products (FDP) and d5-dimer have also been described[9].

Taken together, these may have significant clinical implications due to altered haemostasis.

In the light of these facts, a great therapeutic dilemma may arise if a patient with dengue fever with thrombocytopaenia develops an acute coronary syndrome (ACS) or a patient who has undergone PCI in the recent past develops dengue fever with thrombocytopaenia, as antiplatelet therapy constitutes one of the cornerstones of therapy in ACS or post-PCI settings.

Possible implications of cessation of antiplatelet therapy in dengue complicated by TCP in patients who have undergone PCI

One of the most dreaded and catastrophic complications after PCI and stenting is stent thrombosis (ST). Acute ST (occurring 0-24 hours after stent implantation) carries mortality and myocardial infarction rates of 20-45% and 50-70%, respectively[10]. Although multifactorial in aetiology, the cessation of antiplatelet therapy is an important cause. Trials such as PCI CURE[11], TRITON-TIMI 38[12] and PLATO[13] have established the efficacy of dual antiplatelet therapy (aspirin in combination with oral $P2Y_{12}$ receptor inhibitors also called thienopyridines) in:

– Reducing rates of ST.

– Showing that ticagrelor and prasugrel in a situation of ACS are better than clopidogrel in reducing ischaemic events and ST but with a higher bleeding risk.

In PLATO, ST rates for ticagrelor and clopidogrel were 1.3% and 1.9%, respectively (p=0.009), while in TRITON-TIMI 38 the prasugrel group had lower rates of myocardial infarction, urgent target vessel revascularisation, and ST (2.4% versus 1.1% for the clopidogrel group; p<0.001).

Thus, the use of DAPT after PCI and stent placement seems imperative. Aspirin is an integral part of DAPT and should be continued indefinitely as one of the agents. On the basis of the available data, the optimal range of aspirin dose in patients treated with DAPT that provides maximal protection from ischaemic events and minimises bleeding risk appears to be 75 mg to 100 mg. The current recommendations[14] advocate the use of ticagrelor or prasugrel over clopidogrel for at least 12 months after PCI and stent (BMS/DES) implantation in ACS settings. If patients have tolerated the therapy well with no bleed or they are not at high risk of bleeding events, the DAPT may be continued beyond 12 months. If need be (e.g., patient develops a high risk of bleeding such as concomitant use of an oral anticoagulant, a major bleed occurs or the risk of bleeding is high such as needing intracranial surgery), the $P2Y_{12}$ inhibitor may be discontinued at six months. In the subgroup of patients with stable ischaemic heart disease (patients with a history of ACS >1 year prior who have since remained free of recurrent ACS are considered to have transitioned to stable ischaemic heart disease) who have undergone stent implantation, DAPT should be continued for at least six months when a DES was used and for at least one month if a BMS was used. If well tolerated, the therapy may be continued beyond these time frames or else, in case of DES use when faced with a situation where the drugs need to be discontinued, they may be withheld at three months. These guidelines are applicable to newer-generation DES which are less thrombogenic than first-generation DES[14]. The decision to discontinue antiplatelet therapy should be taken after carefully weighing the risks and benefits associated with the discontinuation of therapy.

It is also important to understand the association between the stent type and rates of ST. Overall, the rates of ST are highest in first-generation DES (sirolimus-eluting and paclitaxel-eluting stents). ST with BMS usually occurs within the first 30 days of implantation, when these stents are prone to thrombus formation[15]. Conversely, with first-generation DES, the greatest concerns are late ST (LST) (30 days to one year) and very late ST (VLST) (beyond one year). Second-generation DES, such as the zotarolimus-eluting stent and everolimus-eluting stents, demonstrate a decreased risk of LST and VLST. In a recent paper, Tada et al[15] reported the cumulative incidence of definite ST at three years to be 1.5% with BMS, 2.2% with first-generation DES, and 1.0% with second-generation DES. On multivariate analysis, the first-generation DES showed a significantly higher risk of stent thrombosis than the BMS, while second-generation DES were associated with a similar risk of ST when compared with the BMS. This goes to show that better technology and pharmacotherapy is available which can reduce the chances of ST.

Recommendations

– In all patients with dengue fever, antiplatelets should be avoided as they carry the risk of triggering Reyes syndrome apart from the worsening of thrombocytopaenia. Reyes syndrome is a rare condition characterised by hepatitis and encephalopathy and triggered by the use of aspirin in patients with viral infections such as varicella, influenza and dengue[8].

– If a patient with dengue fever develops an ACS, chart out a conservative approach and avoid interventional therapy. Antiplatelet drugs (aspirin along with clopidogrel rather than ticagrelor or prasugrel) should be used with caution and platelet counts monitored. In case PCI becomes imperative:

- Use the radial route.
- Use a BMS.
- For periprocedural anticoagulation use bivalirudin rather than heparin as the latter carries the risk of heparin-induced thrombocytopaenia (HIT) which may worsen an already complicated interventional scenario.
- Do not use GP IIb/IIIa inhibitors which are also known to cause thrombocytopaenia.
- The prophylactic use of platelet transfusions in dengue fever has been recommended when platelet counts are below 10-20,000/mm^3 without overt bleed or haemorrhage and below 50,000/mm^3 with bleed or haemorrhage in some guidelines. However, these are highly controversial and may increase hospital stay and increase the risk of pulmonary oedema, thus best avoided[16].

– Stent thrombosis after platelet transfusion has been documented. Cornet et al reported three cases where stent thrombosis occurred within six to 17 hours after platelet transfusion for bleeding or anticipated bleeding[17]. In fact, they proposed that transfusion of platelets be considered a risk factor for thrombotic stent occlusion. Donor thrombocytes may not be inhibited by antiplatelet drugs in the blood stream. The thrombogenic surface of a recently inserted stent may attract and activate donor platelets, resulting in thrombotic occlusion[18].
– In patients at high short-term risk of thrombosis, including those who have undergone PCI with stenting (received BMS within the past one month or DES in past zero to six months), it would be wise to continue DAPT while closely monitoring platelet counts. Switch over from prasugrel or ticagrelor to clopidogrel and maintain use of aspirin at 75-100 mg. If platelet counts fall below 50,000/mm^3, one may strongly consider discontinuation of DAPT or continuation with one antiplatelet agent.
– In patients with dengue and low short-term risk of thrombosis, including patients with stable ischaemic heart disease (SIHD), interrupt the use of DAPT while carefully monitoring the platelet counts and reintroduce one and then the second agent once platelet counts begin to rise.
– Patients with DHF/DSS represent perhaps the most catastrophic situation characterised by alteration in capillary permeability and significant capillary leakage of plasma into extravascular spaces, along with immune activation and high serum levels of tumour necrosis factor (TNF) receptor, interleukin (IL)-8, and other factors. This causes intravascular hypovolaemia and shock. DAPT should be interrupted immediately[8]. This condition not only requires a significant volaemic expansion, but also evaluation and treatment of the accompanying ventricular dysfunction, as in the current treatment of sepsis.

Conclusions

In the light of a paucity of data in the literature, the decision to discontinue antiplatelet therapy in a patient with dengue fever with thrombocytopaenia in peri- and post-PCI settings needs to be based on the evaluation of the patient's risk of bleeding and ischaemic complications. Each case must be decided individually. Discontinuation of antiplatelet therapy appears to carry real challenges, and continuation of antiplatelet therapy should be the rule when the risk of bleeding is low or haemostasis is achievable.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Restenosis after drug-eluting stenting – a call for action

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Percutaneous coronary intervention (PCI) has become the dominant revascularisation modality for patients with obstructive coronary artery disease. This development has been facilitated by advances in catheterisation techniques, antithrombotic therapy, and stent technology[1-3]. Drug-eluting stents (DES) in particular were a breakthrough technology. The high efficacy of DES enabled the expansion of transcatheter treatment to patients with complex disease patterns, such as multivessel and left main stem disease[4].

Current-generation DES are a mature technology with low rates of treatment failure. However, although the rate of restenosis after DES is low, it is not negligible. A systematic review of 158 randomised trials with different stent technologies showed median rates of clinical restenosis (target lesion revascularisation) with DES of 4.00 (2.05-6.40) per 100 patient years[5]. These observations must be tempered by the knowledge that even in so-called "all-comer trials" the majority of patients may not be represented. In fact, in clinical practice the incidence is probably somewhat higher. Registry studies with systematic angiographic surveillance have shown rates of binary restenosis of more than 10%[6].

When it occurs, DES restenosis is more frequently focal as compared with bare metal stent restenosis. This can be explained by the fact that the overall high efficacy of DES in suppressing neointimal hyperplasia means that focal mechanical factors, such as stent underexpansion or fracture, often play a dominant role. Focal mechanical factors represent double jeopardy: not only is the mechanical deficiency itself a risk for restenosis but the lack of contact with the underlying vessel wall inhibits effective delivery of the antiproliferative drug.

The time course of restenosis after DES is an issue of some interest. Although clinical trials comparing outcomes of patients randomised to treatment with DES or bare metal stents generally do not show evidence of more "late catch-up" restenosis with DES[7], studies with sequential angiographic surveillance during follow-up show differences in the time course of changes in luminal diameter with DES compared with bare metal stents. Whereas late lumen loss after bare metal stenting tends to peak within six months[8], late lumen loss after DES implantation seems to increase steadily – albeit at a low level – up to two or even five years[9,10].

The reasons for this temporal difference in late lumen loss are poorly defined. It may be due to a generalised right shift in vessel healing after DES implantation. Alternatively, it may reflect distinctive underlying pathophysiological processes. Indeed, autopsy evidence and studies with intravascular imaging interrogation suggest that the development of *de novo* atherosclerosis

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– also known as neoatherosclerosis – within the implanted stent may be more frequent or occur earlier after DES implantation[11]. This can be mechanistically explained by the increased permeability of the neointima after DES as compared with bare metal stent implantation[12].

Against this background, in the current issue of AsiaIntervention, Flavia Belloni and colleagues investigate differences in characteristics and outcomes of patients with DES restenosis according to the time interval between stenting and presentation with restenosis[13].

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In the setting of a multicentre restenosis registry, 129 patients were studied, 61% of whom had early restenosis – defined as restenosis occurring within nine months – as compared to 39% with late restenosis occurring beyond this time point. Interestingly, the baseline characteristics of patients in both groups were quite similar; the single statistically significant difference – patient presentation at the time of initial stenting – must be cautiously interpreted due to the risks of multiple testing.

In a second step, the authors examined outcomes of patients treated for DES restenosis. Patients were treated with either repeat stenting with DES (60%) or angioplasty with drug-coated balloons (40%). This is in line with both evidence from clinical trials[14] and recommendations from clinical practice guidelines[15]. Here, three observations are noteworthy. First, no clear difference was observed in outcomes according to whether the restenosis was early or late. Second, diabetes mellitus was the only independent predictor of recurrent adverse events after repeat intervention. Further efforts at understanding the interaction between diabetes and restenosis are warranted, and investigation using novel techniques for the quantification of advanced glycosylation end products may be a fruitful approach[16]. Third, the overall outcomes after treatment for restenosis were less than satisfactory, with one in five patients having another adverse event during follow-up.

This latter finding is consistent with earlier reports, which show that DES restenosis, when it occurs, is a more challenging condition to treat compared with bare metal stent restenosis[17]. The reasons for this remain to be elucidated and should be the subject of future study. Two broad explanations may be proposed. First, it is possible that a subset of patients exhibits hyporesponsiveness to the drugs or hypersensivity to the polymer coatings used on DES[18]. This might trigger a more aggressive type of neointimal hyperplasia that is more challenging to treat. Second, differences in the general restenosis substrate may play a role, with tissue types more frequently found in DES restenosis – such as neoatherosclerosis – more resistant to treatment than classic neointimal hyperplasia. In both respects, in the present study, it would have been very interesting to have had some insight into the appearance of the restenotic tissue with intravascular imaging, ideally with high-resolution optical coherence tomography.

Overall, the findings of Belloni and colleagues shed light on the challenges that exist in relation to managing DES restenosis. The unsatisfactory outcomes of patients treated for DES restenosis represent a genuine unmet clinical need. The magnitude of the problem is likely to increase in the coming years as more and more patients are treated by transcatheter approaches. Real progress in clinical outcomes may require a three-pronged approach: better understanding of the specific pathophysiological processes at play, investigation of novel treatment approaches, both local and systemic, and tailoring of treatment to the individual patient based on the cause of restenosis and the characteristics of the neointimal tissue identified by intravascular imaging. We call on the community for a concerted effort to address this neglected issue.

Conflict of interest statement

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Stenting or bypass grafting for left main coronary artery disease: considering short- and long-term trade-offs of each procedure for individualised patient care

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It is universally accepted that patients with significant left main coronary artery (LMCA) disease should receive coronary revascularisation regardless of the spectrum of clinical presentation. However, the optimal revascularisation strategy for such patients has been the subject of intense investigation for decades. Although coronary artery bypass graft (CABG) surgery has been the standard of care for the treatment of LMCA disease for nearly 40 years, percutaneous coronary intervention (PCI) treatment has undergone considerable therapeutic evolution over time and has changed the therapeutic paradigm in the field. Particularly since the widespread use of drug-eluting stents (DES), PCI for LMCA disease has become much more technically feasible and has shown favourable short- and long-term clinical outcomes. Several randomised clinical trials (RCT) have compared PCI with DES and CABG for the treatment of LMCA disease and have generally shown comparable rates of mortality and composite safety outcomes between the two strategies, though more frequent repeat revascularisations with PCI and more frequent stroke with CABG[1]. However, until recently, none of these has been adequately powered or has included contemporary PCI devices. In recent years, lesion assessment and procedural optimisation have become more accurate using invasive imaging or functional tools. In addition, the concomitant development of adjunctive pharmacotherapies, involving periprocedural antithrombotic agents, antiplatelet therapy, statins, or other secondary preventive drugs, has substantially contributed to enhancing PCI outcomes for LMCA disease. In this context, the results of the EXCEL (Evaluation of XIENCE Everolimus Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and the NOBLE (Nordic-Baltic-British Left Main Revascularization Study) RCT, which represent the largest and most contemporary data, have been long awaited[2,3]. Unexpectedly, the two trials apparently showed disparate findings: EXCEL found PCI to be non-inferior to CABG, while NOBLE noted CABG to be superior to PCI, adding some uncertainty regarding clinical decision making between PCI and CABG for patients with LMCA disease. Overall, the available studies were of variable size and were powered for varying composite endpoints at different time periods. All were underpowered for low-frequency events, such as mortality. Against

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this background, a meta-analysis to determine whether there are significant differences in the risk of mortality and other individual or composite endpoints between PCI and CABG in patients with LMCA would be informative.

In this issue of AsiaIntervention, Iqbal and colleagues report a pairwise meta-analysis of six updated RCT comparing PCI and CABG for unprotected LMCA disease[4].

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In addition to the EXCEL and NOBLE trials, the final 10-year results of the LE MANS trial were also included. Estimation of relative treatment effect was stratified into short-term (one-year) and long-term follow-up among a total of 4,717 patients treated with either PCI or CABG. Sensitivity analyses were performed for different endpoint definitions (e.g., myocardial infarction) and the type of stent used. Major findings were as follows: no difference in mortality regardless of follow-up period, higher rates of non-procedural myocardial infarction with PCI at long-term follow-up (risk ratio [RR]: 1.73, 95% confidence interval [CI]: 1.27-2.35) but not at one year (RR: 1.17, 95% CI: 0.77-1.76), higher rate of stroke with CABG at one year (RR: 0.39, 95% CI: 0.21-0.70) but not at long-term follow-up (RR: 0.86, 95% CI: 0.44-1.69), and higher rate of repeat revascularisation with PCI regardless of follow-up period. Finally, the long-term follow-up rate for the composite of these four endpoints was higher in PCI-treated patients (RR: 1.25, 95% CI: 1.12-1.39) and was attributable to the results of those who had a SYNTAX score of 33 or more. The authors should be congratulated for their sophisticated efforts on analyses, as they contributed to the robustness of the study. The findings provide further solid evidence of the relative strengths and limitations of each revascularisation strategy for patients with LMCA disease: PCI offers an early safety advantage and acceptable long-term survival, while CABG offers longer-term durability as well as greater protection from future myocardial infarction. In the same context, a substantial interaction between treatment effect and time for the risk of major adverse events in the recent EXCEL and NOBLE trials deserves attention, i.e., late catch-up in EXCEL or late divergence in NOBLE on the treatment effect of CABG over PCI during follow-up[5]. Limited follow-up could have penalised the CABG group in all of the available trials because the long-term benefits of CABG over PCI may not be fully evident until five to 10 years after the procedure. Whether treatment differences between PCI and CABG will continue to accrue or will be attenuated with longer-term follow-up should be the subject of further investigation.

PCI practices have changed significantly since the landmark SYNTAX trial. Small vessels, generally those with a diameter ≤2.0 mm, are currently not considered large enough for revascularisation. In addition, revascularisation in lesions with diameter stenosis of 50-70% has become less frequent, as these lesions are now commonly known to have functional insignificance. Together with the fact that >60% of patients were eligible for PCI in the EXCEL screening registry, the practical threshold in choosing PCI for LMCA disease is likely to be less stringent in contemporary real-world practice. However, the optimal choice of revascularisation modality for LMCA disease should be made after discussion among Heart Team members, taking into account eligibility for PCI or CABG, the specific circumstances of each patient, and individual preferences. CABG practices have also changed significantly towards considerable reduction in operative mortality and perioperative complications[6]. Patients who would benefit from durable grafts (e.g., those with a complex anatomy, severe left ventricular dysfunction, or diabetes) should be seriously considered as recipients. Because current guidelines on revascularisation for LMCA disease largely rely on the SYNTAX score[7,8], and do not clearly address a considerable group of patients who may experience positive outcomes with either CABG or PCI, the selection of the optimal treatment strategy should be more patient-centred, based on the short- and long-term trade-offs of each procedure as shown in the results of the current meta-analysis.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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The Japanese Circulation Society (JCS)

Prof. Issei Komuro
President of the Japanese Circulation Society

Prof. Takashi Akasaka
Chairperson of the International Relations Committee

The history of the JCS

The JCS is recognised as one of the most influential medical associations in Japan with 26,065 members including 14,000 cardiovascular specialists certified by the society as of June 2017.

The JCS has a long history stretching back over 80 years. The Journal entitled "The Nippon Journal of Clinical Angio-Cardiology" was first published in 1935, and the first general meeting was held in the following year, 1936, which was the beginning of the JCS. For cardiovascular interventionists, we now also have the Japanese Association of Cardiovascular Intervention and Therapeutics (CVIT), which is considered a sister association of the JCS. Many collaborative activities in the field of cardiovascular intervention are organised jointly by both societies.

The current issue of JCS in Asia

Faculty members of the JCS strongly believe that it is necessary to promote the further internationalisation of the JCS. We hope that the JCS will become one of the main internationally recognised societies along with Western medical societies such as the AHA/ACC and the ESC. We would be very happy if many Asian countries would kindly support the JCS to be an Asian representative society, similar to the ESC for European countries. The activities of the JCS are wide-ranging, including the publication of "Circulation Journal" and "Guidelines in Japan", and several scientific meetings. More than 1,400 articles are published per year in Circulation Journal. The editorial members of the journal are working hard to increase the scientific level and impact factor of the journal significantly, and anticipate more submissions of manuscripts from all over the world in order to share our knowledge with one another. At the annual scientific meeting of the JCS we have around 20,000 participants, including over 300 participants from abroad. There are many joint symposia with foreign cardiology societies such as the APSC, AHA, ACC, ESC, KSC and CSC. We have around 300 special sessions with more than 2,500 scientific abstracts each year, with half of these being presented in English. The meeting is held every March in Japan.

The JCS will also start a new forum, namely The 1st JCS Council Forum on Basic CardioVascular Research (The JCS Council-BCVR) on 6 to 7 January 2018. All sessions in this forum will be presented in English.

Furthermore, the JCS has successfully invited the Asian Pacific Society of Cardiology to hold its congress in Kyoto in 2020.

We aim to increase the number of overseas participants at JCS scientific meetings and to encourage foreign medical students and young investigators to carry out their clinical trials and scientific research in cooperation with Asian countries.

We look forward to meeting Asian friends at the annual JCS meeting where we will all share our knowledge.

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Next meetings
Annual Scientific Meeting of the JCS:
March 2018
1st JCS Council Forum on Basic CardioVascular Research (The JCS Council-BCVR):
6 to 7 January 2018

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Defining optimal stent overexpansion strategies for left main stenting: insights from bench testing

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KEYWORDS

- bifurcation
- drug-eluting stent
- left main

Abstract

Aims: Left main stenting frequently requires overexpansion of stents which can be performed by proximal optimisation technique (POT) or final kissing balloon dilation (FKBD). Yet, there are limited data concerning the effect of post-dilation of metallic stents beyond the overexpansion limit. The objectives of this study were to evaluate stent performance after overexpansion using POT or FKBD.

Methods and results: We deployed 4.00 mm drug-eluting platinum-chromium stents in silicone models of 6.00 mm diameter. We compared stent expansion and apposition using: 1) POT with 6.00 mm balloons using low, standard and high pressures (LP, SP and HP, respectively), and 2) final kissing balloon dilation (FKBD) using undersized (US) balloons at SP and optimally sized (OS) balloons at LP and SP. The platinum-chromium 4.00 mm stent can be expanded to an outer diameter of 5.10 mm by POT using a 6.00 mm balloon at LP. Further post-dilatation at higher pressures (SP, HP) resulted in an outer diameter of 6.00 mm. FKBD with US balloons resulted in a high ellipticity index and malapposition; with OS balloons, stent area improved but ellipticity and malapposition were still higher compared to POT. After overexpansion, the radial strength of metallic stents was maintained.

Conclusions: In PCI involving relatively larger vessel diameters such as left main stenting, POT but not FKBD can safely expand the platinum-chromium 4.00 mm stent beyond the overexpansion limit to 6.00 mm with optimal stent apposition and performance. POT may be the technique of first choice to achieve optimal stent expansion in left main stenting but requires higher pressures.

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Abbreviations

DES	drug-eluting stent
EI	ellipticity index
FKBD	final kissing balloon dilation
FKBD-US	final kissing balloon dilation undersized
FKBD-OS/LP	final kissing balloon dilation - optimally sized low pressure
FKBD-OS-SP	final kissing balloon dilation - optimally sized standard pressure
ID	inner diameter
MA	malapposition area
NC	non-compliant
OD	outer diameter
PCI	percutaneous coronary intervention
POT	proximal optimisation technique
POT-LP	proximal optimisation technique low pressure
POT-SP	proximal optimisation technique standard pressure
SAR	surface to artery ratio
SC	semi-compliant

Introduction

With improved percutaneous coronary intervention (PCI) techniques, PCI has emerged as a safe option for revascularisation in selected patients with unprotected left main coronary artery disease with good long-term outcomes[1,2]. However, left main PCI has remained a technically challenging procedure with several key considerations. The left coronary artery is of larger diameter, frequently above 5 mm. In an intravascular ultrasound (IVUS) study on the use of drug-eluting stents (DES) in left main PCI, the maximal diameter of the distal left main was 5.7±0.7 mm on average[3]. Left main stenting often involves bifurcation treatment and deployment of a single stent across vessels with marked disparity in diameters[4]. Thus, key procedural challenges to achieve adequate stent expansion while maintaining minimal malapposition still remain.

In left main stenting using current metallic stents, overexpansion using either proximal optimisation technique (POT) or final kissing balloon dilation (FKBD) is widely performed to minimise stent malapposition. The phenomenon of malapposition is of particular importance for two reasons: one is the acute risk during the procedure where subsequent vessel rewiring and balloon dilatations might engage the malapposed space immediately deforming stent integrity, and the second, in the longer term, is increasing the risk of stent thrombosis[5-7]. For bifurcation lesions, FKBD has traditionally been the method to reach maximal expansion[8,9]. However, clinically, this is limited by side branch diameters and will result in undesired elliptical deformation. POT is another commonly used bifurcation technique that was devised later by Darremont[10] to achieve overexpansion at the carina using short, larger balloons. Although earlier studies have been performed to evaluate the results of stent oversizing and the impact of post-dilation on strut geometry in bench testing situations[9,11-14], there is still a paucity of data concerning the feasibility of aggressive post-dilation of metallic stent platforms within large left main coronary phantoms performed by either FKBD or POT to achieve adequate expansion with optimal apposition[3] and concerning the impact on mechanical stent performance such as radial strength[4]. The objectives of this study were to compare expansion and apposition of stents overexpanded by POT and FKBD from the nominal diameter of 4.00 mm beyond the recommended expansion limit to 6.00 mm in a bench testing scenario and to investigate the mechanical stent performance of overexpanded stents.

Methods

In vivo bench testing of thin-strut (81 µm) platinum-chromium DES (SYNERGY™ II; Boston Scientific, Marlborough, MA, USA) was conducted. All experiments were performed in the Boston Scientific Research and Development Facility at Maple Grove, MN, USA, between July and September 2014. **Table 1** shows the models we used in our bench testing. In brief, we performed the following bench tests using the SYNERGY II drug-eluting stent (DES) in silicone phantom models with a diameter of 6.00 mm:

– To measure the effect of overexpansion on the stent performance of a 4.00 mm SYNERGY stent with 6.00 mm balloons

Table 1. Summary of post-dilation methods performed for the stent proximal ends.

			Stent deployment			First post-dilation			Second post-dilation		
Post-dilation method	Group number	Sample size	Stent	Size (mm)	Deployment pressure (atm)	Post-deployment balloon	Size (mm)	Pressure (atm)	Post-deployment balloon	Size (mm)	Pressure (atm)
POT-SC/LP	1	3	SYNERGY	4.0×28	16	Apex	5.0×15	9	Maverick XL	6.0×15	6
POT-SC/SP	2	10	SYNERGY	4.0×28	16	Apex	5.0×15	12	Maverick XL	6.0×15	14
POT-NC/HP	3	3	SYNERGY	4.0×28	16	NC Quantum	5.0×15	16	NC Emerge	6.0×15	24
FKBD-US/SP	4	3	SYNERGY	4.0×28	16	Apex	5.0×15	12	Apex	3.5×15+ 4.0×15	12
FKBD-OS/LP	5	3	SYNERGY	4.0×28	16	Apex	5.0×15	12	Apex	4.0×15+ 5.0×15	4
FKBD-OS/SP	6	3	SYNERGY	4.0×28	16	Apex	5.0×15	12	Apex	4.0×15+ 5.0×15	12

FKBD: final kissing balloon dilation; HP: high pressure; LP: low pressure; NC: non-compliant; OS: optimally sized; POT: proximal optimisation technique; SC: semi-compliant; SP: standard pressure; US: undersized

(semi-compliant [SC] Maverick™ XL or non-compliant [NC] Emerge™; both Boston Scientific) using:
  - POT at low pressure (LP) of 6 atm (Group 1 POT-SC/LP),
  - POT at standard pressure (SP) of 14 atm (Group 2 POT-SC/SP),
  - POT at high pressure (HP) of 24 atm (Group 3 POT-NC/HP).
- To evaluate the effect of common clinical FKBD methods using:
  - The relatively undersized (US), but commonly used, 3.50 mm and 4.00 mm (Apex™; Boston Scientific) balloons at standard pressure (SP) of 12 atm (Group 4 FKBD-US/SP)
  - The optimally (according to Finet's law) sized (OS) 4.00 mm and 5.00 mm (Apex) balloons at LP of 4 atm (Group 5 FKBD-OS/LP) and at SP of 12 atm (Group 6 FKBD-OS/SP).
- To evaluate the effect of overexpansion on mechanical stent performance by overexpanding the stent beyond the overexpansion limit to 6.00 mm.

The 3.5 and 4.0 mm balloons were used for FKBD as this was the largest combination for kissing balloons used in the clinical setting of our hospital. The inflation pressures needed for full overexpansion of the balloons to the intended diameters were chosen.

Comparison of stent expansion and malapposition among the six models was achieved by measuring the dimensions and mechanical characteristics of the stents after overexpansion **(Table 1)**. Detailed information regarding the methodology is provided in the **Supplementary Appendix**. The malapposition area (MA/mm^2) of each stent was the difference of tube inner diameter (ID) area and stent outer diameter (OD) area. The ellipticity index (EI) is the ratio of maximum stent ID to minimum stent ID. The mechanical performance of the stents was evaluated at various sizes from 4.00 mm (baseline) to 6.00 mm (overexpansion as measured by average maximum compression resistance [hoop force/length: N/mm]). Mechanical characteristics evaluated included radial strength, stent length, elastic recoil and percentage surface to artery ratio (SAR). Forty stents (10 stents per group, at 4.00 mm, 5.00 mm, 5.75 mm and 6.00 mm) were used to collect the radial strength data since this is a destructive test. Stent length was also captured from these stents as it is an input factor in the radial strength calculation (force/length). The average length values from these groups were also used to calculate vessel area at each diameter in the SAR calculation. The recoil was measured sequentially from the same 10 stents deployed to 4 mm, then post-dilated to 5 mm, 5.75 mm and 6.00 mm.

STATISTICAL ANALYSIS

Descriptive statistical analysis was performed with continuous variables expressed as averages (standard deviation) and with categorical variables presented as counts (percentage). The ANOVA test was used for comparison between groups. All statistical tests were carried out at the 5% level of significance in SPSS, Version 21 (IBM Corp., Armonk, NY, USA).

Results

STENT OUTER DIAMETER AND STENT OUTER AREA

A total of 25 stents were subject to bench testing in the following models: POT-SC/LP (n=3), POT-SC/SP (n=10), POT-NC/HP (n=3), FKBD-US/SP (n=3), FKBD-OS/LP (n=3) and FKBD-OS/SP (n=3). Representative phantoms of the respective models post dilation are shown in **Figure 1**. Detailed results of the stent measurements in the various models are tabulated in **Table 2**. Additional data regarding stent measurements are shown in **Supplementary Table 1** in the **Supplementary Appendix**. Using the POT-SC/LP model, the 4.00 mm stent reached a maximum stent outer diameter of 5.10 mm using a 6.00 mm SC balloon at 6 atm. In POT-SC/SP and POT-NC/HP, further post-dilatation with higher pressures of 14 atm and 24 atm, respectively, resulted in the maximum stent outer diameter reaching 6.00 mm and 6.22 mm, respectively, with a stent outer area of 30.30 mm^2 and 28.60 mm^2 as the final result. These were the only models in which the stent outer area reached the target stent outer area of 28.30 mm^2 (based on a stent outer diameter of 6.00 mm). The POT-SC/SP model was repeated 10 times without any fractures on visual inspection, demonstrating a safety margin above the designated expansion limit, and with minimal malapposition in a 6.00 mm vessel. We achieved the highest stent outer diameters

Table 2. Actual stent measurements after overexpansion.

Group number	Post-dilation method	Sample size	Stent ID				Stent OD			Tube ID max			
			Stent ID max (mm)	Stent ID min (mm)	EI_{ID}	Stent ID area (mm^2)	Stent OD max (mm)	Stent OD min (mm)	Stent OD area (mm^2)	Tube ID max (mm)	Tube ID min (mm)	Tube ID area (mm^2)	Malapposed area (ID_{Tube}-OD_{Stent}) (mm^2)
1	POT-SC/LP	3	5.00	5.00	1.0	19.60	5.10	5.10	20.80	6.40	5.90	29.20	8.40
2	POT-SC/SP	10	5.90	5.90	1.0	27.20	6.00	6.00	28.60	6.20	6.20	29.70	1.10
3	POT-NC/HP	3	6.07	6.07	1.0	28.77	6.22	6.22	30.30	6.22	6.22	30.30	0
4	FKBD-US/SP	3	6.30	4.10	1.5	21.40	6.50	4.30	22.80	6.70	5.60	29.00	6.20
5	FKBD-OS/LP	3	5.50	4.60	1.2	19.70	5.70	4.80	20.90	6.50	5.80	29.10	8.20
6	FKBD-OS/SP	3	6.70	4.70	1.4	25.70	6.90	4.90	27.20	6.90	5.30	29.00	1.80

EI: ellipticity index; FKBD: final kissing balloon dilation; ID: inner diameter; HP: high pressure; LP: low pressure; NC: non-compliant; OD: outer diameter; OS: optimally sized; POT: proximal optimisation technique; SC: semi-compliant; SP: standard pressure; US: undersized

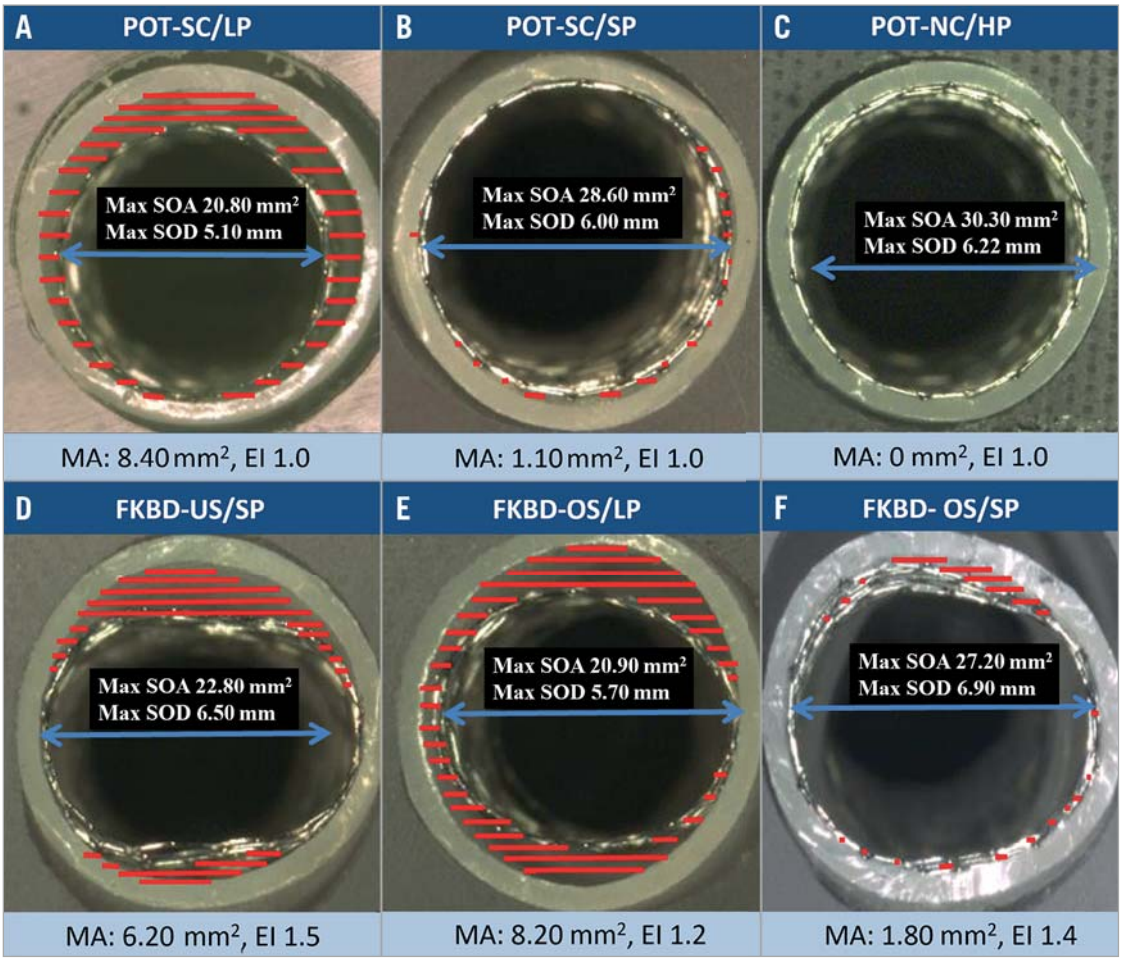

Figure 1. *Cross-sections of stents (proximal edge) post dilation in bench testing. A) & B) Cross-sections of the proximal edge of the stents after post-dilation by POT using 6.00 mm balloons (semi-compliant [SC] Maverick XL) at low pressure (LP) of 6 atm (POT-SC/LP) and standard pressure (SP) of 14 atm (POT-SC/SP), respectively. Optimal ellipticity index (EI) was seen in the POT models. C) The SYNERGY stent was post-dilated to 6 mm using the new NC Emerge 6 mm balloon at very high pressures of 24 atm (POT-NC/HP). D) - F) Cross-sections of the proximal edge of the stents after post-dilation by FKBD using Apex balloons: i) the relatively undersized (US), but commonly used, 3.50 mm and 4.00 mm balloons at standard pressure (SP) of 12 atm (Panel D - FKBD-US/SP), ii) optimally sized (OS) 4.00 mm and 5.00 mm balloons at LP of 4 atm (Panel E - FKBD-OS/LP), and iii) at SP of 12 atm (Panel F - FKBD-OS/SP), correspondingly. FKBD resulted in an elliptical shape of the proximal edge of the stents. Higher pressures will result in larger diameters and stent areas but also in increased ovalisation and malapposition. FKBD: final kissing balloon dilation; LP: low pressure; MA: malapposed area; POT: proximal optimisation technique; RBP: rated burst pressure; SOD: stent outer diameter; US: undersized*

of 6.90 mm in the FKBD-OS/SP model. However, the stent outer area of 27.20 mm^2 in FKBD-OS/SP was still significantly lower compared to that of POT-SC/SP and POT-NC/HP. **Figure 2A** and **Figure 2B** show the significant differences in the stent outer diameters and stent outer areas following expansion among the six models. We further investigated the relation of stent diameters to pressures as they are gradually overexpanded by 6.00 mm balloons, showing that the largest outer stent diameter is possible with an NC balloon **(Figure 3)**.

ELLIPTICITY INDEX (EI)

Among the five models, we found that POT-SC/SP and POT-NC/HP resulted in the most optimal EI. With POT, the EI was 1.0 whereas all FKBD models resulted in elliptical stents (with the EI ranging from 1.2 to 1.5) with significant potential for malapposition, in particular with the use of US balloons. Under the FKBD-US/SP model where balloon diameters are frequently used in the clinical setting, the 3.50 mm and 4.00 mm balloons resulted in the highest EI of 1.5. **Figure 2C** shows the significant differences in EI among the different models.

MALAPPOSED AREA (MA)

Among the five models, the POT-NC/HP resulted in the least amount of MA **(Table 2, Figure 2D)**. Of note, among the POT models, the POT-LP model also exhibited a high MA (8.40 mm^2) which only improved with higher pressures employed in the

POT-SC/SP or NC/HP models. Importantly, with FKBD, MA was higher in the FKBD- US/SP, OS/LP and OS/SP models (MA was 6.20, 8.20 and 1.80 mm^2, respectively).

STENT MECHANICAL PERFORMANCE AT OVEREXPANSION LIMITS

Figure 4 shows the impact of overexpansion on stent mechanical performance. Additional data regarding stent performance measurements are shown in **Supplementary Table 2** in the **Supplementary Appendix**. The radial strength of the stent was similar among the control, 5.00 mm and 5.75 mm groups; however, it significantly increased at 6.00 mm diameter (0.26±0.01; 0.27±0.02; 0.28±0.04; 0.38±0.04 N/mm, respectively, p<0.001). Stent recoil significantly decreased from 2.9% to 1.4% at larger sized diameters (p<0.01). There was a significant change in measured average stent length from 16.1±0.2 mm at 4.0 mm to 17.5±0.5 mm and 16.8±0.6 mm at 5.0 and 5.75 mm, respectively (p<0.01). Percentage stent surface to artery ratio calculated on the manufacturer-provided data decreased from 14.2% at 4.0 mm to 9.4% at 6.00 mm **(Supplementary Table 3)**.

Discussion

In this study, we investigated whether a 4.00 mm SYNERGY stent could be overexpanded beyond the recommended expansion limit to 6.00 mm. We subsequently compared different expansion techniques to achieve optimal stent apposition in a 6.00 mm phantom model. In addition, we evaluated the impact of overexpansion on the mechanical characteristics of the stent.

The main findings were that:

– The 4.00 mm thin-strut platinum-chromium stent can be expanded to a 6.00 mm outer stent diameter using high-pressure SC and NC coronary balloons. Of note, if low pressures were used, a maximal stent diameter of only 5.10 mm could be obtained using correctly sized balloons in the POT-SC/LP model.
– POT-SC/SP and POT-NC/HP resulted in more optimal EI and minimal MA while achieving adequate overexpansion compared to FKBD.
– FKBD also requires high-pressure inflation to achieve significant overexpansion, resulting in stent eccentricity and focal malapposition.
– Radial strength was still maintained despite stent overexpansion. Stent recoil and % surface to artery ratio decreased as stents were overexpanded.

Studies have shown that clinical outcomes after PCI are linked to the ability of metallic stents to reach adequate stent expansion and maintain elastic recoil, without compromising on radial strength, thereby achieving a large final lumen. Incomplete stent expansion is considered a predictor of stent thrombosis, and high-pressure post-dilation has generally been recommended to avoid incomplete stent apposition and to reduce the risk of adverse outcomes[16]. A consensus statement from the European Bifurcation Club recommended the use of POT to restore stent geometry and

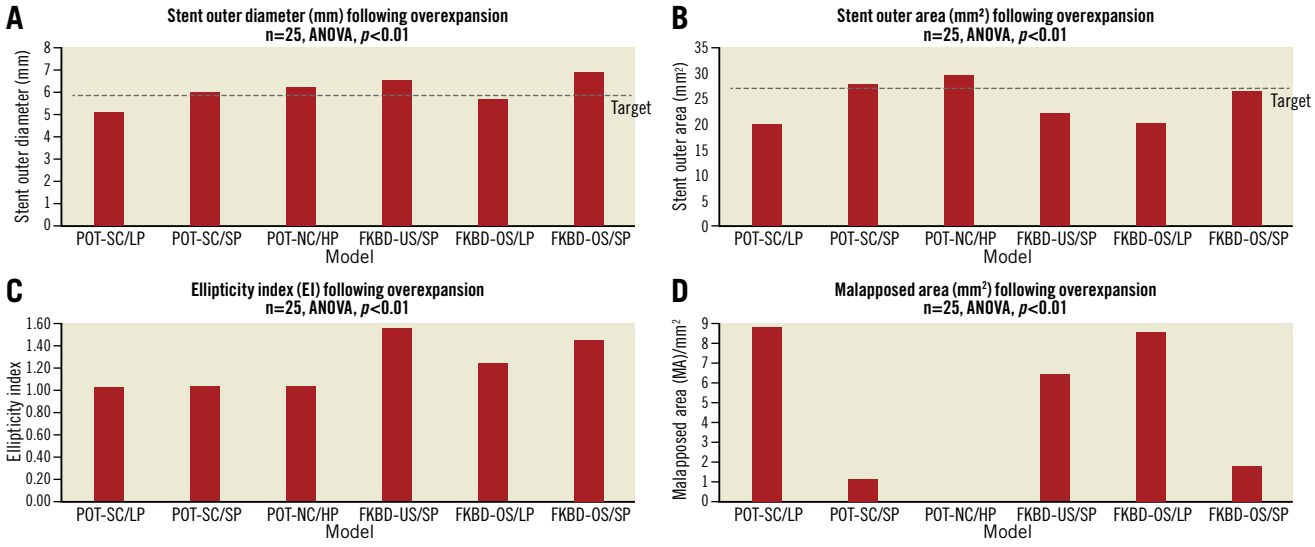

Figure 2. *Comparison of stent measurements among the models. A) Stent outer diameter (mm) following overexpansion. Stent outer diameter could reach a target of 6.0 mm in three of the six models as shown. B) Stent outer area (mm^2) following overexpansion. The stent outer area could reach the target of 28.3 mm^2 in only the POT-SC/SP and NC/HP models. The target area is based on a 6.0 mm circular stent diameter. C) Ellipticity index following overexpansion. An ideal ellipticity index of 1.0 was achieved in the POT models but not in the FKBD models. D) Malapposed area (mm^2) following overexpansion. Among the models tested, POT-NC/HP resulted in the least amount of MA. The POT-SC/LP model also exhibited a high MA (8.40 mm^2) which only improved with higher pressures employed in the POT-SC/SP and POT-NC/HP models. FKBD: final kissing balloon dilation; HP: high pressure; LP: low pressure; NC: non-compliant; OS: optimally sized; POT: proximal optimisation technique; SC: semi-compliant; SP: standard pressure; US: undersized*

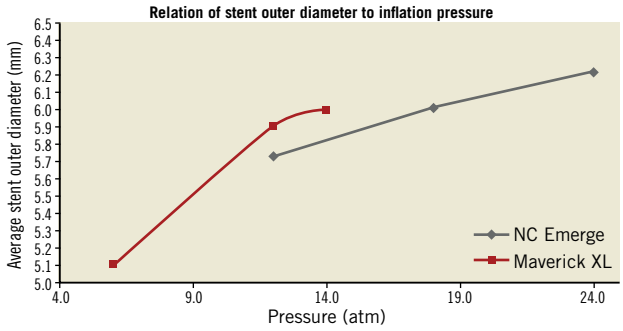

Figure 3. *The relation of the change in stent diameters to pressure used for stent expansion using 6.00 mm balloons (SC Maverick and NC Emerge). Very high pressures were required to overexpand the stents at 5.5 to 6.0 mm diameters. The preserved radial strength of the SYNERGY allows it to be post-dilated with a 6 mm balloon to RBP without fractures. Note: Maverick XL RBP=14 atm; NC Emerge RBP=18 atm.*

minimise malapposition in large vessels and proximal to the carina in bifurcation lesions[10]. It is especially useful in the presence of large side branches as it allows the operator to match the proximal segment of the main branch stent with the main branch diameter by means of a short balloon adapted to the proximal segment. This study added information on the high pressures needed to reach maximum overexpansion typically necessary in left main PCI. However, such adequately sized balloons may not always be available and FKBD is still frequently the final step in left main PCI.

Numerous studies have documented that more complete stent expansion is associated with a reduction in late restenosis[17]. The MUSIC trial showed how the use of intravascular ultrasound (IVUS) criteria (such as the EI) may improve acute and six-month clinical and angiographic outcomes[18]. In a study by Kang et al[19], the minimal stent area was an important factor in predicting angiographic restenosis. This was found to be 5.0 mm^2 for the left circumflex artery ostium, 6.3 mm^2 for the left anterior descending artery ostium, 7.2 mm^2 for the polygon of confluence, and 8.2 mm^2 for the proximal left main above the polygon of confluence.

The recommended stent overexpansion is generally between 0.5 mm and 0.75 mm above the largest nominal diameter. Previous studies have reported results of DES overexpansion experiments in bench testing[20] and with the use of computer modelling[21]. In an earlier study by Basalus et al, bench testing on the impact of large partial post-dilation for overexpanded DES on micro-CT assessment showed differences in strut dimensions which varied in relation to position and type of stent platform tested[11]. However, to the best of

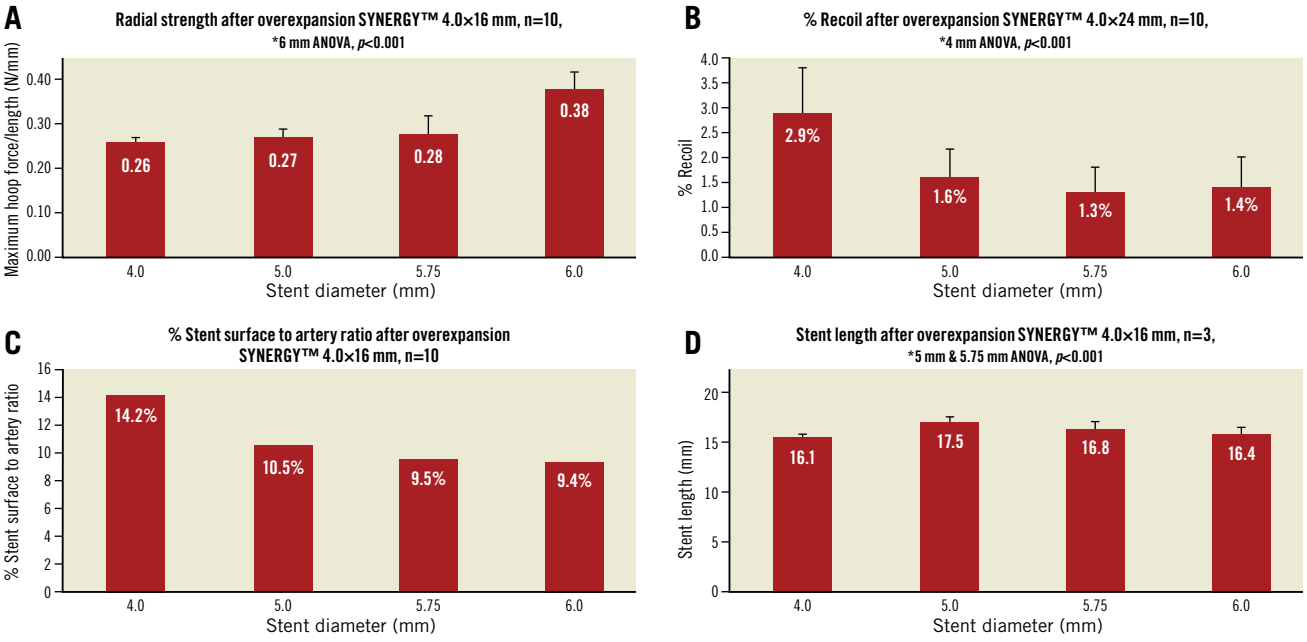

Figure 4. *Impact of overexpansion on stent mechanical performance. A) Radial strength is still maintained even at the overexpansion limit. Radial strength was not affected in overexpanded stents. There were no significant differences in the radial strength; it actually showed an increasing trend as measured by average maximum compression resistance (hoop force/length: N/mm) among the 4.00 mm, 5.00 mm, 5.75 mm and 6.00 mm groups (p=0.20). B) Stent recoil shows a decreasing trend when the stent reaches the overexpansion limit. Stent recoil was significantly decreased as the stent size increased (p<0.01). C) Percentage surface to artery ratio change in relation to stent diameter. Percentage stent surface to artery ratio (calculated as a ratio of stent outer surface area and outer vessel area multiplied by 100) decreases as the diameter of the stent increases from 4.00 mm to 6.00 mm. D) Stent length changes as the stent approaches the overexpansion limit. There was a significant change in measured average stent length when the stents were expanded from a diameter of 4.00 mm to 6.00 mm (p<0.01). Detailed measurements are provided in online Supplementary Table 2.*

our knowledge, neither has a comparison of the different post-dilation strategies such as POT and kissing balloon dilation been carried out nor has the mechanical response of overexpanded stents been evaluated. In our bench test model, the FKBD technique resulted in more elliptical stent geometry with higher malapposition compared with POT, regardless of the size of balloon or pressures used.

In a clinical study conducted by Shand et al[3], the use of DES in left main stenting was evaluated with IVUS. The BioMatrix Flex™ (Biosensors, Bülach, Switzerland) (3.5 and 4.0 mm stents), PROMUS Element™ (Boston Scientific) (3.5 and 4.0 mm stents) as well as the Resolute Integrity® (Medtronic, Minneapolis, MN, USA) (3.5 mm stent) were implanted followed by post-dilation with 5.5 or 6.0 mm balloons. In a subgroup of 31 patients who had undergone left main PCI with post-stent IVUS images available for analysis, the mean maximal stent area (at the proximal left main) and mean maximal stent diameter achieved were 19.7±3.7 mm^2 and 5.5 (4.7-6.4) mm for the BioMatrix Flex 4.0 mm stent and 20.6±2.8 mm^2 and 5.3 (4.3-6.3) mm for the PROMUS Element 4.0 mm stent. The results appear comparable with the stent measurements achieved in our study. Our study showed that overexpansion of a 4.0 mm metallic stent platform can be achieved beyond the recommended overexpansion limit with minimal malapposition and optimal ellipticity, which holds potential for favourable clinical outcomes. We believe that our study set-up represented a frequent clinical situation where the diameter of the left main artery is larger than that of clinically available (and approved) stents. Most coronary stents are only available up to 4 mm, whereas previous IVUS studies[3] showed that the diameter of most left main arteries ranges from 5-6 mm in diameter. For these vessels, the risk of coronary artery rupture will be minimal. The use of IVUS in left main stenting as recommended in European guidelines[1] will also confer additional safety against adverse procedural outcomes such as coronary artery rupture by providing additional information about the vessel dimensions. This, however, should be further studied in clinical trials using intravascular imaging. This would be particularly relevant if we were to evaluate the suitability of current-generation DES for the treatment of left main stenosis in which vessel diameters routinely extend beyond 5.00 mm.

In the present study, stent diameters were measured directly rather than calculated from geometric assumptions and different imaging modalities. In the silicone phantoms used in our study, the stent diameters were significantly smaller than the diameters indicated on the manufacturers' compliance charts of the post-dilatation balloons **(Supplementary Table 4)**. This illustrates the serious constrainment of overexpanded metallic stents on the post-dilatation balloons. This may be of clinical significance since the inability of the stent balloon to reach its target size during deployment of the stent and subsequent elastic recoil are two important contributory factors towards stent underdeployment[22]. The findings support the recommendation that adequately sized balloons and pressures are necessary to facilitate adequate expansion.

The results of the mechanical performance of overexpanded stents as the stent diameter increases in size from 4.00 mm to 6.00 mm provide interesting insights. The effect on the mechanical response in overexpanded stents is still unknown and may be difficult to predict[5]. It has been shown previously that extremely oversized post-dilation, for example caused by kissing post-dilation, considerably modifies the strut configuration[11]. There are concerns that distortion of the stent crowns may occur with stent overexpansion with several potential risks – a change in the mechanical response of the stent, a decrease in the stent resistance to fatigue, and damage to polymer coating[9]. The graphical data in **Figure 4A** suggest that, despite overexpansion, the radial strength would not be affected, as the stent size increased after overexpansion and in fact increases when the diameter reaches 6.00 mm.

This is potentially advantageous, as radial strength is a key component towards eliminating acute elastic recoil post stenting. The higher radial strength may be attributed to a change in the geometrical arrangement of the stent struts. The struts exhibit a "column-like" effect as the circumferential struts straighten out and lose their curved interlinked architecture, resulting in an increased resistance to radial forces. Such a finding was demonstrated in a crown deformation analysis of the stent struts after post-dilation by Foin et al[4]. At 6 mm, the stent segments would have been stretched outwards to their limits and nearly straightened out. This extreme state may contribute to an increase in radial strength. Another explanation for the increase in radial strength can be attributed to the decrease in stent length as stents approach their expansion limit. The radial strength values are normalised to stent length (N/mm) so stent length impacts on these values.

There was a decrease in the stent recoil as the stent expanded from 4.00 mm towards 6.00 mm. This finding may be expected, as mechanically the more "column-like" structure of the struts at larger sizes is less likely to recoil than a "spring-like" shape of a "v" at smaller sizes. Stent length change can be unpredictable, as it is a complex function that is dependent on many variables such as the method of deployment, type of balloon used, manner of dilation and final stent diameter.

To our knowledge, this is the first time that bench testing has compared the two post-dilation strategies in an overexpansion model and evaluated the mechanical performance of DES overexpansion. In addition, we have performed advanced finite element computer simulations of the complete stenting procedures. These simulations were based on predetermined pressures and diameters of balloons and stents used in a virtual stent model for every step during the deployment sequence and with assessment of the final stent outcomes **(Figure 5A)**. The results confirmed the experimental findings and provided insights during the balloon inflation during FKBD and additional information on the resulting forces exerted on the stent by the vascular wall. In summary, these simulations revealed that the use of POT results in a highly uniform distribution of these contactile forces in contrast to the FKBD **(Figure 5B, Figure 5C)**.

Limitations

The limitations of our study are inherent to bench testing. Firstly, our data refer to *in vitro* stent deployments performed in standard

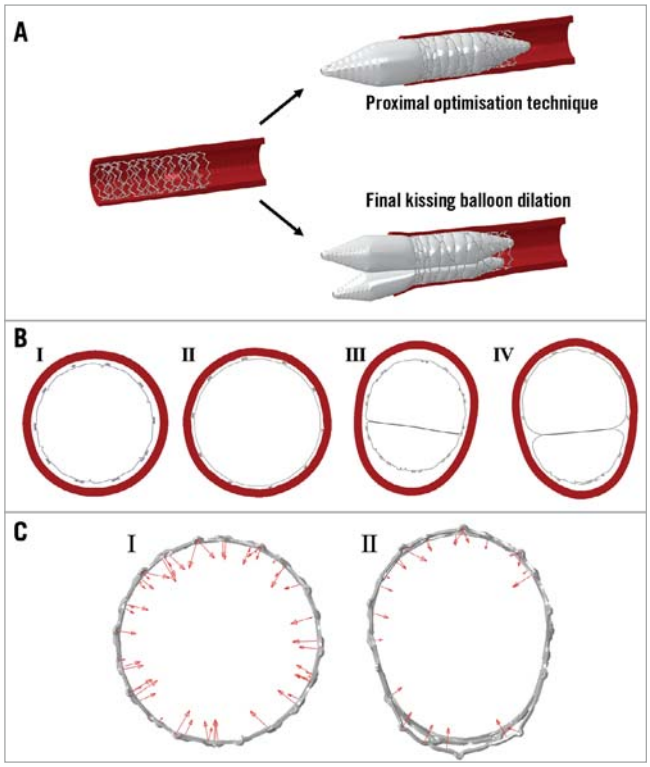

Figure 5. *Computer simulations of the stenting procedures. A) Different models used for overexpansion. This figure illustrates the two types of overexpansion strategy, namely the proximal optimisation technique (POT) and final kissing balloon dilation (FKBD), studied in both the bench testing and modelling process. B) Cross-section of stents (proximal edge) post dilation in virtual testing. Left to right: I) POT-SC/LP with some malapposition, II) POT-SC/SP with full apposition, III) FKBD-OS/LP with ellipticity and some malapposition, IV) FKBD-OS/SP with ellipticity and some malapposition. FKBD: final kissing balloon dilation; LP: low pressure; OS: optimally sized; POT: proximal optimisation technique; SC: semi-compliant; SP: standard pressure C) Distribution of contactile forces on stents after virtual implantation. The cross-section of a computer simulation post POT (I). The arrows indicate the uniform distribution of the contact forces seen during the computer modelling. The right image (II) shows the cross-section of a computer simulation post FKBD. The arrows indicate a non-uniform distribution of the contact forces seen during the computer modelling.*

laboratory environments in silicone phantom models. *In vivo* behaviour and stent artery response during stent deployment of different sizes in diseased arterial walls constraining the stents in a real-world clinical setting may be different. Other vascular characteristics including vascular wall stiffness, calcification, plaque characteristics and distortion, as well as more complex procedures involving bifurcation and overlapping stents, may affect the resultant expansion of stents deployed in a real-world setting. Secondly, assessment of the side branch in the bifurcation lesion was not available. This is because the effect of kissing balloon dilation in improving blood flow to the side branch during bifurcation stenting has been previously studied[8,21,23,24]. However, in left main stenting, the effect of POT for overexpansion has not been widely studied as it is not routinely carried out, since most operators would consider kissing balloon dilation adequate to achieve optimal stent apposition in the main branch. The main aim of this study was to evaluate the impact of different approaches, namely POT and FKBD, in achieving full apposition in large left main vessels and to compare the impact of POT and FKBD on the main vessel. This is especially important as the left main diameter is generally underestimated and the maximum overexpansion diameters of the stents commonly used in the catheterisation laboratory are unknown to operators. Thirdly, our sample size is relatively small. One stent design and size was tested and no claim on overexpansion of other sizes and designs can be made. Further studies are indicated to perform similar investigations for other stent designs and diameters and to assess long-term structural integrity. Lastly, we have studied POT as a separate entity from FKBD though in reality POT is also frequently performed with FKBD. In our bench testing scenario, while we assume that single use of POT is equivalent to the use of POT with intermediate FKBD, the results still support the recommendation that POT should be the final step regardless of whether FKBD is performed in cases of stent overexpansion.

Conclusions

In conclusion, our study shows that POT but not FKBD can expand the platinum-chromium 4.00 mm stent beyond the overexpansion limit of 5.75 mm with optimal stent apposition and performance in bench testing. In PCI involving relatively larger vessel diameters, such as left main stenting, POT may be the technique of first choice to achieve optimal stent expansion but requires adequately sized balloons with high pressures. The impact on the mechanical performance of the stents after overexpansion would merit further evaluation.

Impact on daily practice

For left main percutaneous coronary intervention (PCI) which is sometimes up to 6 mm in diameter, full pressure (16 atm) large size non-compliant balloons are necessary during the proximal optimisation technique (POT) to achieve a predicted stent diameter of 6 mm and avoid malapposition seen in different final kissing balloon post-dilatation approaches. Platinium-chromium stents maintain their mechanical characteristics at these diameters.

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Conflict of interest statement

R.J. van Geuns has received speakers fees from Boston Scientific. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix. Methodology.

Supplementary Table 1. Stent measurements groups 1-6.

Supplementary Table 2. Stent performance measurements.

Supplementary Table 3. Stent performance at overexpansion limits - surface to artery ratio.

Supplementary Table 4. Compliance table of stents/balloons used.

Supplementary Figure 1. Illustration of the bench testing methods performed.

The supplementary data are published online at: www.asiaintervention.org

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Stent versus bypass grafting for the treatment of left main stem disease: a meta-analysis of six randomised controlled trials

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KEYWORDS

- coronary artery bypass grafting
- left main stem
- meta-analysis
- percutaneous coronary intervention

Abstract

Aims: We performed a meta-analysis of all randomised controlled trials to compare percutaneous coronary intervention (PCI) with stents versus coronary artery bypass grafting (CABG) for the treatment of left main stem disease.

Methods and results: We searched PubMed, the Cochrane Library, ClinicalTrials.gov, and major cardiovascular congresses for articles comparing PCI versus CABG for the treatment of left main stem disease. We utilised either fixed or random effects models to calculate the pooled risk ratio (RR) and 95% confidence interval (CI). Six trials with a total of 4,717 patients treated with either PCI (n=2,355) or CABG (n=2,362) were eligible and included. There were no differences in all-cause (RR: 1.03, 95% CI: 0.84-1.25, p=0.78) and cardiac mortality (RR: 1.03, 95% CI: 0.78-1.37, p=0.83) between PCI- and CABG-treated patients at the longest available follow-up. PCI-treated patients had a higher incidence of repeat revascularisation (RR: 1.65, 95% CI: 1.40-1.94, p<0.0001). However, there was no difference in myocardial infarction (RR: 1.36, 95% CI: 0.87-2.12, p=0.17) and stroke (RR: 0.86, 95% CI: 0.44-1.69, p=0.66).

Conclusions: There are no differences in mortality, myocardial infarction and stroke in PCI- or CABG-treated patients with left main stem disease. However, PCI-treated patients are more likely to need repeat revascularisation.

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Introduction

The optimal revascularisation strategy for patients with unprotected left main stem (LMS) disease remains debatable. Cohen and Gorlin published a case series of coronary artery bypass grafting (CABG) in unprotected LMS in 1975 showing a long-term mortality benefit[1]. Subsequently, several registries and randomised controlled trials (RCT) confirmed the survival benefit of CABG over medical treatment, especially in moderate- to high-risk groups[2,3]. Traditionally, percutaneous coronary intervention (PCI) for unprotected LMS has remained a class III indication (i.e., harmful) in the international guidelines[4,5]. However, with recent technical and technological advances, PCI has challenged the supremacy of CABG and has been the subject of several RCT. European Society of Cardiology (ESC) revascularisation guidelines in 2014 for the first time upgraded PCI for LMS to a class I indication for patients with LMS disease and a SYNTAX score ≤22 (and class IIa for patients with a SYNTAX score 23-32) based on data from the SYNTAX (SYNergy Between PCI With TAXUS and Cardiac Surgery) trial[6,7]. Two more large clinical trials, NOBLE (Coronary Artery Bypass Grafting Vs Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis) and EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation), have been reported since then[8,9]. The results of these trials provide important but somewhat divergent data. We have therefore performed an updated meta-analysis of all RCT to evaluate clinical outcomes with PCI using stents compared with CABG in patients with unprotected LMS disease.

Methods

SEARCH STRATEGY AND SELECTION CRITERIA

Randomised trials comparing PCI with a stent versus CABG were searched in PubMed, the Cochrane Library, and ClinicalTrials.gov, as well as major cardiovascular congresses. The search was limited to the English language. The subject keywords percutaneous coronary intervention, angioplasty, stents, left main stem, bypass grafting and randomised trial were applied to identify studies. The last search was performed in January 2017 by two independent investigators (J-Z. Cai and Y-X. Zhu).

INCLUSION AND EXCLUSION CRITERIA

Two investigators independently screened the title and abstract of the retrieved reports and reviewed the full articles of relevant citations in detail. Any discrepancies or disagreements were settled by a third investigator. Only randomised controlled clinical trials comparing clinical outcomes between CABG and PCI using stents for the treatment of unprotected LMS disease and with a fully published status were included. The clinical outcomes of interest were all-cause death, cardiac death, myocardial infarction (MI), stroke, and repeat revascularisation. We evaluated clinical outcomes for each trial at one year as well as at the longest reported follow-up. The risk of bias for individual trials was assessed in accordance with the Cochrane Collaboration's tool.

STATISTICAL ANALYSIS

Risk ratio (RR) and mean differences with 95% confidence interval (CI) were utilised as summary statistics. The Mantel-Haenszel fixed effects model and inverse variance fixed effects model were used for categorical variables and continuous variables, respectively. We performed the I^2 test and chi-square test to evaluate heterogeneity among studies. An I^2 >50% or p-value <0.10 was considered as significant heterogeneity. A random effects model was performed to calculate the risk estimation if a significant heterogeneity was detected. Sensitivity analyses were carried out by omitting one study at a time. The Egger's linear regression tests were employed to test for funnel plot asymmetry at the p<0.10 level of significance. All the statistical analyses were performed using Review Manager, Version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata, Version 13.0 (StataCorp., College Station, TX, USA).

Results

Six eligible RCT were identified after the screening process, as illustrated in **Figure 1**. The trials included were PRECOMBAT[10] (Premier of Randomised Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) with five-year follow-up, SYNTAX[7] with five-year follow-up, LE MANS[11] (left main stenting) trial with 10-year follow-up, Boudriot et al[12] with one-year follow-up, NOBLE[8] with five-year follow-up, and EXCEL[9] with three-year follow-up. These trials randomised 4,717 patients with unprotected LMS disease to treatment with either PCI with stents (n=2,355) or CABG (n=2,362) and are summarised in **Table 1**.

ALL-CAUSE AND CARDIAC DEATH

All-cause mortality was reported in all six trials. The pooled RR showed no significant differences between PCI- and CABG-treated

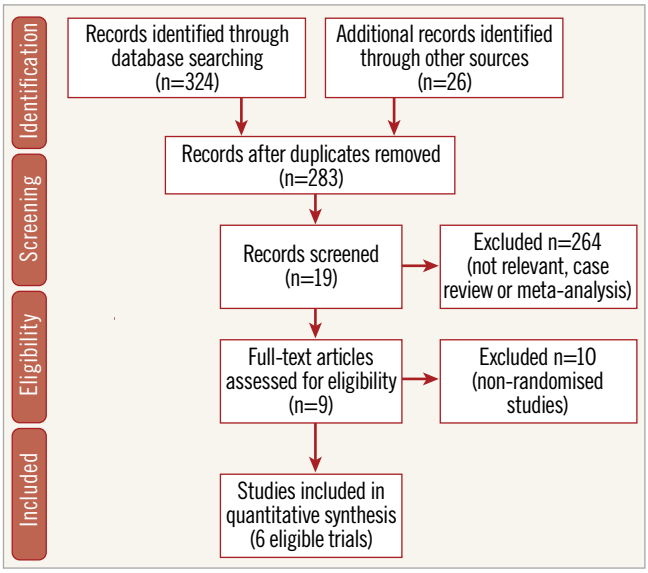

Figure 1. *Study flow chart. Flow diagram illustrating the screening and study selection process for the meta-analysis.`*

Table 1. Study and patient characteristics.

Study	Treatment (n)		Follow-up (years)	Definition of primary MACCE	Age		Male		DM		Multivessel		SYNTAX score	
					PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG
LE MANS	BMS/DES (52)	CABG (53)	10	Cardiac death, MI, RR, ST, or stroke	61 (11)	61 (8)	60	73	19	17	60	75	25 (9)	25 (7)
Boudriot et al	SES (100)	CABG (101)	1	Death, MI, and RR	66 (n/a)	69 (n/a)	72	77	40	33	37	45	24 (n/a)	23 (n/a)
PRECOMBAT	SES (300)	CABG (300)	5	Death, MI, stroke, or ischaemia-driven TVR	62 (10)	63 (10)	76	77	34	33	84	71	24 (9)	26 (11)
SYNTAX	PES (357)	CABG (348)	5	Death, MI, stroke, and RR	65 (10)	66 (10)	72	76	24	26	70	66	30 (14)	30 (13)
NOBLE	BES/PES/SES (598)	CABG (603)	5	Death, non-procedural MI, RR, or stroke	66 (10)	66 (9)	80	76	15	15	(n/a)	(n/a)	23 (8)	22 (8)
EXCEL	EES (948)	CABG (957)	3	Death, stroke, MI, or ischaemia-driven revascularisation	66 (10)	66 (10)	76	78	30	28	52	51	21 (6)	21 (6)

Values are mean (SD) or %. BES: biolimus-eluting stents; CABG: coronary artery bypass grafting; DES: drug-eluting stents; DM: diabetes mellitus; EES: everolimus-eluting stents; MI: myocardial infarction; PES: paclitaxel-eluting stents; RR: repeat revascularisation; SES: sirolimus-eluting stents; ST: stent thrombosis; TVR: target vessel revascularisation

groups for all-cause mortality at one-year (RR: 0.81, 95% CI: 0.59-1.12, p=0.21; I^2=0%) **(Figure 2A)** or long-term (RR: 1.03, 95% CI: 0.84-1.25, p=0.78; I^2=18%) **(Figure 2B)** follow-up. Cardiac death was reported in only two trials at one-year follow-up leading to statistical heterogeneity (I^2=62), and in four trials at long-term follow-up (I^2=25%). Nevertheless, there was no difference in cardiac death at one-year (RR: 1.03, 95% CI: 0.38-2.78, p=0.95) or long-term (RR: 1.03, 95% CI: 0.78-1.37, p=0.83) follow-up.

MYOCARDIAL INFARCTION

MI was reported in all six trials, although there were differences in the definition of MI, especially preprocedural MI. There was no significant difference in MI at one-year (RR: 0.86, 95% CI: 0.65-1.14, p=0.30; I^2=0%) **(Figure 3A)** or the longest available follow-up (RR: 1.36, 95% CI: 0.87-2.12, p=0.17; I^2=51%) **(Figure 3B)** between PCI- and CABG-treated patients. However, analysing only non-procedural MI revealed that, whilst there was no difference at one year (RR: 1.17, 95% CI: 0.77-1.76, p=0.46; I^2=0%) **(Figure 3C)**, CABG-treated patients had lower rates of MI (RR: 1.73, 95% CI: 1.27-2.35, p=0.0005; I^2=0%) **(Figure 3D)** at long-term follow-up. As the EXCEL trial reported spontaneous (as opposed to non-procedural) MI, sensitivity analysis excluding EXCEL also showed a reduction in MI among CABG-treated patients (RR: 1.79, 95% CI: 1.22-2.62, p=0.003; I^2=7%).

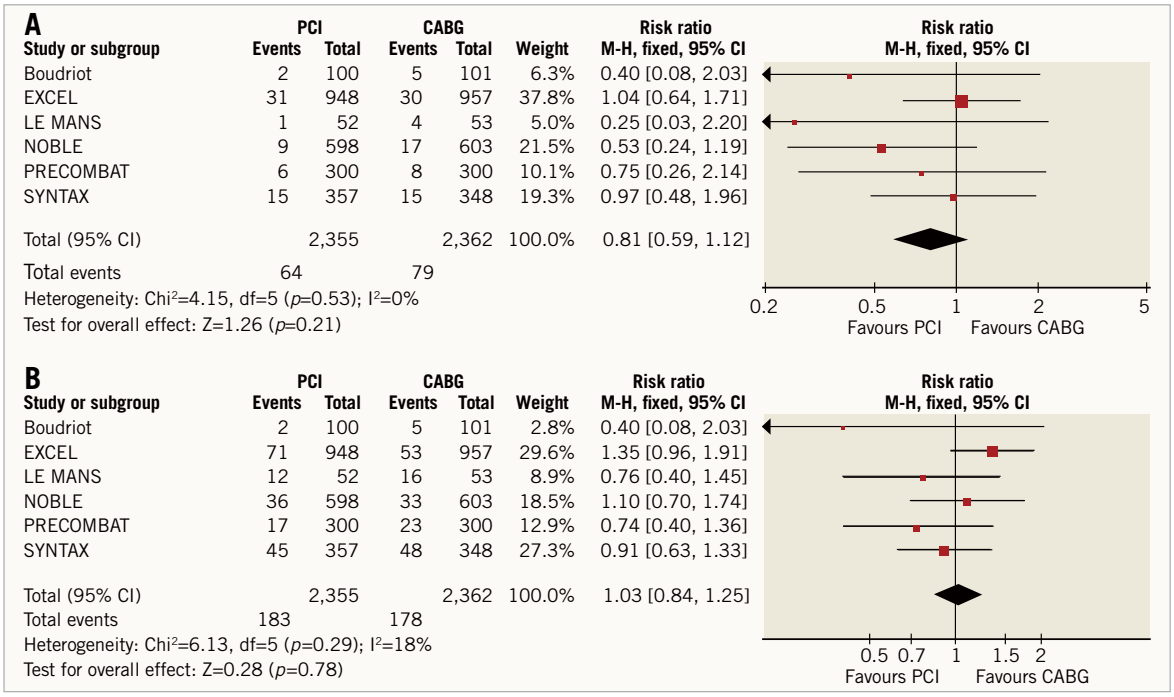

Figure 2. *Forest plots of risk ratios for all-cause mortality between PCI- and CABG-treated groups. There was no difference in all-cause mortality at one-year (A) or long-term (B) follow-up. The size of data markers indicates the weight of each trial included in the meta-analysis for all-cause death. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention*

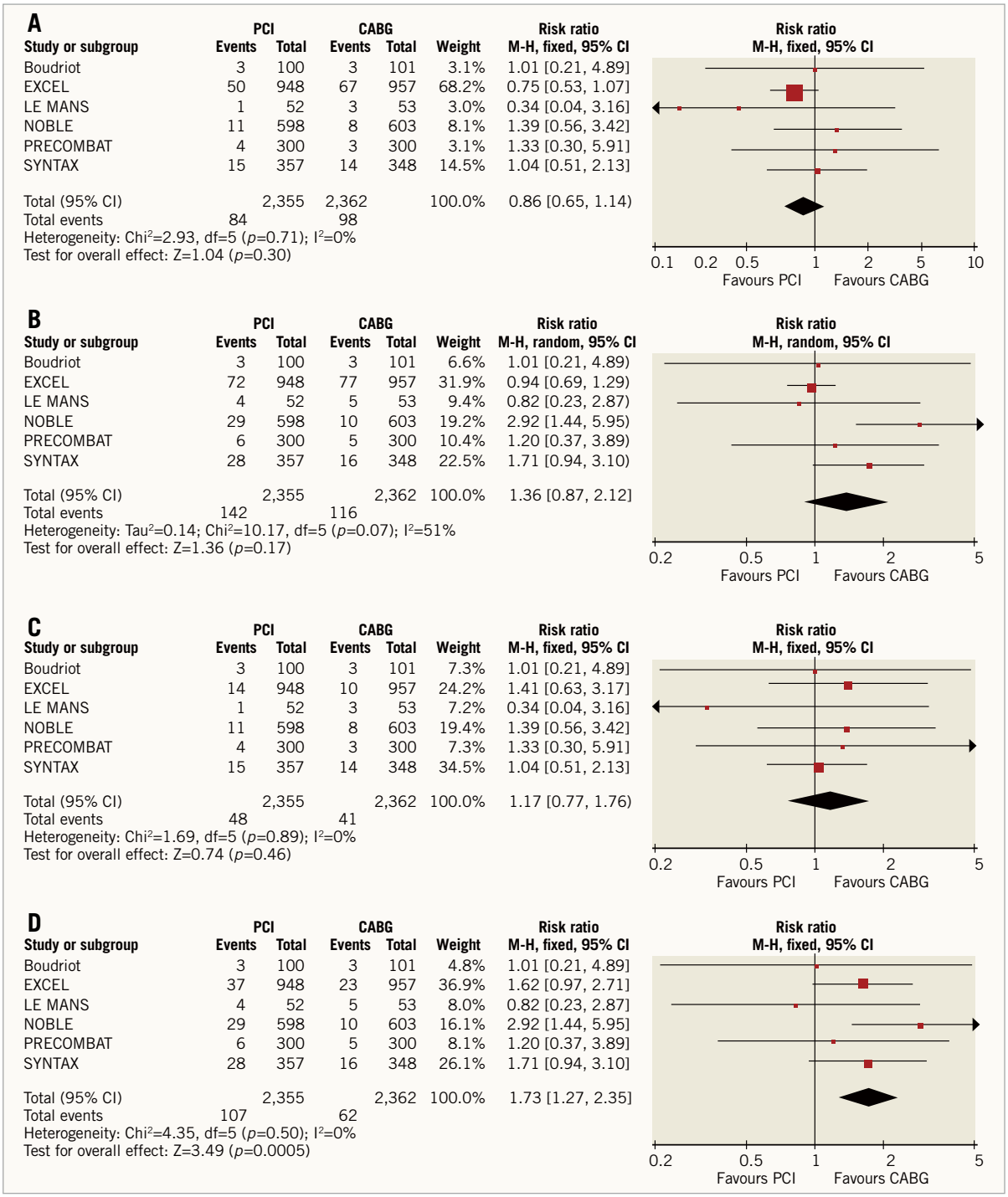

Figure 3. *Risk ratios for myocardial infarction between PCI- and CABG-treated groups. Forest plots showing risk ratio for all MI at one-year (A), all MI at long-term follow-up (B), non-procedural MI at one-year (C) and non-procedural MI at long-term follow-up (D). The size of data markers indicates the weight of each trial included in the meta-analysis for myocardial infarction. CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention*

STROKE AND REPEAT REVASCULARISATION

Stroke was reported in five trials. There was a lower incidence of stroke in PCI-treated patients at one year (RR: 0.39, 95% CI: 0.21-0.70, p=0.002; I^2=0%) **(Figure 4A)**, but there was no difference between revascularisation strategies at long-term follow-up (RR: 0.86, 95% CI: 0.44-1.69, p=0.66; I^2=51%) **(Figure 4B)**.

Repeat revascularisation was reported in all trials. PCI-treated patients had a higher incidence of repeat revascularisation at one year (RR: 1.80, 95% CI: 1.35-2.40, p<0.0001; I^2=0%) **(Figure 4C)**

as well as at long-term follow-up (RR: 1.65, 95% CI: 1.40-1.94, p<0.0001; I^2=19%) **(Figure 4D)**.

COMPOSITE OF MAJOR ADVERSE CARDIOVASCULAR AND CEREBRAL EVENTS

Major adverse cardiovascular and cerebral events (MACCE) as a composite of all-cause death, MI, stroke and revascularisation could be calculated for all trials despite the differences in definition of MI, revascularisation and incomplete data about stroke. There were no differences in MACCE at one-year follow-up (RR: 0.98, 95% CI: 0.82-1.16, p=0.78; I^2=39%) **(Figure 5A)**; however, on long-term follow-up, MACCE rates were much higher in PCI-treated patients (RR: 1.25, 95% CI: 1.12-1.39, p<0.0001; I^2=36%) **(Figure 5B)**. Further analysis based on the SYNTAX score was available in five trials and showed that there was no difference in the two revascularisation strategies for a SYNTAX score 1-32

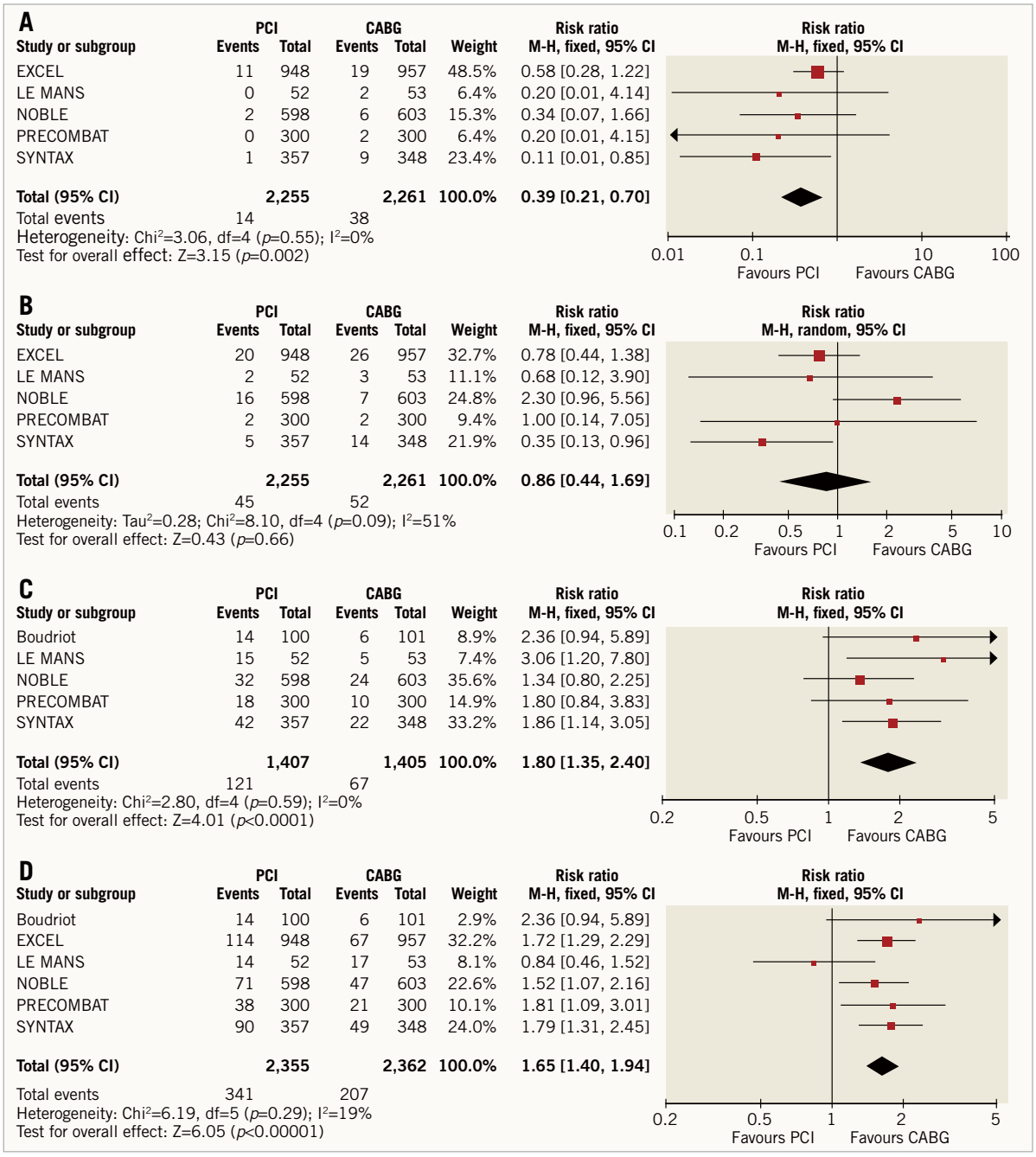

Figure 4. *Risk ratios for stroke and repeat revascularisation. Forest plots showing the risk ratio for stroke at one-year (A), stroke at long-term follow-up (B), repeat revascularisation at one-year (C) and repeat revascularisation at long-term follow-up (D) between the PCI- and CABG-treated groups. Size of data markers indicates weight of each trial included in the meta-analysis for stroke and repeat revascularisation. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention*

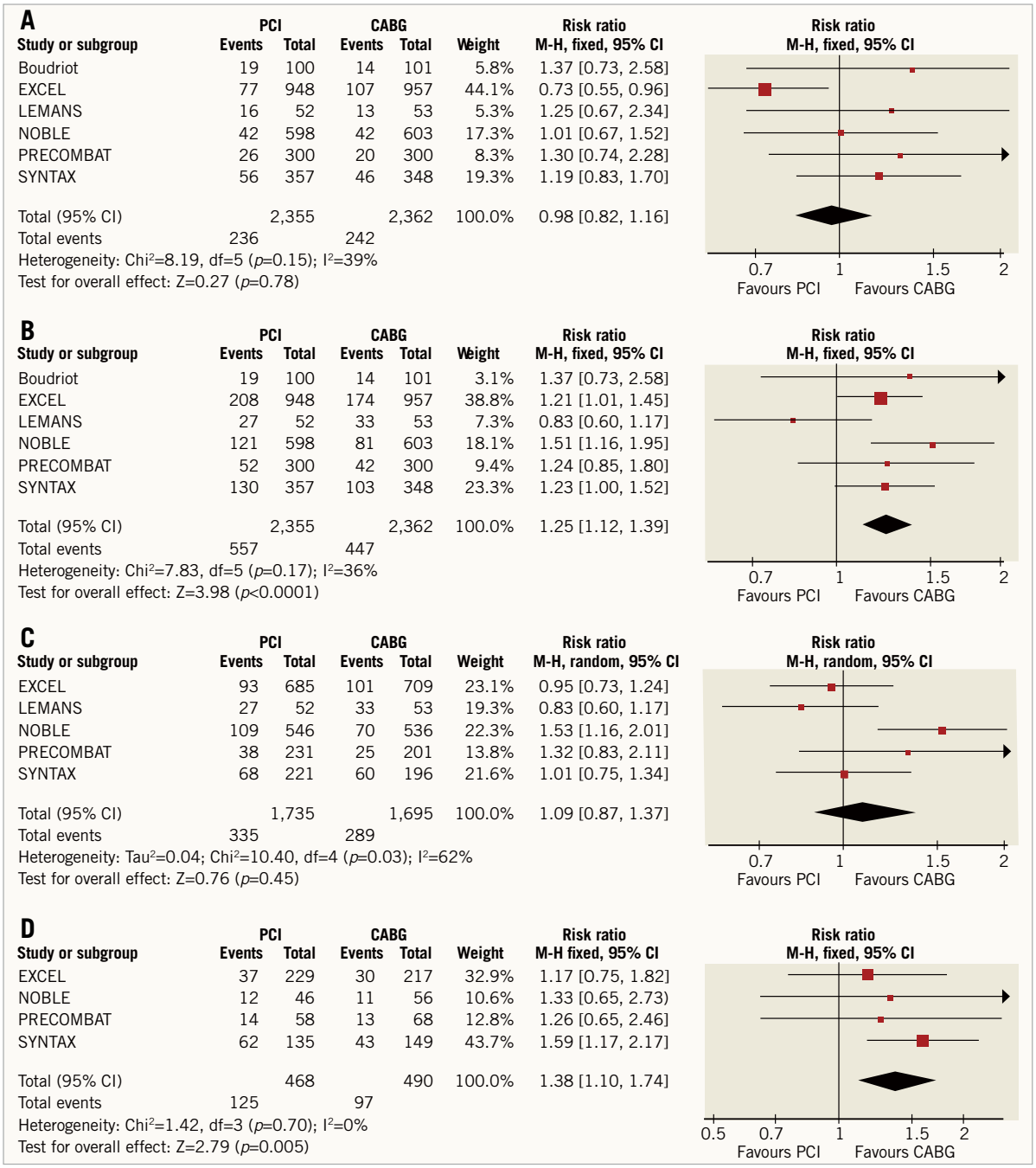

Figure 5. *Risk ratios for MACCE between the PCI- and CABG-treated groups. Forest plots showing the risk ratio for major adverse cardiovascular and cerebral events (MACCE) at one-year (A), MACCE at long-term follow-up (B), MACCE for SYNTAX score ≤32 (C) and MACCE for SYNTAX score >32 (D). The size of data markers indicates the weight of each trial included in the meta-analysis for MACCE. CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention*

(RR: 1.09, 95% CI: 0.87-1.37, p=0.45; I^2=62%) **(Figure 5C)**, but superiority of CABG for a SYNTAX score of 33 or more (RR: 1.38, 95% CI: 1.10-1.74, p=0.005; I^2=0%) **(Figure 5D)**.

PUBLICATION BIAS AND SENSITIVITY ANALYSES

The risk of bias for individual trials was low in accordance with the Cochrane Collaboration's tool **(Supplementary Figure 1)**. There was no publication bias observed with Egger's linear regression except for cardiac (p=0.081) and all-cause death (p=0.064), which may be attributed to the different follow-up duration of the included studies and not all studies reporting cardiac death **(Supplementary Figure 2)**. Sub-analysis of trials using first-generation (LE MANS, Boudriot, PRECOMBAT, SYNTAX) or predominantly newer-generation stents (NOBLE and EXCEL) did

not show any major differences in MACCE **(Supplementary Figure 3)**. Finally, meta-analysis with the exclusion of the LE MANS trial (as it used both bare metal stents [BMS] and drug-eluting stents [DES]) showed no significant difference in outcomes **(Supplementary Figure 4)**.

Discussion

To date, this is the largest meta-analysis of randomised controlled trials comparing the clinical outcomes of PCI with stent(s) versus CABG for the treatment of unprotected LMS disease. We found no difference in all-cause and cardiac mortality between the two treatment strategies. All MI was similar at one year but higher afterwards in PCI-treated patients. Stroke rates were lower in PCI-treated patients at one year but the difference disappeared on long-term follow-up. Revascularisation rates remained higher in the PCI-treated group.

The trials included in this meta-analysis had differences in inclusion/exclusion criteria, complexity of coronary disease (LMS bifurcation disease, SYNTAX score, etc.), technical aspect of the procedure (type of stent, use of intravascular ultrasound, use of arterial grafts), definition of clinical endpoints, and duration of follow-up. Despite these differences, it is reassuring to see that both PCI and CABG provided effective treatment of unprotected LMS disease with no difference in survival. The LE MANS trial was the first randomised trial of PCI (n=52) vs. CABG (n=53). Only 35% had drug-eluting stents (DES) and 81% had a left internal mammary artery but the primary outcome of major adverse cardiac events (MACE) at one year was similar in the two groups[13]. This trial now has 10-year follow-up data available showing that mortality (21.6% vs. 30.2%, p=0.41), MI (8.7% vs. 10.4%; p=0.68), stroke (4.3% vs. 6.3%, p=0.58) and repeat revascularisation rates (26.1% vs. 31.3%; p=0.39) were similar between PCI and CABG[11]. Boudriot et al (n=201) and PRECOMBAT (n=600) compared PCI with sirolimus-eluting stenting versus CABG using predominantly arterial grafts and found no difference in death or MI, whilst revascularisation rates remained high in the PCI arm[10,12]. The SYNTAX trial compared PCI with a paclitaxel-eluting stent versus CABG but also went one step further to dissect the relationship of extent/complexity of coronary disease with revascularisation strategy[7]. It showed that both PCI and CABG may provide optimal revascularisation in the lower and middle terciles of SYNTAX score but, for the high score tercile, CABG was clearly superior[7]. NOBLE (n=1,201) and EXCEL (n=1,905) have compared PCI with newer-generation DES versus CABG. In NOBLE, there was no difference in mortality (12% vs. 9%, p=0.77) and stroke (5% vs. 2%, p=0.073), but higher rates of non-procedural MI (7% vs. 2%, p=0.004) and revascularisation (16% vs. 10%, p=0.032) in the PCI group[8]. In EXCEL, there was no difference in mortality (PCI 8.2% vs. CABG 5.9%, p=0.11), cardiac death (PCI 4.4% vs. CABG 3.7%, p=0.48), stroke and MI at three years; however, ischaemia-driven revascularisation was higher in the PCI arm (12.6% vs. 7.5%, p<0.001)[9]. A recent pooled analysis at the patient level of four registries showed an association of intravascular ultrasound guidance during PCI with better outcomes in patients with left main disease undergoing revascularisation with DES. Although in most patients in the EXCEL, NOBLE and PRECOMBAT trials intravascular ultrasound was performed for guiding stent deployment, the risk of ischaemia-driven revascularisation in the PCI arm was also higher in comparison with CABG.

It is also reassuring to see that the results of RCT and our meta-analysis are consistent with several registries comparing the two revascularisation strategies for the treatment of unprotected LMS disease. In the Bologna registry (n=311), there was no difference in mortality and MI but repeat revascularisation was higher in the PCI group[14]. The DELTA registry also showed no difference in mortality, MI or stroke between PCI- (n=1,874) and CABG-treated (n=901) patients; however, revascularisation remained higher in the PCI group[15]. An Italian registry of patients with unprotected LMS stenosis treated with PCI (n=107) or CABG (n=142) reported no difference in mortality (HR: 0.3, 95% CI: 0.055-1.404, p=0.17) at one year. PCI offered a lower composite endpoint of death and/or MI (HR: 0.26, 95% CI: 0.08-0.60, p<0.001) and death, MI, or stroke (HR: 0.38, 95% CI: 0.18-0.82, p=0.01)[16]. However, repeat revascularisation was 20% in the PCI versus 4% in the CABG group. The non-randomised MAIN-COMPARE (Revascularisation for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularisation) registry assessed 1,138 patients undergoing CABG and 1,102 patients undergoing PCI (318 with BMS, 784 with DES). At three- and five-year follow-up, outcomes among a propensity-matched cohort of patients were comparable in terms of death and MACE, whereas repeat revascularisation was higher in the PCI group[17]. It would be appropriate to bear in mind that complex distal bifurcation or trifurcation LMS disease requiring multiple stents may affect PCI outcomes[18-20]. However, a study comparing PCI with DES (n=556) and CABG (n=309) in unprotected LMS bifurcation disease showed similar rates of death (HR: 0.95, 95% CI: 0.62-1.45), a similar composite endpoint of death/MI/stroke (HR: 0.97, 95% CI: 0.64-1.48) and higher repeat revascularisation with PCI (HR: 4.42, 95% CI: 2.39-8.18) at five-year follow-up. The outcomes were comparable between the simple stenting and complex stenting groups except for target vessel revascularisation (HR: 1.94, 95% CI: 1.22 to 3.10)[21].

A previous meta-analysis of four trials (without EXCEL and NOBLE) including 1,611 patients showed that PCI, as compared to CABG, was associated with a significant reduction in the risk of stroke, an increased risk of repeat revascularisation, and a similar risk of mortality or MI, resulting in a higher risk of MACE but a similar risk of MACCE[22]. Similarly, a recent meta-analysis of five trials (excluding LE MANS) showed similar results[23]. The LE MANS trial was excluded from this meta-analysis due to limited use of DES (35%). However, the LE MANS trial now has 10-year follow-up and provides useful insights into further revascularisation in both the PCI and CABG arms. Furthermore, our sensitivity analysis has shown no difference in outcomes with or without LE MANS or difference in outcomes based on type of

stent used. Due to differences in the primary composite endpoints and definition of endpoints, we have chosen to compare the individual outcomes and focused mainly on mortality, MI and stroke. Our results have therefore conclusively shown comparable hard outcomes between PCI- and CABG-treated patients with significant LMS disease.

It is reassuring to see that both PCI and CABG provide effective treatment of unprotected LMS disease with no difference in survival. There are trends towards less stroke in PCI-treated patients and less MI in CABG-treated patients. The main advantage seen with CABG was a reduction in repeat revascularisation. This difference persisted even with the use of DES. However, one may argue that, without impact on survival, the need for revascularisation is not a hard endpoint and many patients would accept it to avoid the need for CABG.

Limitations

This meta-analysis has several potential limitations. The results are based on trial level data and share the limitations of the original trials. The definitions of clinical endpoints were not identical in all studies. Follow-up data among trials were variable, ranging from one year to 10 years. Finally, the trials included in this meta-analysis used a variety of stent platforms, and most of the available data are from older and non-everolimus-eluting stents. Thus, the pooled event rates, including repeat revascularisation, may not accurately reflect the performance of any one particular stent.

Conclusions

PCI and CABG offer comparable survival in patients with unprotected LMS disease. There were trends towards less MI in the CABG group and less stroke in the PCI group. CABG is associated with a significantly lower risk of repeat revascularisation. The Heart Team should make an individualised revascularisation decision based on the extent of downstream disease (SYNTAX score >32 favouring CABG), surgical risk (high risk favouring PCI), local resources/expertise and patient preference.

Impact on daily practice

The international guidelines, particularly those from the European Society of Cardiology/European Association for Cardio-Thoracic Surgery and American College of Cardiology/American Heart Association[24], provide a balanced, practical, patient-oriented, and evidence-based approach for coronary revascularisation. We believe future iterations of guidelines should update PCI for LMS to a class I (level of evidence A), at least for patients with a SYNTAX score ≤32. As per guideline recommendations, use of the Heart Team for decision making and intracoronary imaging to guide PCI should remain the standard of care. The final revascularisation decision should be made by the Heart Team and the individual patient after considering the evidence base, international guidelines, contemporary practice, and local resources and expertise[25,26].

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Figure 1. Risk of bias across domains of study quality.

Supplementary Figure 2. Publication bias for studies in the meta-analysis.

Supplementary Figure 3. Risk ratios for MACCE between PCI- and CABG-treated groups according to stent type.

Supplementary Figure 4. Meta-analysis of five trials comparing PCI with DES vs. CABG.

The supplementary data are published online at: www.asiaintervention.org

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Early and late restenosis of drug-eluting stents: an observational study about predictors, clinical presentation and response to treatment (the LATE DES study)

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KEYWORDS

- acute gain
- coronary angioplasty
- drug-eluting balloon
- drug-eluting stent
- in-stent restenosis
- late lumen loss

Abstract

Aims: The aim of the study was to evaluate differences in clinical presentation, angiographic and clinical predictors, and response to treatment of early (<9 months) vs. late (≥9 months) in-stent restenosis (ISR) of drug-eluting stents (DES).

Methods and results: One hundred and twenty-nine patients with DES restenosis (defined by angiography as diameter stenosis >50% at the stent segment or its edges) were enrolled: 79 (61%) had early DES restenosis (6±2 months) and 50 (39%) late DES restenosis (18±8 months). ISR treatment strategy was left to the operator's choice: DES or drug-eluting balloon (DEB). The primary endpoint was the incidence of major adverse cardiovascular events (MACE) at follow-up. Patients with early DES restenosis more frequently had an acute coronary syndrome as clinical presentation at the index procedure as compared to those with late DES restenosis (OR 2.63, 95% CI: 1.12-6.25; p=0.027). The treatment of DES restenosis was DES implantation in 78 (60%) patients and DEB in 51 (40%) patients, without differences between early and late DES ISR. MACE after ISR treatment occurred in 25 (19%) patients, without differences between early and late DES ISR (16 [20%] vs. 9 [18%]; p=0.75, respectively). Diabetes mellitus was the only independent predictor of MACE at follow-up (OR 4.6, 95% CI: 1.3-19.3; p=0.03). MACE-free survival was similar after treatment in early or late ISR (p=0.097) and according to ISR treatment (p=0.73).

Conclusions: Early DES restenosis occurred more frequently after DES implantation for ACS compared with late DES restenosis. This, however, did not translate into a difference in MACE rate after ISR treatment at follow-up. Treatment choice for ISR did not affect prognosis. Diabetes mellitus remains the only independent predictor of MACE after treatment of DES ISR.

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Introduction

Drug-eluting stents (DES) were introduced into clinical practice with the primary purpose of reducing the incidence of in-stent restenosis (ISR). Indeed, ISR has emerged as a relevant drawback related to the implantation of bare metal stents (BMS), largely limiting their efficacy because of an incidence of up to 30%. Initial trials evaluating the safety and efficacy of DES in non-complex coronary lesions showed an impressively low rate of ISR (<10%)[1,2]. However, despite exciting results being reported during the initial trials evaluating the safety and efficacy of first-generation DES, the real-world use of DES, often in complex coronary lesions (such as bifurcations, saphenous vein graft, chronic total occlusion), has clearly shown that ISR still occurs after DES implantation, depending on clinical, lesion- and procedure-related factors[3]. In particular, the occurrence of late stent ISR has emerged as an important issue related to DES implantation. Indeed, some studies have raised the possibility of a late catch-up phenomenon[4-8], as if antiproliferative drugs might simply delay the occurrence of ISR, the temporal window of DES restenosis presentation being wider compared with that of BMS. Yet, studies evaluating clinical presentation, angiographic and clinical predictors, and response to treatment of early vs. late ISR are still lacking. Of importance, pathogenic mechanisms of early and late ISR of DES may be different. In particular, early ISR seems to be related to procedural factors, while late ISR may be associated with an individual susceptibility, with a delayed arterial healing and a persistent inflammatory response to the stent polymer (hypersensitivity reaction)[7,8]. Furthermore, several studies have reported that neoatherosclerosis may play an important role in late ISR[9,10]: histological and *in vivo* imaging studies show that neoatherosclerosis consists of an accumulation of lipid foamy macrophages within the neointima with or without necrotic core formation and calcification[11,12].

Our study aimed to evaluate differences in clinical presentation, angiographic and clinical predictors, and response to treatment of early (<9 months) vs. late (>9 months) ISR of DES.

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Methods

STUDY DESIGN AND CLINICAL ENDPOINTS

The LATE DES study is a registry which enrolled patients presenting with DES restenosis between January 2009 and June 2011 in 15 centres across the Rome area **(Figure 1)**. DES restenosis was defined by angiography as recurrent diameter stenosis >50% at the stent segment or its edges (5 mm segments adjacent to the stent). Each centre decided to enrol patients respecting the exclusion criteria which were: surgical or medical management to treat DES restenosis (n=15); known hypersensitivity reactions towards materials or components used in percutaneous coronary intervention (PCI) (n=7); suspected low compliance to dual antiplatelet therapy (e.g., planned surgical interventions, bleeding risk) (n=12); DES restenosis of a stent implanted in overlap with a different stent (n=10); pregnancy (n=2); life expectancy <12 months (n=9); previous history for treated ISR (n=17).

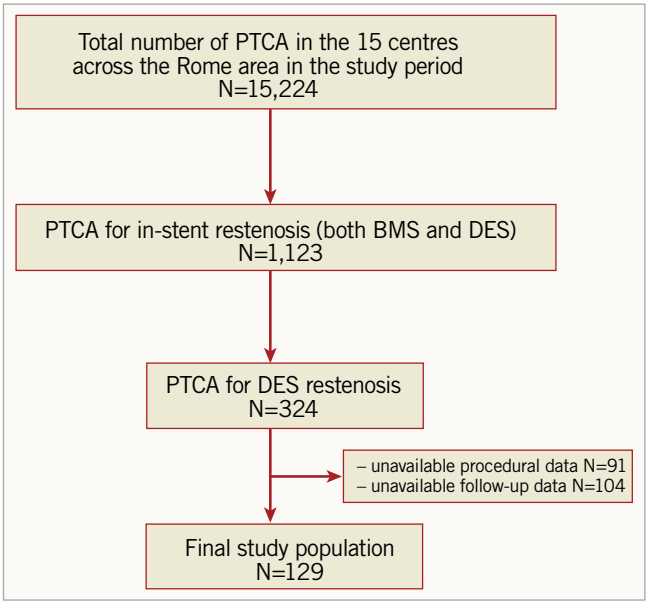

Figure 1. *Flow chart showing the origin of the sample size of the study.*

Post-index coronary angiography was performed because it was clinically driven either due to recurrent angina or to evidence of ischaemia by stress test.

Clinical and procedural data of both ISR PCI and the previous PCI in which the DES was implanted were recorded. The treatment strategy for ISR was left to the operator's choice: DES (first- or second-generation) or drug-eluting balloon (DEB). Case report forms were completed at each site by local investigators and submitted to the coordinating centre (Policlinico A. Gemelli, Rome, Italy). Data were monitored and reviewed for completeness and consistency. When required, specific queries were sent back from the coordinating centre to the sites. Patient follow-up was performed by telephone or clinic visit at one, six and 12 months. The primary endpoint was the incidence of major adverse cardiovascular events (MACE), defined as the composite of death from cardiac causes, non-fatal myocardial infarction (MI), clinically driven target vessel revascularisation (TVR) or rehospitalisation due to unstable or progressive angina according to the Braunwald unstable angina classification[13]. Cardiac death was ascertained by contacting the family doctor or the hospital where the patient died. MI was diagnosed by detection of rise and fall of cardiac biomarkers (preferably troponin) above the 99th percentile of the upper reference limit, together with evidence of myocardial ischaemia with at least one of the following: ischaemic symptoms; electrocardiographic changes indicative of new ischaemia (new ST-T changes or new left bundle branch block); development of pathological Q-waves in the electrocardiogram; imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities. TVR was carried out in the presence of a diameter stenosis >50% in the culprit vessel in patients with recurrence of symptoms and/or evidence of inducible myocardial ischaemia. Target

lesion revascularisation (TLR) was defined as either repeat percutaneous or surgical revascularisation for a lesion anywhere within the stent or the 5 mm borders proximal or distal to the stent. All planned staged procedures in patients with multivessel disease were performed during the index admission and were not included in MACE. The protocol indicated that, during follow-up, all repeat interventions were required to be clinically justified. The Academic Research Consortium definition was used to assess the presence of stent thrombosis.

The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of each enrolling centre.

ANGIOGRAPHIC ANALYSIS

All coronary angiograms were analysed at the angiographic core laboratory by trained personnel blinded to clinical characteristics and timing of restenosis by using standard methodology. The analyses were performed at the coordinating centre (Policlinico A. Gemelli, Rome, Italy). The Mehran and the modified American College of Cardiology/American Heart Association classifications were used to assess lesion morphology[14,15]. An automatic edge-detection system (CASS II System; Pie Medical, Maastricht, the Netherlands) was used for offline quantitative measurements. Carefully selected orthogonal, angiographic views (without vessel foreshortening or side branch overlap) were obtained after nitroglycerine administration. Matched projections were repeated after intervention and at follow-up. In-lesion and in-segment (the treated segment plus 5 mm proximal/distal margins) analyses were performed. Reference vessel diameter, minimal lumen diameter, percent of diameter stenosis, late loss, loss index, and binary restenosis rate (>50% diameter stenosis) were determined.

STATISTICAL ANALYSIS

Data distribution was assessed according to the Kolmogorov-Smirnov test. Continuous variables were compared using an unpaired Student's t-test or Mann-Whitney U test, as appropriate, and data were expressed as mean±standard deviation or as median (range). Categorical data were evaluated using the chi^2 test. Univariate logistic regression analysis was performed to evaluate predictors of early vs. late DES ISR.

Since the "right censoring" condition applies for the follow-up data, a Cox proportional hazard ratio (HR) model has been used for the survival analysis. Event-free survival was measured from the date of discharge to the occurrence of a MACE or to the date of last follow-up evaluation at one year. Thus, as primary analysis, we performed a simple Cox regression analysis using all variables on their original continuous scale to estimate the unadjusted HRs of all variables. We also calculated the 95% confidence interval (CI) of the coefficient of the Cox regression. Adjusted HRs were calculated by including in the multivariable Cox regression analysis model variables showing p≤0.15 at univariate Cox regression analysis and the variables age and sex because they were considered biologically relevant. The validity of the proportional hazards assumption was tested adding a time-dependent interaction variable for each of the predictors, and estimates of the C-index for the Cox regression model were calculated. Survival curves using the Kaplan-Meier method were produced for the occurrence of MACE according to the early or late ISR and to the treatment choice for ISR (DES or DEB) and compared by the log-rank test.

All tests were two-sided and a p-value of <0.05 represented statistically significant differences. All analyses were performed using SPSS, Version 20 (IBM Corp., Armonk, NY, USA).

Results

CLINICAL, PROCEDURAL AND ANGIOGRAPHIC CHARACTERISTICS OF PATIENTS WITH EARLY VS. LATE DES RESTENOSIS

The clinical characteristics of the overall study population and according to the presence of early or late DES restenosis are listed in **Table 1**. One hundred and twenty-nine patients with DES restenosis were enrolled (mean age 66±9 years, 84 [65%] male). Seventy-nine (79; 61%) patients presented with early (6±2 months) DES restenosis and 50 (39%) patients with late (18±8 months) DES restenosis. No differences in risk factors, angiographic and procedural variables were detected between the early and late DES restenosis groups. Of importance, patients with early DES restenosis more frequently had an acute coronary syndrome as clinical presentation at the index procedure compared with late DES restenosis (66 [84%] vs. 33 [66%], p=0.027) **(Figure 2)**. No differences were found in clinical presentation of DES restenosis between early and late DES ISR. Moreover, angiographic patterns of in-stent restenosis, according to the Mehran classification, did not differ between the two study groups.

Of note, at univariate logistic regression analysis, ACS as clinical presentation at the index procedure was the only predictor for early vs. late DES restenosis (OR 2.63, 95% CI: 1.12-6.25; p=0.027). Quantitative coronary angiography (QCA) data of the index and ISR procedures are reported in **Table 2** and show no significant differences between early and late DES ISR.

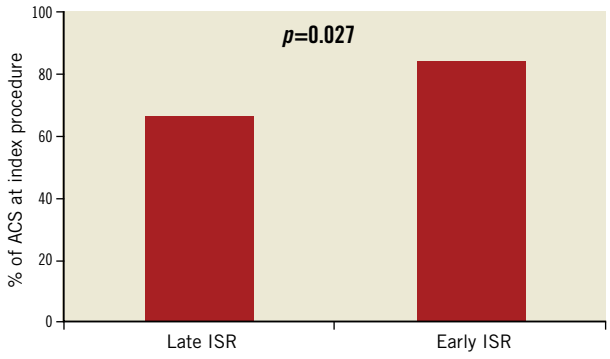

Figure 2. *Prevalence of acute coronary syndromes (ACS) at index procedure according to timing of ISR (early vs. late).*

Table 1. Baseline clinical, angiographic and procedural characteristics in the overall population and according to the timing of restenosis.

		Overall (n=129)	Restenosis >9 months (n=50, 39%)	Restenosis ≤9 months (n=79, 61%)	*p*-value
Clinical variables					
Age, years, mean±SD		66±9	67±9	65±10	0.31
Male, n (%)		84 (65)	32 (64)	52 (66)	0.83
Risk factors	Hypertension, n (%)	90 (70)	35 (70)	55 (70)	0.96
	Hypercholesterolaemia, n (%)	72 (56)	27 (48)	45 (60)	0.74
	Diabetes mellitus, n (%)	49 (38)	20 (40)	29 (37)	0.71
	Active smoking, n (%)	28 (22)	12 (24)	16 (20)	0.61
	Family history of CAD, n (%)	36 (28)	10 (20)	26 (33)	0.11
	Chronic kidney disease, n (%)	9 (7)	3 (6)	6 (8)	0.73
	Body mass index, mean±SD	27±5	26±3	27±5	0.40
Clinical presentation at index procedure	Stable angina, n (%)	30 (23)	17 (34)	13 (16)	0.027
	ACS, n (%)	99 (77)	33 (66)	66 (84)	
Clinical presentation of ISR	Stable, n (%)	104 (81)	41 (82)	63 (80)	0.75
	ACS, n (%)	25 (19)	9 (18)	16 (20)	
Procedural and angiographic variables of the index procedure					
Target vessel	LMS, n (%)	3 (2)	1 (2)	2 (2.5)	0.96
	LAD, n (%)	70 (54)	29 (58)	41 (33)	
	LCX, n (%)	29 (22)	10 (20)	19 (15)	
	RCA, n (%)	25 (19)	9 (18)	16 (12)	
	SVG, n (%)	2 (1.5)	1 (2)	1 (1)	
Lesion type	A, n (%)	28 (22)	10 (20)	18 (14)	0.91
	B, n (%)	39 (30)	16 (32)	23 (18)	
	C, n (%)	62 (48)	24 (48)	38 (29)	
Stent implantation procedure	DES type, n (%)				0.21
	First-generation	71 (55)	31 (62)	40 (51)	
	Paclitaxel-eluting stent	31 (44)	14 (45)	18 (45)	
	Sirolimus-eluting stent	40 (56)	17 (55)	22 (55)	
	Second-generation	58 (45)	19 (38)	39 (49)	
	Zotarolimus-eluting stent	27 (47)	10 (53)	19 (49)	
	Everolimus-eluting stent	31 (53)	9 (47)	20 (51)	
	Stent length, mm, mean±SD	27.4±14.7	27.7±15.9	27.4±13.6	0.92
	Stent diameter, mm, mean±SD	2.9±0.4	2.9±0.3	2.9±0.5	0.94
	Stent pressure, atm, mean±SD	15.0±2.2	15.2±2.2	14.8±2.3	0.38
	Balloon post-dilation				
	Performed, n (%)	94 (73)	33 (66)	61 (47)	0.16
	Balloon diameter, mm, mean±SD	3.1±0.7	3.1±0.8	3.1±0.6	0.96
	Balloon pressure, atm, mean±SD	16.0±4.7	15.2±5.1	17.2±4.0	0.14
ISR treatment	DES, n (%)	78 (60)	29 (58)	49 (62)	0.71
	First-generation	30 (38)	14 (48)	26 (53)	
	Paclitaxel-eluting stent	14 (47)	6 (43)	12 (46)	
	Sirolimus-eluting stent	16 (53)	8 (57)	14 (54)	
	Second-generation	48 (62)	15 (52)	23 (47)	
	Zotarolimus-eluting stent	23 (48)	8 (53)	12 (52)	
	Everolimus-eluting stent	25 (52)	7 (47)	11 (48)	
DEB, n (%)		51 (40)	21 (42)	30 (38)	0.57

ACS: acute coronary syndrome; CAD: coronary artery disease; ISR: in-stent restenosis; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LMS: left main stem; RCA: right coronary artery; SVG: saphenous vein graft

Table 2. Quantitative coronary angiography (QCA) results.

	Overall (n=129)	Restenosis >9 months (n=50)	Restenosis ≤9 months (n=79)	*p*-value
Baseline index procedure				
RVD, mm, mean±SD	2.7±0.4	2.8±0.4	2.7±0.3	0.32
Lesion length, mm, mean±SD	21.1±10.9	21.5±10.1	21.0±12.0	0.83
MLD, mm, mean±SD	0.7±0.4	0.6±0.4	0.7±0.4	0.51
DS, %, mean±SD	83±16	84±13	79±19	0.11
Post index procedure				
MLD, mm, mean±SD	2.4±0.5	2.4±0.5	2.4±0.5	0.95
DS, %, mean±SD	15±11	16±13	14±10	0.38
Acute gain, mm, mean±SD	1.9±0.6	1.9±0.6	1.8±0.7	0.77
Restenosis baseline				
RVD, mm, mean±SD	3.0±2.0	3.1±2.6	2.8±0.5	0.43
Lesion length, mm, mean±SD	15.1±9.1	15.2±9.0	14.5±8.2	0.73
MLD, mm, mean±SD	0.9±0.5	0.9±0.5	0.9±0.5	0.94
DS, %, mean±SD	77±15	76±15	77±16	0.82
LLL, mm, mean±SD	1.47±0.57	1.50±0.61	1.41±0.53	0.49
Restenosis pattern (Mehran classification)				
Focal, n (%)	73 (56%)	28 (56%)	45 (57%)	0.78
Diffuse, n (%)	56 (44%)	22 (44%)	34 (43%)	

DS: diameter stenosis; LLL: late lumen loss; MLD: minimal lumen diameter; RVD: reference vessel diameter

Table 3. Clinical outcome after DES restenosis treatment.

	Overall (n=129)	Restenosis >9 months (n=50, 39%)	Restenosis ≤9 months (n=79, 61%)	*p*-value
Cumulative MACE, n (%)	25 (19)	9 (18)	16 (20)	0.75
Cardiac death, n (%)	4 (3)	1 (2)	2 (2.5)	0.85
Non-fatal MI, n (%)	5 (4)	1 (2)	3 (3.5)	0.57
TVR, n (%)	13 (10)	6 (12)	7 (9)	0.56

MACE: major adverse cardiac events; MI: myocardial infarction; TVR: target vessel revascularisation

CLINICAL OUTCOME FOLLOWING TREATMENT OF DES RESTENOSIS

The treatment of DES restenosis in the overall population was DES implantation in 78 (60%) patients and drug-eluting balloon (DEB) in 51 (40%) patients, without differences between early and late DES ISR **(Table 1)**. MACE after ISR treatment occurred in 25 (19%) patients in the overall population, without difference between early and late DES ISR (16 [20%] vs. 9 [18%], p=0.75, respectively). In addition, no differences were found according to early vs. late DES ISR for cardiac death, non-fatal MI and TVR **(Table 3)**. Moreover, no difference in MACE incidence was found according to the treatment strategy for ISR (DES vs. DEB). At univariate regression analysis, diabetes mellitus (HR 5.4, 95% CI: 1.4-21.3; p=0.016) and lesion length (HR 1.07, 95% CI: 1.01-1.41; p=0.030) were the only predictors of MACE **(Table 4)**. The presence of an early DES restenosis (HR 2.43, 95% CI: 0.88-7.69; p=0.092) was not significantly associated with MACE. Of importance, at multivariate regression analysis, diabetes mellitus was the only independent predictor of MACE at follow-up (HR 4.6, 95% CI: 1.3-19.3; p=0.03) **(Table 4)**. Finally, Kaplan-Meier analysis showed no significant difference in MACE-free survival after treatment according to early or late ISR (p=0.097) **(Figure 3A)** and according to ISR treatment (DES or DEB) (p=0.73) **(Figure 3B)**.

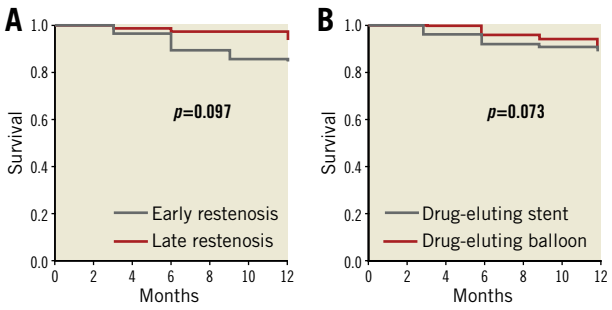

Figure 3. *Kaplan-Meier analysis showing MACE-free survival after ISR treatment. A) According to early or late ISR. B) According to treatment choice (DES or DEB).*

Discussion

The main findings of the LATE DES registry, one of the largest registries enrolling patients presenting with DES ISR, are the following: 1) patients with early DES restenosis more frequently had an acute coronary syndrome as clinical presentation at the index procedure as compared to those with late DES restenosis; 2) MACE after ISR treatment at one-year follow-up occurred in 19% of patients in the overall population, without difference between early and late DES ISR or according to treatment choice for ISR (DES or DEB); 3) diabetes mellitus was the only independent predictor of MACE at follow-up after DES ISR treatment.

Table 4. Univariate and multivariate regression analysis.

	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Diabetes mellitus	5.4	1.4-21.3	0.016	4.6	1.3-19.3	0.03
Stenosis length	1.07	1.01-1.41	0.030			

Of importance, here we provide to the best of our knowledge the first evidence that early DES restenosis occurs more frequently in patients presenting with ACS at the index procedure as compared with late DES restenosis. Inflammation has been shown to play an important role both in atherosclerotic plaque progression and destabilisation and in ISR[9,16,17]. Indeed, DES were designed to obtain a site-specific delivery of drugs with anti-inflammatory and antiproliferative properties, in order to counteract the mechanisms leading to ISR[18]. However, patients presenting with ACS have a more pronounced local and systemic inflammatory activation compared with stable patients[19], probably not completely counteracted by the eluted drug, and possibly leading to early DES restenosis. On the other hand, in patients without ACS as clinical presentation, the eluted drug is able to counteract the inflammatory response following DES implantation and to prevent early ISR; late DES ISR may be mainly related to a chronic inflammatory response to polymer and/or neoatherosclerosis[9,10]. In addition to inflammation, other mechanisms may support our finding. For example, in the setting of ACS, the presence of thrombus and coronary hypercontractility may lead to implantation of an undersized stent, predisposing to restenosis.

Treatment of DES ISR is particularly challenging and associated with a poor outcome[20]. In our registry, one patient in five had experienced a MACE after DES ISR treatment at one-year follow-up. Of note, no differences were observed in MACE rate according to early or late ISR or according to the treatment for DES ISR (repeat stenting with DES or DEB). Initial observational studies showed that repeat stenting with DES to treat DES ISR provided better results compared with balloon angioplasty[21]. However, the implantation of a new DES raised concern related to the presence of multiple layers of struts in the vessel wall and the risk of stent thrombosis and recurrent restenosis. DEB have been suggested as an alternative approach to treat DES ISR[22], and data from randomised controlled trials suggested that DEB are superior to balloon angioplasty and similar to first-generation DES[23]. Moreover, in the RIBS III study there was a suggestion that the use of second-generation DES was superior to first-generation DES; also, the use of intracoronary imaging was associated with better long-term outcomes[20,24]. In particular, a meta-analysis by Palmerini et al demonstrated that, among the second-generation DES, durable fluoropolymer-based CoCr-EES were associated with the lowest rates of long-term adverse events and maximum efficacy[25].

Finally, in keeping with previous studies, diabetes mellitus was the only predictor of recurrence of MACE after DES ISR treatment[26,27]. The development of drug-eluting stents has significantly improved the results of percutaneous revascularisation among diabetic patients, but a number of challenges remain, including higher rates of restenosis and stent thrombosis. Stent implantation in a coronary artery induces an inflammatory response, including mobilisation of progenitor cells and ingrowth of smooth muscle cells. Diabetic patients have accelerated neointimal hyperplasia and high rates of subsequent restenosis after stent placement[28], resulting from neointimal hyperplasia mechanisms including increased TGF-ß signalling and a direct influence of hyperglycaemia on smooth muscle cell migration[29]. Restenosis is more common after placement of longer stents or in arteries with smaller diameters, and diabetic patients more frequently present longer, more complex coronary artery lesions, and smaller reference vessels[30]. Taken together, these factors contribute to higher rates of restenosis when compared to non-diabetic patients.

A previous study by our group confirmed these observations, reporting that diabetic patients exhibit substantially more severe coronary atherosclerosis than non-diabetic patients at the time of a first acute coronary event, suggesting a more severe coronary atherosclerosis that may lead to late ISR[31]. The present study confirms that ISR after DES implantation is not a benign condition because it may lead to myocardial infarction in 10% of cases[32], and the re-restenosis rate remains relatively high, independent of the treatment modality used[33].

Two main implications arise from the present study. Firstly, as patients with early DES restenosis more frequently had an acute coronary syndrome as clinical presentation at the index procedure compared with late DES restenosis, they may need more aggressive medical surveillance that may allow an early diagnosis of stent failure. Secondly, our observation of a similar outcome among patients with early vs. late ISR regardless of the treatment for DES ISR (repeat stenting with DES or DEB) results in a new finding, but suggests, at the same time, the need for further study to understand which should be the treatment of choice for ISR.

Limitations

We acknowledge some limitations in the present study. Firstly, the study design is not that of a randomised study but rather of a hypothesis-generating registry with a relatively limited sample size. Secondly, patients did not have coronary angiography performed after ISR treatment, so we cannot exclude that some recurrent ISR might have been missed. Thirdly, no intracoronary imaging technique was mandated to guide ISR treatment. Fourthly, the majority of DES were first-generation DES, which are not used any more, thus it remains undetermined whether the same findings apply to second-generation DES. However, it remains of great interest to investigate the long-term consequences of first-generation DES implantation. In addition, due to the lack of intracoronary imaging at the time of ISR, the potential different mechanisms of ISR in first- and second-generation DES remain unknown.

Conclusions

The LATE DES registry showed that patients with early DES restenosis, compared to patients with late DES restenosis, more frequently presented with an ACS at the index procedure; however, the two groups did not differ in terms of the occurrence of MACE after ISR treatment at one-year follow-up either with DES or with DEB. Diabetes was the only independent predictor of MACE.

Impact on daily practice

Both early and late ISR are still observed in the real world, especially when complex coronary lesions are faced. The LATE DES registry showed that patients with early DES restenosis more frequently had an acute coronary syndrome (ACS) as clinical presentation at the index procedure compared to those with late DES restenosis. This may suggest a closer medical surveillance in ACS patients to allow an early diagnosis of stent failure, especially in diabetic patients. Diabetes, in fact, was the only independent predictor of MACE after ISR treatment in the present study.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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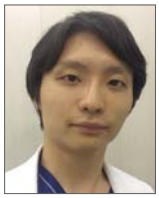
Impact of target lesion coronary calcium score on outcomes following drug-eluting stent implantation



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KEYWORDS

- calcified stenosis
- drug-eluting stent
- multislice computed tomography (MSCT)
- non-invasive imaging

Abstract

Aims: The aim of this study was to evaluate the impact of computed tomography scan-based coronary artery calcium scoring of the target lesion on outcomes following percutaneous coronary intervention using second-generation drug-eluting stents.

Methods and results: We retrospectively investigated 124 consecutive patients who underwent coronary artery calcium scoring prior to cobalt-chromium everolimus-eluting stent implantation. Eight-month clinical and angiographic outcomes were evaluated. Target vessel failure (TVF) was defined as a composite of cardiac death, target vessel myocardial infarction, and target vessel revascularisation. A significant difference in lesion calcium score was observed between patients with and without TVF (median 216.7 vs. 42.8, p=0.025). The area under the receiver operating characteristic curve for prediction using lesion calcium scoring was 0.74 (95% confidence interval [CI]: 0.53-0.94) for TVF. When using a cut-off value of 140, the sensitivity and specificity of the lesion calcium score for predicting TVF were 87.5% and 69.8%, respectively. Among the 103 patients with either no or mild angiographic calcification, 24 patients (23.3%) had a lesion calcium score ≥140 and they were at higher risk for TVF (20.8% vs. 1.3%, p=0.002).

Conclusions: Computed tomography-based detection of coronary artery calcification of the target lesion was associated with poor prognosis after cobalt-chromium everolimus-eluting stent implantation.

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Abbreviations

CAC	coronary artery calcification
CI	confidence interval
CoCr-EES	cobalt-chromium everolimus-eluting stents
CT	computed tomography
DES	drug-eluting stents
MI	myocardial infarction
PCI	percutaneous coronary intervention
QCA	quantitative coronary angiography
ROC	receiver operating characteristic
TLR	target lesion revascularisation
TVF	target vessel failure
TVR	target vessel revascularisation

Introduction

Coronary artery calcification (CAC) of the target lesion has been reported to be a risk factor for adverse events after percutaneous coronary intervention (PCI)[1-6]. Previous studies have evaluated CAC of the target lesion mainly using angiography. However, angiographic detection of CAC is characterised by poor sensitivity, with poor ability to detect small amounts of calcification[7,8], and is not quantitative. Computed tomography (CT) is the only non-invasive test with a high sensitivity and specificity for detection of CAC[9]. Using CT, small amounts of calcification can be detected, with its volume and density being easily quantified. The CT scan-based calcium score, which is calculated from the calcified plaque volume and the maximal calcium lesion density, was developed by Agatston et al[7]. This method has been demonstrated to be useful for evaluating cardiovascular risk[10-13]. Previously, we have reported that a high lesion calcium score was associated with worse outcomes following PCI using first-generation drug-eluting stents (DES)[14]. However, the impact of the target lesion calcium score on outcomes following PCI using second-generation DES is still unknown. The objective of this study was to elucidate the impact of the CT scan-based lesion calcium score on outcomes following PCI using cobalt-chromium everolimus-eluting stents (CoCr-EES).

Methods

The study population consisted of patients who underwent CoCr-EES (XIENCE V®, XIENCE PRIME®, or XIENCE Xpedition®; Abbott Vascular, Santa Clara, CA, USA) implantation to repair coronary lesions at our institution between October 2010 and December 2013. Among patients receiving CoCr-EES, those who also received an alternative stent type to the same lesion were excluded. Data of patients who underwent non-invasive coronary CT as part of a routine diagnostic process within six months before PCI were extracted and analysed. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. The study was approved by the Medical Ethics Committee of Mitsui Memorial Hospital.

Detailed protocols of the CT scans are described in the **Supplementary Appendix**. All scans were analysed by an experienced cardiologist who was blinded to clinical follow-up data. Calcium scores for the target lesion and the whole coronary tree were calculated. Anatomical landmarks, such as side branches, were used to determine the target lesion on CT scans. The target lesion calcium score of the patients who underwent CoCr-EES implantation for more than two lesions was defined as the maximum lesion calcium score of the treated lesions.

Coronary angioplasty was performed using standard techniques[15,16]. Neither a scoring nor a cutting balloon was used in any of the lesions. Glycoprotein IIb/IIIa inhibitors were not used in any of the patients since they were not commercially available in Japan during the study period. CoCr-EES were available in diameters of 2.25 mm to 3.5 mm. The use of dual antiplatelet therapy was recommended for at least six months. Coronary angiograms obtained before stent implantation, after stent implantation, and eight months after implantation were analysed using a computer-based system (CMS software, version 6.0; Medis medical imaging systems, Leiden, the Netherlands). In-stent, proximal edge, and distal edge segments were analysed. Eight-month clinical outcomes of the study population were obtained from reviews of medical records. Target vessel failure (TVF) was defined as a composite of cardiac death, target vessel myocardial infarction (MI) and target vessel revascularisation (TVR). Definitions of angiographic parameters, angiographic outcomes, and clinical outcomes other than TVF are described in the **Supplementary Appendix**.

STATISTICAL ANALYSIS

Categorical variables are presented as frequency and were compared using Fisher's exact test. Continuous variables are expressed as the mean±standard deviation or median (interquartile range), depending on their distribution, as assessed by visual inspection and Kolmogorov-Smirnov test, and were compared using the Student's t-test or Mann-Whitney U test. The receiver operating characteristic (ROC) curves were constructed to evaluate the discriminating power of the lesion calcium score in predicting adverse events. A cut-off point that maximises the sum of sensitivity and specificity was selected. Univariate logistic regression analyses were used to identify the variables associated with adverse events. Variables with $p<0.10$ in the univariate analyses were included in the multivariate logistic regression analysis to identify the independent predictors for adverse events. Values of $p<0.05$ were considered to be statistically significant, and all p-values were two-sided. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[17].

Results

During the study period, 421 patients with 572 *de novo* lesions underwent CoCr-EES implantation. Because of concomitant use of other types of stent, seven patients and 13 lesions were excluded. Among the 414 patients with 559 lesions, 131 patients (31.6%) with 156 lesions (27.9%) had undergone CT CAC scanning within six months before PCI. One patient without clinical

follow-up and six patients without appropriate CT data at the time of analysis were excluded. This resulted in 124 patients with 149 lesions being evaluated.

Baseline patient characteristics are listed in **Table 1**. The mean age was 67.9±10.3 years. The median total calcium score was 420.5 (96.0-1,040.2). Baseline lesion and procedural characteristics are shown in **Table 2**. Moderate or severe angiographic calcification was observed in 24 lesions (16.1%). The median lesion calcium score of the overall population was 42.6 (4.8-180.1). The calcium scores of the lesions with angiographically moderate or severe calcification were significantly higher than those of the lesions without (328.2 [194.1-439.3] vs. 29.7 [3.2-111.4], p<0.001). Procedural and clinical success rates were both 100%. **Table 3** presents serial quantitative coronary angiographic data. Angiographic follow-up was performed in 134 lesions (89.9%). The angiographic in-segment binary restenosis rate was 6.7%. An eight-month clinical follow-up was performed for all patients **(Table 4)**. There was no death documented during that period. Myocardial infarction, TLR, and TVF occurred in three, six, and eight patients, respectively.

Table 1. Baseline patient characteristics.

Number of patients		124
Age, years		67.9±10.3
Male		103 (83.1)
BMI		24.1±3.5
Hypertension		96 (77.4)
Dyslipidaemia		112 (90.3)
Diabetes mellitus		52 (41.9)
Current smoker		19 (15.3)
Haemodialysis		8 (6.5)
Previous MI		12 (9.7)
Previous PCI		23 (18.5)
Previous CABG		6 (4.8)
Acute coronary syndrome		10 (8.0)
Multivessel disease		31 (25.0)
Baseline medication	Dual antiplatelet therapy	124 (100)
	Aspirin+clopidogrel	119 (96.0)
	Aspirin+ticlopidine	4 (3.2)
	Aspirin+prasugrel	1 (0.8)
	Statin	119 (96.0)
Total calcium score		420.5 [96.0-1,040.2]

Numbers are reported as n (%), mean±standard deviation, or median [interquartile range]. BMI: body mass index; CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 2. Baseline lesion and procedural characteristics.

Number of lesions		149
Target vessel	LMCA	4 (2.7)
	LAD	66 (44.3)
	LCX	48 (32.2)
	RCA	31 (20.8)
ACC/AHA classification	A	4 (2.7)
	B1	29 (19.5)
	B2	56 (37.6)
	C	60 (40.3)
Angiographic moderate/severe calcification		24 (16.1)
Bifurcation lesion		51 (34.2)
Average number of stents		1.18±0.44
Average stent diameter, mm		2.98±0.43
Total stent length, mm		25.4±12.6
Balloon-to-artery ratio		1.17±0.20
Maximum stent deployment pressure, atm		13.8±3.5
Rotablator use		3 (2.0)
Post-dilatation		76 (51.0)
Bail-out procedure		2 (1.3)
Lesion calcium score		42.6 [4.8-180.1]
Lesion success		149 (100)

Numbers are reported as n (%), mean±standard deviation, or median [interquartile range]. LAD: left anterior descending; LCX: left circumflex; LMCA: left main coronary artery; RCA: right coronary artery

Table 3. Results of quantitative coronary angiographic analysis.

		Pre (n=149)	Post (n=149)	Follow–up (n=134)
Lesion length, mm		14.3 [9.2–23.2]	–	–
Reference diameter, mm	In–stent	–	3.02±0.48	2.88±0.50
	In–segment	2.69±0.59	2.95±0.58	2.86±0.57
Minimum lumen diameter, mm	In–stent	–	2.67±0.43	2.39±0.58
	In–segment	0.83±0.44	2.30±0.56	2.12±0.63
Diameter stenosis, %	In–stent	–	11.53±5.70	17.13±14.34
	In–segment	69.48±14.66	22.25±9.66	26.42±15.13
Acute gain, mm	In–segment	–	2.11±0.59	–
Late loss, mm	In–stent	–	–	0.26±0.41
	In–segment	–	–	0.18±0.51
Binary restenosis		–	–	9 (6.7)

Numbers are reported as n (%), mean±standard deviation, or median [interquartile range].

Table 4. Eight-month clinical outcomes.

Death	0 (0.0)
Myocardial infarction	3 (2.4)
Stroke	0 (0.0)
TVR	6 (4.8)
TLR	6 (4.8)
Stent thrombosis	1 (0.8)
TVF	8 (6.5)

Numbers are reported as n (%). TLR: target lesion revascularisation; TVF: target vessel failure; TVR: target vessel revascularisation

As depicted in **Figure 1**, there was a significant difference in the lesion calcium score between lesions and patients with and without adverse events. The ROC curves for the prediction of TLR and TVF are illustrated in **Figure 2**. When using a cut-off value of 140, the sensitivity and specificity of the lesion calcium score for predicting TVF were 87.5% (95% confidence interval [CI]: 47.3-99.7%) and 69.8% (95% CI: 60.6-78.0%), respectively. The positive predictive value was 16.7% (95% CI: 7.0-31.4%), while the negative predictive value was 98.8% (95% CI: 93.4-100%).

The baseline demographics of patients with and without a lesion calcium score ≥140 are shown in **Supplementary Table 1**. The patients with higher lesion calcium scores were significantly older (70.7±7.2 vs. 66.5±11.3, p=0.030). A numerically larger proportion of patients were on haemodialysis in the high lesion calcium score group (11.9% vs. 3.7%, p=0.12). The baseline lesion and procedural characteristics and the results of the quantitative coronary angiography (QCA) categorised by lesion calcium score are shown in **Supplementary Table 2** and **Supplementary Table 3**. The lesions with a higher calcium score were significantly longer (18.8 [9.5-28.2] mm vs. 12.7 [8.8-18.7] mm, p=0.015). The lesions with a higher calcium score had

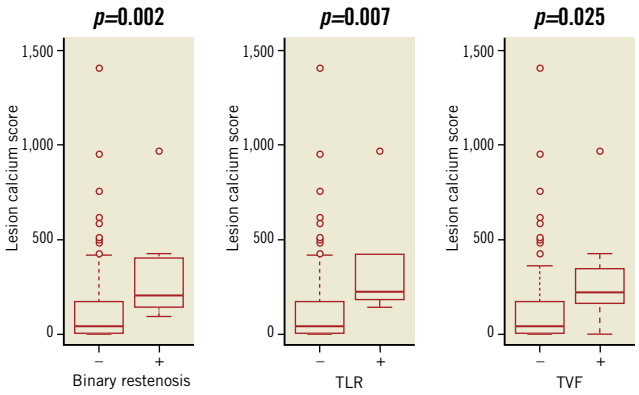

Figure 1. *Comparison of lesion coronary calcium score. There was a significant difference in the lesion calcium score between lesions with and without restenosis (median 202.4 vs. 41.1, p=0.002), patients with and without TLR (median 216.7 vs. 42.8, p=0.007), and patients with and without TVF (median 216.7 vs. 42.8, p=0.025). TLR: target lesion revascularisation; TVF: target vessel failure*

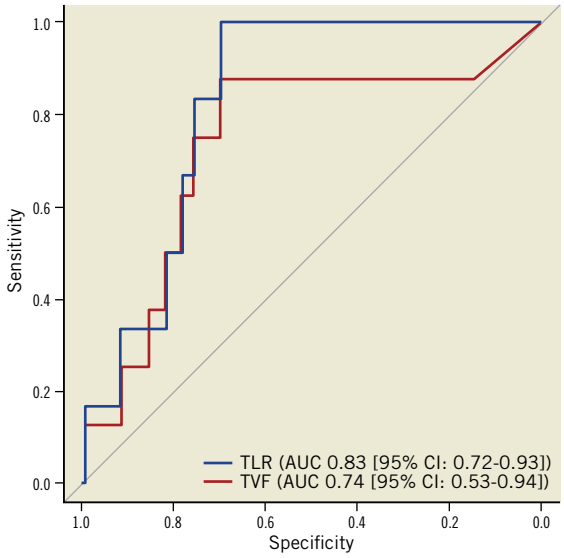

Figure 2. *Receiver operating characteristic curve for prediction of TLR and TVF using lesion calcium score. The AUC for prediction of TLR and TVF using the lesion calcium score was 0.83 (95% CI: 0.72-0.93) and 0.74 (95% CI: 0.53-0.94), respectively. AUC: area under the curve; TLR: target lesion revascularisation; TVF: target vessel failure*

worse angiographic outcomes (in-stent late loss, 0.46±0.62 mm vs. 0.17±0.18 mm, p<0.001; binary restenosis, 18.2% vs. 1.1%, p<0.001). **Supplementary Table 4** shows the eight-month clinical outcomes of the patients categorised by their lesion calcium score. TVF and TLR occurred more frequently in patients with a lesion calcium score ≥140 (TVF, 16.7% vs. 1.3%, p=0.002; TLR, 14.3% vs. 0.0%, p=0.0012). **Table 5** shows the results of the logistic regression analyses for TVF. Four variables (previous MI, previous PCI, previous coronary artery bypass grafting, and acute coronary syndrome at presentation) showed perfect separation and were not suitable for logistic regression analysis for TVF. A separate Fisher's exact test was performed to confirm that there were no significant differences or trends in the prevalence of these variables in patients with and without TVF and these variables were excluded from the multivariate analysis **(Supplementary Table 5)**. Multivariate analysis revealed that a lesion calcium score ≥140 was an independent predictor of TVF (adjusted odds ratio, 9.62; 95% CI: 1.03-90.0).

The baseline patient, lesion, and procedural characteristics and the results of QCA of the patients and lesions with either no or mild angiographic calcification categorised by lesion calcium score are shown in **Supplementary Table 6**, **Supplementary Table 7**, and **Supplementary Table 8**. Notably, among the 103 patients with either no or mild angiographic calcification, 24 lesions (23.3%) had a lesion calcium score ≥140. In this population, the sensitivity and specificity of a lesion calcium score ≥140 for predicting TVF were 83.3% (95% CI: 35.9-99.6%) and 80.4% (95% CI: 71.1-87.8%), respectively. The positive predictive value was 20.8% (95% CI: 7.1-42.2%), while the negative predictive value was

Table 5. Logistic regression analysis for TVF.

	Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Lesion calcium score ≥140	16.2	1.92–137.0	0.011	9.62	1.03–90.0	0.047
Age, every 10 years	0.98	0.49–1.97	0.96			
Male sex	0.59	0.11–3.13	0.53			
BMI, every 1.0	0.97	0.78–1.21	0.78			
Hypertension	0.46	0.10–2.05	0.31			
Dyslipidaemia	0.73	0.08–6.52	0.78			
Diabetes mellitus	2.45	0.56–10.7	0.24			
Current smoker	0.78	0.09–6.71	0.82			
Haemodialysis	6.11	1.01–36.9	0.049	3.73	0.49–28.6	0.21
Multivessel disease	0.41	0.048–3.47	0.41			
Statin use	0.25	0.025–2.55	0.24			
Bifurcation lesion	2.63	0.60–11.5	0.20			
LL, every 1.0 mm	1.08	1.02–1.16	0.013	1.05	0.99–1.12	0.13
RD, every 0.5 mm	1.39	0.77–2.51	0.27			
Rotablator use	8.14	0.66–101.0	0.10			

BMI: body mass index; CABG: coronary artery bypass grafting; CI: confidence interval; LL: lesion length; MI: myocardial infarction; PCI: percutaneous coronary intervention; RD: reference diameter; TVF: target vessel failure

98.7% (95% CI: 93.1-100%). Among this population, the patients with a lesion calcium score ≥140 still had a significantly higher rate of TVF compared to the lesions with less calcium (20.8% vs. 1.3%, p=0.002) **(Supplementary Table 9)**.

Discussion

In this retrospective cohort study, the lesion calcium score differed significantly between the patients with and without adverse events. ROC analysis revealed that the lesion calcium score is predictive of adverse events following CoCr-EES implantation. A calcium score of more than 140 was an independent predictor of adverse events.

The presence of CAC has been reported to be associated with adverse events during the balloon angioplasty, bare metal stent, and first-generation DES era[1-4,18]. The introduction of second-generation DES successfully reduced the rate of adverse events compared with bare metal stents and first-generation DES[19-21]; however, calcified lesions remained a challenge. *Post hoc* analyses of several trials had shown that CAC is a risk factor for adverse events after second-generation stent implantation[5,6]. Our study confirmed this result using a different modality for CAC detection.

Several methods for evaluating lesion CAC have been used in previous studies, with angiographic evaluation being used most frequently. Only the original diagnostic invasive coronary angiography is required for evaluation and there is no need for additional radiation exposure. However, since the sensitivity for detecting CAC is low, a small amount and low density of CAC is difficult to detect[7,8]. In the present study, a number of patients with either no or mild angiographic calcification had lesion calcium scores greater than 140, and they were at high risk for adverse events. This suggests that coronary angiography alone is not enough to detect the amount and density of calcium that has a negative impact on outcomes following PCI. Notably, patients with a lesion calcium score <140 had only one TVF event with no TLR, which was considerably lower compared with previous studies evaluating the efficacy of CoCr-EES in general[22,23]. This also indicates the usefulness of CT for detection of lesion CAC that affects the outcomes following PCI.

CT is the only non-invasive test for CAC detection that is highly accurate[11]. The calcium score of the target lesion can be calculated easily using dedicated software[9]. Our data indicate that the evaluation of CAC using CT is useful for determining patients and lesions with a poor prognosis. Yet, it is not cost-effective to perform CAC scoring in every patient who opts for PCI. However, given the established utility of CAC scanning and CT angiography in diagnosing coronary artery diseases[24], the number of patients who undergo cardiac CT during their initial diagnostic process is increasing. In the present study, 31.6% of the patients who underwent CoCr-EES implantation at a *de novo* lesion had undergone CAC scanning within six months before PCI. When we plan PCI for such patients, reviewing the initial CT data to confirm the calcium burden of the target lesion may provide the physician and the patient with additional information about future adverse events. The present study suggests a calcium score of 140 as a threshold for identifying patients at risk for adverse events; however, the sample size of this study was small and further studies are needed to confirm this result.

Methods to minimise the impact of CAC are still not known. Statins have been investigated as a potential anticalcification drug. However, prospective randomised controlled trials have shown that statins do not prevent CAC progression and may even

increase CAC[25,26]. Rotational atherectomy may be one solution, but a prospective randomised controlled trial showed that the use of rotational atherectomy was associated with higher late lumen loss with no impact on clinical outcomes[27]. Additional studies are required to elucidate the optimal strategies to improve the outcomes of patients with calcified coronary lesions.

Whether stent implantation itself has any effect on the progression of the underlying calcification is also not known. The present study showed that CT can accurately quantify lesion CAC prior to stent implantation, but evaluation of lesion CAC after stent implantation is almost impossible due to blooming and motion artefacts[28]. Bioresorbable vascular scaffolds, which are radiolucent, have been developed and are now being used in daily practice. Previous reports revealed that a clear CT image of the target lesion can be obtained even after bioresorbable vascular scaffold implantation[29,30]. Serial CT analyses may be useful to investigate the behaviour of lesion calcification after bioresorbable vascular scaffold implantation.

Limitations

The present study has several limitations. First, the sample size was small and adverse events occurred in less than ten patients. The results of the QCA showed that lesions with higher lesion calcium score had worse angiographic outcomes. Together with the results of the previous studies[1-6,14,18], it is plausible to conclude that the lesion CAC detected by CT is associated with poor outcomes following PCI. However, the multivariate analyses conducted may be inadequate and confounding biases may not have been fully excluded. Second, this study was a retrospective single-centre study. The study population consisted of patients who underwent coronary CT during their initial diagnostic process at our institution. Thus, applying these results to the general population undergoing PCI may be inappropriate. The CT scans were performed within six months before PCI, not just before PCI. The amount of calcium may have changed by the time of PCI and may have influenced the outcomes in some cases. Third, we did not consider the distribution of CAC within the lesion. Eccentric calcification is associated with less acute gain compared with concentric calcification[1]. Intimal and medial calcification has been reported to be associated with different pathophysiology[31], and spotty calcification has been reported to be associated with vulnerable plaques and progression of atherosclerosis[32,33]. Not only the volume and density, but also the distribution and types of CAC within the lesion, might have an impact on outcomes after PCI. Fourth, because we analysed patients who underwent only CoCr-EES implantation, the result cannot be extrapolated to other types of DES. Finally, this was a *post hoc* analysis and the results should be considered hypothesis-generating rather than causal.

Conclusions

CT-based detection of CAC of the target lesion was associated with poor prognosis after CoCr-EES implantation. Coronary angiography alone may not be enough to detect the calcification that has a negative impact on outcomes following PCI; CT may provide additional information about future adverse events. CT images, if present, should be carefully reviewed when planning PCI.

Impact on daily practice

The result of the present study suggests that coronary angiography alone is not enough to detect the amount and density of calcium that has a negative impact on outcomes following PCI and that CT can provide additional information about future adverse events. A cut-off lesion calcium score of 140 may be useful in detecting patients who are at higher risk for adverse events. CT images, if present, should be carefully reviewed when planning PCI.

Conflict of interest statement

K. Tanabe is a member of the Advisory Board for Abbott Vascular Japan and receives honoraria for lectures from Abbott Vascular and Toshiba Medical Systems. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix. Computed tomography protocol. Definitions of angiographic parameters and outcomes. Definition of clinical outcomes.

Supplementary Table 1. Patient characteristics by lesion calcium score.

Supplementary Table 2. Baseline lesion and procedural characteristics by lesion calcium score.

Supplementary Table 3. Results of QCA by lesion calcium score.

Supplementary Table 4. Eight-month clinical outcomes by lesion calcium score.

Supplementary Table 5. Fisher's exact test for variables that showed perfect separation.

Supplementary Table 6. Patient characteristics of those with no or mild angiographic calcification.

Supplementary Table 7. Baseline lesion and procedural characteristics of lesions with no or mild angiographic calcification.

Supplementary Table 8. Results of QCA of lesions with no or mild angiographic calcification.

Supplementary Table 9. Eight-month clinical outcomes of lesions with no or mild angiographic calcification.

The supplementary data are published online at: www.asiaintervention.org

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Two-year outcomes of a bioresorbable everolimus-eluting scaffold using a strategy of meticulous lesion preparation and routine post-dilation: the Australian ESHC-BVS registry

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KEYWORDS

- bioresorbable scaffold
- drug-eluting stent
- percutaneous coronary intervention

Abstract

Aims: The Absorb bioresorbable vascular scaffold (BVS) was the first commercially available coronary stent to provide vessel scaffolding of a temporary nature following percutaneous coronary intervention. While results in clinical trials have varied, outcomes using a BVS-specific implantation strategy have not been well studied. We report two-year real-world data on the Absorb BVS implanted following meticulous lesion preparation and with a strategy of routine post-dilation.

Methods and results: Absorb BVS implantation was attempted in 152 lesions in 100 patients at two Sydney hospitals as part of the prospective ESHC-BVS registry. Lesions treated included complex lesions reflective of real-world practice with lesion length being >20 mm in 24%, and 16% featuring moderate/severe calcification. In total, type C lesions made up 37% of all lesions treated. A BVS-dedicated implantation strategy was utilised encompassing meticulous lesion preparation and routine post-dilation. Predilation was performed in 100% of lesions and post-dilation in 95% of scaffolds to a mean of 19.6±4.6 atm. Two-year clinical follow-up data were available for 99% of patients. At two years, the rate of all-cause mortality was 3% and cardiac death 1%. The cumulative incidence of target lesion revascularisation at two years was 4%, while the incidence of myocardial infarction was 2% and scaffold thrombosis 1%.

Conclusions: Using a strategy of meticulous lesion preparation and routine post-dilation, the Absorb BVS was associated with good clinical outcomes at long-term follow-up with low rates of target lesion revascularisation, myocardial infarction and scaffold thrombosis at two years. These findings support the dedicated scaffold implantation technique employed in this registry.

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Introduction

Contemporary drug-eluting stents have significantly improved outcomes following balloon angioplasty through preventing acute vessel closure and vessel recoil as well as providing drug delivery capability to inhibit neointimal hyperplasia[1,2]. Bioresorbable scaffolds aim to provide these benefits while in the longer term avoiding the disadvantages associated with permanent metallic caging of the treated vessel. Such disadvantages may include preventing positive vessel remodelling, inhibiting physiological vasodilatation, acting as a persistent nidus for stent thrombosis, stent fracture and/or neoatherosclerosis, as well as hindering assessment of the stented segment with CT angiography[3,4].

The Absorb™ bioresorbable scaffold (Abbott Vascular, Santa Clara, CA, USA) was the first bioresorbable scaffold to be commercially available, with promising early results in clinical trials, including non-inferiority to current-generation drug-eluting stents in multiple large randomised controlled trials[5-8]. Longer-term follow-up and results in real-world registries have, however, varied, which has been postulated to be influenced by differences in implantation techniques[9-14].

The properties of bioresorbable scaffolds, including the Absorb device, are different to contemporary metallic stents and, given these unique properties, the optimal implantation technique is likely to vary from that used for metallic stents. While expert consensus has highlighted the importance of lesion preparation and post-dilation, this has not been adequately validated through clinical data[15]. The concerning findings of ABSORB II long-term follow-up may reflect early operator experience with the device and a failure to employ currently recommended implantation techniques[16].

We report two-year clinical outcomes from the real-world ESHC-BVS registry, where the Absorb bioresorbable scaffold was implanted using a dedicated strategy of meticulous lesion preparation and routine post-dilation.

Methods

The ESHC-BVS registry is a Human Ethics Research Committee-approved single-arm, prospective, open-label registry utilising the Absorb bioresorbable vascular scaffold (BVS) in real-world coronary disease in the setting of stable angina and acute coronary syndrome (ACS). The design of this registry has been described previously[17]. All patients in whom treatment with an Absorb BVS was attempted at our two institutions were enrolled, with written consent obtained for follow-up of clinical outcomes. Funding for the Absorb BVS used in the registry was sourced internally. The series reported includes the first 100 patients in the registry who underwent percutaneous coronary intervention (PCI) using the Absorb BVS between December 2010 and October 2013, with a total of 152 lesions treated. The final decision to implant an Absorb BVS was made by the treating interventionalist. Factors influencing the decision to implant an Absorb BVS included young patient age (<70 years), long lesion length (>28 mm) and treatment of the mid-left anterior descending artery, the potential future site of attachment of a left internal mammary graft. Contraindications to BVS implantation included in-stent restenotic lesions, extreme proximal vessel tortuosity, extreme calcification, residual stenosis >30% after lesion preparation, planned major surgery within six months, or high likelihood of inability to tolerate or comply with dual antiplatelet therapy. Patients who were participating in another trial were also excluded. A wide spectrum of lesions was treated with patient and lesion complexity being a reflection of real-world clinical practice.

PROCEDURES

All patients were pre-treated with aspirin in combination with a $P2Y_{12}$ inhibitor. Procedural anticoagulation was at the discretion of the interventionalist and included unfractionated heparin or bivalirudin, with optional use of tirofiban. A dedicated BVS implantation strategy was employed placing emphasis on the importance of meticulous lesion preparation and scaffold post-dilation. Predilation was mandatory and encompassed use of non-compliant balloons, cutting balloons, and rotational atherectomy where deemed necessary. Scaffold implantation did not proceed without visual confirmation of complete expansion of the predilation balloon at the lesion, without the presence of balloon indentation.

The process of scaffold deployment followed the manufacturer's guidelines in all cases, using two atmosphere pressure increases every five seconds. At least 2 mm of non-diseased vessel proximal and distal to the target lesion was covered. Intracoronary imaging with intravascular ultrasound (IVUS) or optical coherence tomography (OCT) was available in all cases and was performed at the discretion of the interventionalist, but was not considered mandatory. Twelve months of dual antiplatelet therapy with aspirin in combination with clopidogrel, prasugrel or ticagrelor was prescribed for all patients on discharge.

OUTCOMES

Outcome data were collected prospectively by researchers independent of the interventionalists performing the procedures. This occurred primarily through phone call follow-up and completion of a patient questionnaire at 30 days, 12 months and two years, as well as review of clinical notes and reporting by the treating cardiologist. Where required, data were verified through review of coronary angiograms, and hospital documentation. Post-procedure high-sensitivity troponin-T levels were measured routinely on day 1.

The following clinical endpoints were assessed: cardiac death, and scaffold thrombosis (definite/probable/possible) as defined by the Academic Research Consortium criteria[18], myocardial infarction as defined by the universal criteria[19], and the need for target and non-target lesion revascularisation. Target lesion revascularisation included any revascularisation within 5 mm of the proximal or distal ends of the scaffold. Major adverse cardiac events (MACE) comprised a composite of death, myocardial infarction, or target lesion revascularisation. Procedural success was defined as successful delivery and deployment of a BVS at the intended target lesion without any major adverse cardiac event within seven days of the procedure. All cases of periprocedural myocardial infarction were included in the tally of MACE.

Results

Baseline patient characteristics, lesion and procedural data are summarised in **Table 1** and **Table 2**. This series includes one hundred patients with 152 lesions treated with a total of 167 scaffolds.

Table 1. Baseline characteristics.

Baseline characteristics		
Patient characteristics		
Patients, n		100
Male, %		68
Age, years		62.1±12.4
Diabetes mellitus, %		19
Hyperlipidaemia, %		71
Hypertension, %		74
Current smoker, %		13
Ex-smoker, %		32
Previous MI, %		15
Prior revascularisation, %		31
PCI, %		26
CABG, %		10
Clinical presentation		
Stable angina, %		56
NSTE-ACS, %		40
STE-ACS, %		4
Antiplatelet therapy on discharge		
Aspirin, %		100
Clopidogrel, %		64
Prasugrel, %		35
Ticagrelor, %		1
Lesion data		
Lesion characteristics		
Lesion number, n		152
Target vessel, %	Left main	1
	LAD (mid-LAD)	42 (30)
	Circumflex	13
	RCA	42
	SVG	2
Multivessel BVS, % of patients		15
ACC lesion type, %	A	10
	B1	34
	B2	19
	C	37
Length >28 mm, %		19
Moderate/severe calcification, %		16
Bifurcation, %		4
CTO, %		6
Quantitative coronary angiography		
Lesion length, mm		20.9±13.0
Range lesion length, mm		7.5-87.1
Dmax prox, mm		2.84±0.46
Dmax distal, mm		2.66±0.49
Minimal, mm		0.89±0.59

Table 2. Procedural and device data.

Lesion preparation	
Predilation, %	100
Rotational atherectomy, %	2.0
Scoring balloon, %	1.3
Procedural anticoagulation	
Unfractionated heparin, %	80.1
Bivalirudin, %	19.9
Tirofiban, %	8.3
Intracoronary imaging	
Intravascular ultrasound, %	6.5
Optical coherence tomography, %	9.3
Scaffold no. and size	
Mean no. of scaffolds per patient	1.67±0.94
Scaffold overlap, % lesions treated	18
Mean scaffold length, mm	22.74
Mean scaffold diameter, mm	2.98
2.5×18 mm	13.2%
2.5×28 mm	16.8%
3.0×18 mm	23.4%
3.0×28 mm	21.0%
3.5×12 mm	1.8%
3.5×18 mm	13.2%
3.5×28 mm	10.8%
Deployment and post-dilation	
Mean deployment pressure, atm	13.9±1.6
Post-dilation, %	95
Non-compliant post-dilation balloon, %	100
Mean post-dilation pressure, atm	19.6±4.6
Post-dilation balloon diameter	
Equal to scaffold, %	33
0.25 mm > than scaffold, %	45
0.5 mm > than scaffold, %	21

Patient selection was based on factors believed to provide the greatest advantage of temporary rather than permanent vessel scaffolding. This included younger patients (<70 years), patients with long segment disease (>28 mm), and those with disease involving the mid portion of the LAD (the site of future attachment of a left internal mammary artery graft). Financial constraints limited enrolment numbers with the treating institutions not receiving any reimbursement for the study device.

Mean patient age was 62.1 (±12.4) and ranged from 19 to 83 years. The majority of patients treated were male (68%). Diabetes mellitus was present in 19%, hyperlipidaemia in 71% and hypertension in 74%, with 13% being active smokers. The indication for BVS implantation was stable angina (or angina equivalent) in 56%, non-ST-elevation acute coronary syndrome (NSTE-ACS) in 40%, and ST-elevation acute coronary syndrome (STE-ACS) in 4%.

A wide range of lesions was treated, with lesion complexity being largely reflective of real-world practice **(Figure 1)**. The ACC lesion classification in the series was 10% type A, 34% type B1, 19% type B2, and 37% type C. Of the 152 lesions treated, 24% featured a length of >20 mm, 16% exhibited moderate/severe calcification, 7% were chronic total occlusions and 3% were vein grafts. Long lesion lengths necessitated a high rate of BVS to BVS overlap, being performed in 18% of lesions. The degree of scaffold overlap was minimised owing to concern regarding the greater strut thickness of the device when compared to metallic stents. Bifurcation lesions requiring an up-front two-wire strategy comprised 4% of lesions treated.

Vessel preparation was carried out prior to scaffold implantation in all cases. This involved predilation in 100%, rotational atherectomy in 2.0% and use of scoring balloons in 1.3%. Scaffold sizing to the vessel took into careful consideration the need to avoid exceeding the expansion limits of the implanted device. Scaffolds were deployed at moderately high pressure (mean 13.9±1.6 atm). Post-dilation was performed in 95% of scaffolds to a mean of 19.6±4.6 atm. The post-dilation balloon was sized 1:1 with the

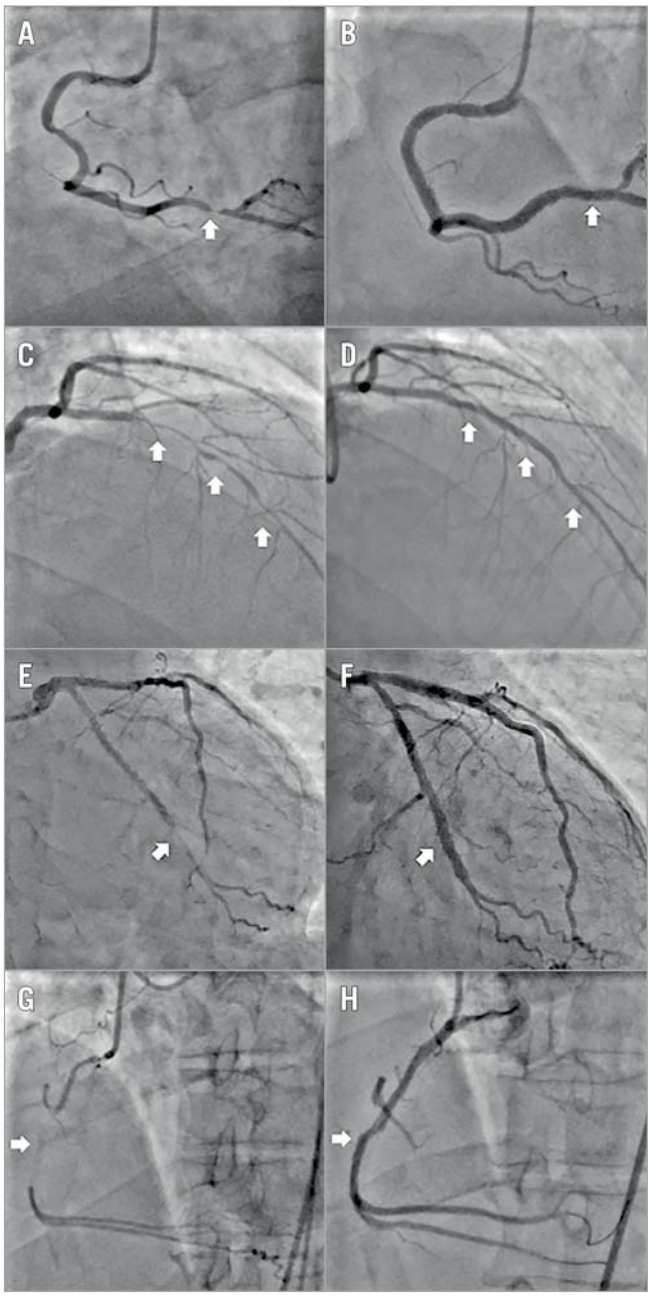

Figure 1. *Examples of lesions treated. A) & B) Severe mid RCA tortuosity and distal RCA disease treated with an Absorb BVS. C) & D) Severe diffuse disease of the LAD treated with two overlapping Absorb BVS in the mid and distal vessel with a further Absorb BVS more distally. E) & F) Severe circumflex disease treated with an Absorb BVS. G) & H) Mid RCA chronic total occlusion treated with an Absorb BVS following retrograde cross.*

scaffold in 33%, and was 0.25 mm and 0.5 mm larger than the scaffold in 45% and 21%, respectively.

Procedural anticoagulation was achieved with unfractionated heparin in 80.1% and bivalirudin in 19.9%, with the addition of tirofiban in 8.3%. Intracoronary imaging with IVUS or OCT was available in all cases, with IVUS utilised in 6.5% and OCT in 9.3%.

Failure to deliver the BVS to the target lesion occurred on two occasions, both in the setting of a highly tortuous and heavily calcified right coronary artery. This resulted in a BVS device failure rate of 1.2%. On both occasions a metallic drug-eluting stent was successfully delivered to the target lesion. There were no cases of scaffold dislodgement from the delivery balloon.

There were four cases of periprocedural myocardial infarction, all of which were not associated with ST-elevation or Q-wave formation, and did not result in any further adverse events in follow-up. Two-year clinical follow-up data were available for 99% of patients. The one patient who was lost to follow-up withdrew consent for surveillance after relocating overseas.

Outcomes in clinical follow-up are summarised in **Table 3-Table 5**. There was one cardiac death, resulting in a cardiac death rate of 1% at two-year follow-up. This case was also classified as a possible scaffold thrombosis by ARC criteria, occurring in a 71-year-old smoker who died suddenly while on vacation overseas, 17 months following treatment of a mid-LAD bifurcation where through-the-scaffold balloon inflation into the small diagonal side branch had not been attempted.

The incidence of myocardial infarction in the follow-up period was 2% at two years, excluding the periprocedural events. Target lesion revascularisation was required in 4% of patients at two years. All cases of target lesion revascularisation occurred in the first 12 months, with no further cases recorded between 12 months and two years.

Table 3. Clinical outcomes.

	30-day (%)	6-month (%)	12-month (%)	24-month (%)
Death (all-cause)	0	0	0	3
Cardiac death	0	0	0	1
Myocardial infarction (type 1)	0	2	2	2
STE-ACS	0	1	1	1
NSTE-ACS	0	1	1	1
Scaffold thrombosis* (any)	0	1	1	2
Definite/probable	0	1	1	1
Possible	0	0	0	1
In-scaffold restenosis	0	1	2	2
TLR	0	2	4	4
PCI	0	1	2	2
CABG	0	1	2	2
Non-TLR	0	2	2	2
MACE**	4	7	8	9

*Definite/probable/possible stent thrombosis by ARC criteria.
**Composite of cardiac death, target lesion revascularisation, and myocardial infarction (including periprocedural myocardial infarction).

The rate of definite/probable scaffold thrombosis at two years was 1% per patient and 0.6% per scaffold, owing to a single case which occurred in the setting of premature interruption to dual antiplatelet therapy four months following scaffold implantation. The patient had been treated with two overlapping 3.0×18 mm Absorb BVS in the proximal LAD for long segment disease. Repeat coronary angiography at three months showed the scaffolds to be widely patent. Ticagrelor was transiently ceased for non-cardiac surgery at

Table 4. Clinical outcome – case summary.

Case	Age	Gender	DM	Vessel	ACC/AHA class	Predilation	OCT/IVUS guidance	BVS device	Post-dilation	Clinical event
1	77	M	N	LAD	C	Yes	No	3.0×18 mm. Further 3.0×18 mm distally with overlap	Yes. 3.25 non-compliant balloon at 20 atm	STE-ACS at 4 months due to scaffold thrombosis following cessation of DAPT. Suboptimal scaffold apposition on IVUS at time of STEMI. BMS implanted within scaffold following angioplasty with 3.5 mm non-compliant balloon.
2	76	M	N	RCA	C	Yes	No	3.0×28 mm	Yes. 3.25 non-compliant balloon at 16 atm	NSTE-ACS at 10 months. Severe in-scaffold restenosis on angiography with severe neointimal hyperplasia confirmed on OCT. No scaffold malapposition. Treated with 3.0×38 mm zotarolimus-eluting stent across entire scaffolded segment.
3	60	M	Y	RCA	C	Yes	No	3.5×28 mm. Further 3.5×28 mm, 2.5×28 mm, 2.5×18 mm distally with overlap	Yes. 4.0 non-compliant balloon at 20 atm	Unstable angina at 7 months. Coronary angiography showing severe in-scaffold restenosis of proximal RCA and progression of circumflex atheroma. Treated with CABG.
4	62	M	N	LAD	C	Yes	No	3.0×28 mm	Yes. 3.25 non-compliant balloon at 20 atm	Recurrence of exertional angina at 5 months. Coronary angiography showing severe focal disease at proximal edge of scaffold. Treated with CABG.
5	71	M	N	LAD	C	Yes	No	3.0×28 mm	Yes. 3.0 non-compliant balloon at 16 atm	Sudden death at 17 months. Possible scaffold thrombosis by ARC criteria.

Table 5. Predictors of clinical events.

	Target lesion revascularisation (%)	Myocardial infarction (type 1) (%)	Scaffold thrombosis (definite/probable) (%)	In-scaffold restenosis (%)	Cardiac death (%)
OCT/IVUS guidance	0	0	0	0	3.8
No OCT/IVUS guidance	3.2	1.6	0.8	1.6	0
Relative risk (95% CI)	0.52 (0.03-9.42)	0.94 (0.05-19.04)	1.57 (0.07-37.46)	0.94 (0.05-19.04)	14.11 (0.59-337.16)
p-value	0.660	0.968	0.781	0.968	0.102
Scaffold diameter 2.5 mm	0	0	0	0	0
Scaffold diameter ≥3.0 mm	3.4	1.7	0.8	1.7	0.8
Relative risk (95% CI)	0.26 (0.01-4.69)	0.46 (0.02-9.47)	0.77 (0.03-18.62)	0.46 (0.02-9.47)	0.77 (0.03-18.62)
p-value	0.359	0.617	0.873	0.617	0.873
Lesion length ≥28 mm	6.8	3.4	3.4	0	3.4
Lesion length <28 mm	1.6	0.8	0	0.8	0
Relative risk (95% CI)	4.24 (0.62-28.87)	4.24 (0.27-65.83)	12.40 (0.52-296.91)	1.38 (0.06-32.99)	12.40 (0.52-296.91)
p-value	0.140	0.302	0.120	0.843	0.120
Scaffold overlap	3.7	3.7	3.7	0	3.7
No scaffold overlap	2.4	0.8	0	1.6	0
Relative risk (95% CI)	1.54 (0.17-14.28)	4.63 (0.30-71.73)	13.50 (0.56-322.81)	0.90 (0.44-18.23)	13.50 (0.56-322.81)
p-value	0.702	0.273	0.108	0.945	0.108

which time the patient experienced an anterior ST-elevation myocardial infarction, with scaffold thrombosis confirmed on coronary angiography. Intravascular ultrasound revealed suboptimal apposition of the proximal scaffold, which was corrected by balloon angioplasty and implantation of a 3.0×12 mm bare metal stent within the proximal scaffold. Post-dilation was performed with a 3.5 mm non-compliant balloon to high pressure. There were no further events recorded up to two-year follow-up.

The second case of target lesion revascularisation involved a patient treated with a 3.0×28 mm Absorb BVS to the mid LAD, who experienced a recurrence of angina five months following BVS implantation, with a stress test being positive for myocardial ischaemia. Coronary angiography revealed a patent BVS but significant progression of disease at the proximal edge of the scaffold and in the circumflex artery. Revascularisation options were discussed and the patient underwent coronary artery bypass surgery (CABG).

The third case of target lesion revascularisation involved a patient treated with a total of four BVS to the posterior descending artery (PDA) and proximal, mid and distal right coronary artery (RCA), who experienced recurrence of angina seven months after RCA intervention. Coronary angiography revealed diffuse restenosis of the proximal RCA BVS as well as progression of previously moderate disease in the circumflex artery. The three remaining scaffolds in the PDA and mid/distal RCA were patent. The patient underwent coronary artery bypass surgery.

The final instance of target lesion revascularisation occurred in a patient treated with a 3.0×28 mm BVS to the mid RCA. The patient experienced non-ST-elevation ACS 10 months following BVS implantation with coronary angiography revealing severe in-scaffold restenosis of the BVS. OCT confirmed this to be due to diffuse neointimal hyperplasia. No malapposition or underexpansion of the BVS was demonstrated. Predilation of the restenotic segment was performed with a 3.0 mm AngioSculpt scoring balloon (Biotronik, Bülach, Switzerland) prior to implantation of a 3.0×38 mm metallic zotarolimus-eluting stent (Resolute™; Medtronic, Minneapolis, MN, USA) across the entire length of the BVS. Post-dilation was performed using a 3.5 mm non-compliant balloon to 18 atmospheres. The patient did not have any further events recorded during the two-year follow-up period.

Non-target lesion revascularisation occurred in a further two cases in the two-year period, both due to progression of disease remote from the target segment. There were two cases of non-cardiac death. Follow-up of patients in the registry is ongoing.

Discussion

Bioresorbable scaffolds are a recent advance in PCI. In the short term, such devices are designed to seal intimal flaps to avoid acute vessel closure following balloon angioplasty, provide radial strength to prevent vessel recoil and deliver an antiproliferative drug to inhibit neointimal hyperplasia[1,2]. In the longer term, bioresorbable scaffolds are intended to address the drawbacks of conventional metallic stents. Persistence of metallic caging of the vessel inhibits vasodilation in response to ischaemia and anti-anginal therapy, and may act as a nidus for late clinical events through late stent thrombosis, neoatherosclerosis and stent fracture[3,4].

Despite the promised long-term advantages of bioresorbable scaffolds, such devices should not be associated with any increase in early or late major clinical events when compared to current-generation drug-eluting stents. The Absorb BVS, the first commercially available bioresorbable scaffold, has been found to be non-inferior to a current-generation metallic drug-eluting stent in multiple large randomised controlled trials with respect to clinical events at 12 months[5-8].

Other results have been variable, there having been an unacceptably high incidence of scaffold thrombosis of 1.5% at 30 days and 2.1% at six months in the GHOST-EU study[9], and a large meta-analysis substantiating the possible increased risk of device thrombosis associated with the Absorb BVS[20]. Moreover, longer-term follow-up of ABSORB II has revealed an increased relative risk of target vessel myocardial infarction in the Absorb group at three years compared to the XIENCE stent (Abbott Vascular)[14]. These safety concerns have prompted removal of the device from commercial use.

Whether unfavourable outcomes relate to fundamental shortcomings of the device, or represent early challenges of understanding the bioresorbable technology and its optimal use is uncertain. The variability in clinical outcomes among various registries and randomised controlled trials has been postulated to be related to differences in implantation techniques among the different studies.

Adverse ABSORB II findings at three-year follow-up may reflect a lack of early insight regarding the optimal implantation technique for the device[14,16]. Expert consensus now recommends a dedicated BVS-specific implantation strategy, emphasising the importance of meticulous lesion preparation and routine post-dilation[15]. Such an approach gives consideration to the unique properties of the Absorb BVS in terms of factors such as strut thickness, crossing profile and deliverability, radial/longitudinal strength and finite expansion limits. While implementation of this strategy has been linked to a possible reduction in the incidence of scaffold thrombosis, more comprehensive clinical data have been lacking[21].

Implantation of all Absorb BVS at our two institutions occurred as part of the prospective ESHC-BVS registry. A strategy of meticulous lesion preparation and routine high-pressure post-dilation has been strongly advocated at our institutions since the inception of this registry.

Patient and lesion characteristics treated in this cohort were reflective of real-world practice with 19% of patients being diabetic, 44% being treated for ACS, and 56% of lesions being of B2/C complexity. The mean patient age of 62.1 years reflected a tendency to treat younger patients given the longer duration of benefit of avoiding permanent vessel caging in these individuals. Other factors influencing the decision to implant a BVS included long segment disease (>28 mm) where the use of metallic stents could act as a nidus for late target lesion failure, and could impede future revascularisation options. Treatment of the mid-left anterior descending artery was seen as an indication for use of a BVS over a metallic stent, so that the potential for future revascularisation by left internal mammary artery grafting could be maintained[22].

Predilation was performed in all cases. This included presentations with ACS where the benefits of adequate lesion preparation were believed still to outweigh the risks of distal embolisation induced by balloon angioplasty.

Full expansion of the predilation balloon was seen as mandatory prior to scaffold implantation, with there being a low threshold to utilise non-compliant balloons. Cutting balloons and rotational atherectomy were used as adjunct techniques where necessary. Meticulous lesion preparation was considered essential to avoid scaffold underexpansion, with this having been shown to be a major factor contributing to scaffold thrombosis[15,20,21]. This strategy also helped to overcome the higher crossing profile and reduced deliverability of the Absorb BVS, facilitating successful delivery of the device in 98.8% of cases.

Scaffold selection paid particular attention to vessel size to avoid exceeding the limited expansion limits of the implanted scaffold. Quantitative coronary angiography (QCA) and vessel sizing relative to predilation balloons was used to assist in this regard. Scaffold implantation was performed at moderately high pressure (mean 13.9±1.6 atm) to assist in achieving full scaffold expansion and maximising strut apposition. This also served to facilitate delivery of the post-dilation balloon with reduced risk of scaffold fracture arising from the passage of post-dilation balloons against malapposed proximal struts. Post-dilation was performed in 95% of scaffolds. Non-compliant balloons were used in all cases sized to at least the nominal pressure of the scaffold, to a maximum of 0.5 mm larger than the scaffold, with balloon inflation performed to high pressures (mean 19.6±4.6 atm). This post-dilation strategy further maximised scaffold apposition to the vessel wall while improving scaffold expansion in the minority of cases where this remained suboptimal despite previous measures.

Good clinical outcomes were achieved in long-term follow-up with the BVS-specific implantation strategy employed. At two years, the rate of target lesion revascularisation was 4%, definite/probable scaffold thrombosis 1% and cardiac death 1%. Furthermore, the BVS-specific implantation strategy allowed results to be accomplished while minimising the need for intracoronary imaging. Use of OCT and IVUS combined was limited to only 15.8% of cases, thereby contributing to minimising cost.

Our results confirm that minimising scaffold underexpansion and malapposition through the BVS-specific implantation technique described allows use of the Absorb BVS with limited events in the first two years of follow-up in a real-world cohort.

Our findings help to validate expert consensus guidelines regarding optimal implantation strategies for the Absorb BVS, including meticulous lesion preparation, careful consideration of scaffold sizing, and high-pressure post-dilation. A BVS-specific implantation strategy incorporating these principles should be employed in all cases where the Absorb BVS is utilised.

Limitations

While the rate of clinical events in follow-up was low, the findings are limited by relatively small patient numbers. In addition, the prospective, single-arm design of the registry does not specifically allow comparison of different implantation techniques as would be made through a randomised controlled trial.

Conclusions

Good outcomes were achieved to two-year follow-up with the Absorb BVS in real-world coronary disease utilising a dedicated

strategy incorporating meticulous lesion preparation, judicious scaffold sizing and routine high-pressure post-dilation. These findings support the implantation strategy employed in this registry.

Impact on daily practice

The properties of bioresorbable scaffolds are different to metallic stents, which may influence the optimal implantation technique and account for the variability of long-term results with the Absorb BVS in clinical trials. Our findings demonstrate the good outcomes which can be achieved at two years with the Absorb BVS in real-world coronary disease, utilising an implantation strategy tailored for the device. An implantation strategy comprising meticulous lesion preparation, judicious scaffold sizing and routine high-pressure post-dilation should be strongly considered when evaluating future poly-lactide bioresorbable stent platforms.

Conflict of interest statement

N. Jepson has received speaker's fees from Abbott Vascular. D. Robaei has received an educational grant from Abbott Vascular. The other authors have no conflicts of interest to declare.

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Imaging comparisons of bioresorbable scaffolds as seen by optical coherence tomography

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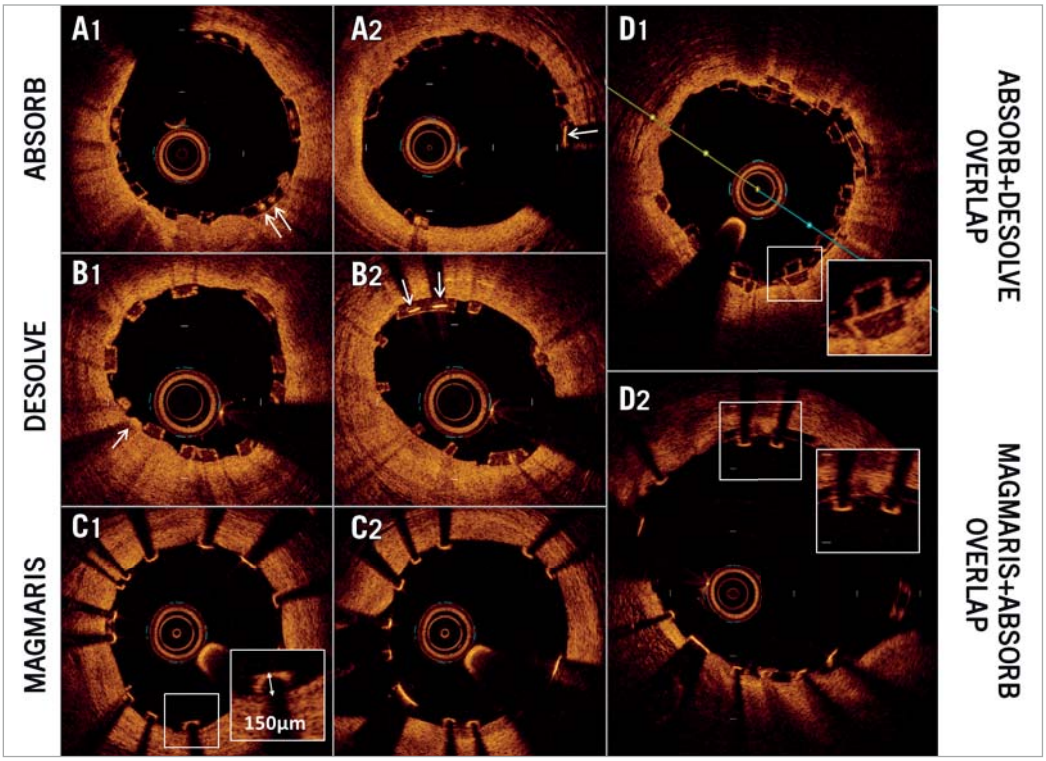

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Intracoronary imaging is recommended to guide bioresorbable scaffold (BRS) deployment. Here, we describe the distinguishing features of three CE-marked BRS – Absorb™ (Abbott Vascular, Santa Clara, CA, USA), DESolve® (Elixir Medical, Sunnyvale, CA, USA) and Magmaris™ (Biotronik, Berlin, Germany) – as imaged by optical coherence tomography (OCT) immediately post implantation.

Absorb (poly[L-lactide], PLLA) and DESolve (PLLA-based) scaffolds have characteristic box-shaped struts with minimal attenuation. Absorb struts **(Panel A1, Panel A2)** exhibit very low backscatter (appearing almost black), whereas DESolve struts **(Panel B1, Panel B2)** exhibit slight backscatter (appearing lightly shaded), reflecting proprietary differences in the polymer constituents. The Magmaris (magnesium-based) scaffold appears on OCT similar to a metallic stent **(Panel C1, Panel C2)**. All three BRS have struts 150 µm thick. As opposed to Absorb and DESolve, only the luminal surface of Magmaris can be seen, potentially giving a false impression of malapposition – measurement is helpful in uncertain cases **(Panel C1)**. Absorb has numerous "flare spots" throughout the length of the scaffold (**Panel A1**, arrows), located at hinge points of high strain and thought to represent micro-gaps in the polymer. DESolve has fewer and less apparent flare spots (**Panel B1**, arrow). Absorb and DESolve scaffold edge markers are visible (**Panel A2**, **Panel B2**, arrows) – these are located 0.9 mm and 0.3 mm from the proximal and distal edges, respectively, for Absorb, and 1 mm from either edge for DESolve. Identifying markers on OCT and co-registering them angiographically guides implantation of overlapping scaffolds in cases where markers are poorly seen on fluoroscopy. Magmaris edge markers are difficult to distinguish from the scaffold. The appearance of overlapped BRS scaffolds can be clearly appreciated on OCT **(Panel D1, Panel D2)**. With the current uncertainty regarding the long-term results of BRS, a clear understanding of their imaging features is of the utmost utility.

Conflict of interest statement

Chee Yang Chin has received honoraria from ACIST Medical Systems. Chee Tang Chin has received educational grants from Abbott Vascular, Biotronik and OrbusNeich, honoraria from Medtronic and Boston Scientific, and research support from Terumo, Medtronic, AstraZeneca and Eli Lilly. The other authors have no conflicts of interest to declare.

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Potential risk of deflecting stent struts after side branch dilation with inappropriate guidewire recrossing in a coronary bifurcation lesion

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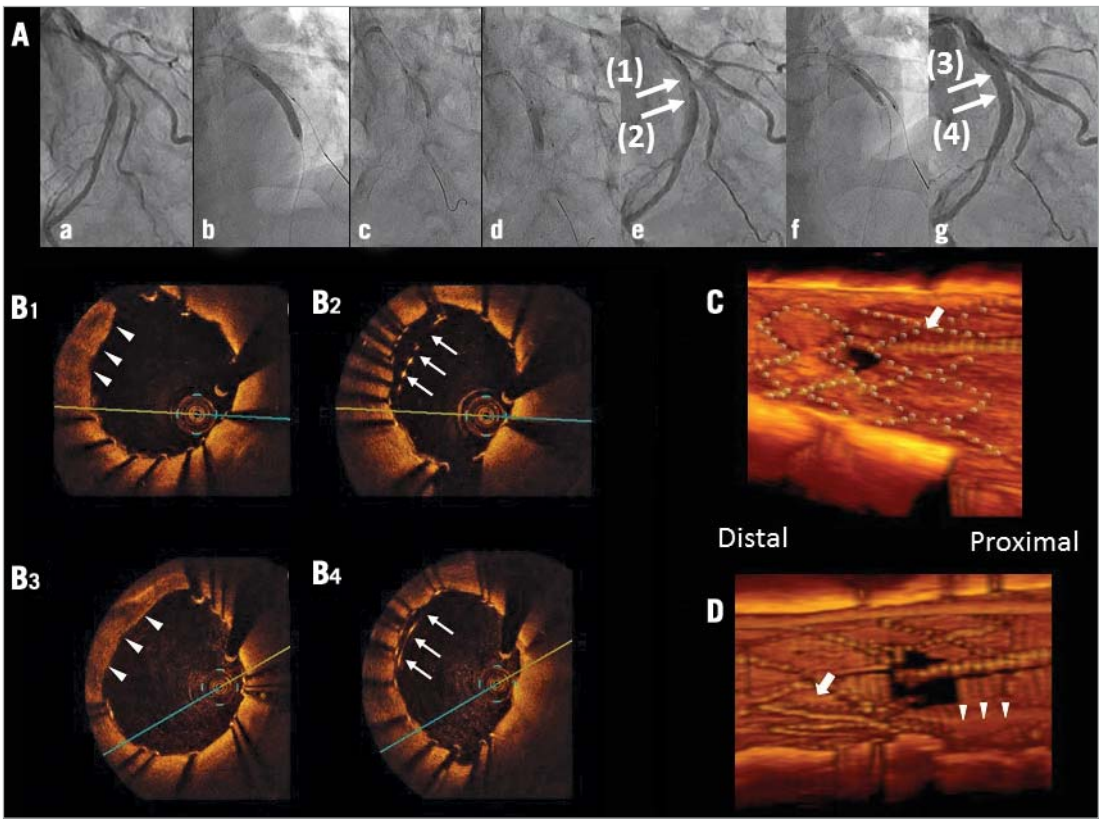

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A 64-year-old male underwent percutaneous coronary intervention (PCI) for a 1,1,1 lesion in the left anterior descending artery (LAD)-diagonal (Dx) bifurcation **(Panel Aa)**. A biolimus-eluting 3.5/24 mm stent (Nobori®; Terumo Corp., Tokyo, Japan) was implanted in the middle LAD **(Panel Ab)** followed by respective sequential dilations of Dx and LAD with 2.0 mm **(Panel Ac)** and 3.5 mm balloons (Maverick²™; Boston Scientific Corp., Marlborough, MA, USA, and Raiden 3; Kaneka Medix, Osaka, Japan, respectively) **(Panel Ad)** after guidewire (GW) recrossing **(Panel Ae)**. Finally, a kissing balloon inflation (KBI) was then performed **(Panel Af, Panel Ag)**, after optical coherence tomography (OCT) showed an unscaffolded area proximally **(Panel B1)** and double layered struts distally to the bifurcation **(Panel B2)**. Although the strut-unscaffolded area remained proximally **(Panel B3)**, KBI improved the malapposition of the distal double strut layer **(Panel B4)**.

The three-dimensional OCT images reconstructed after the intervention clearly showed the GW recrossing through a proximal cell into the Dx ostium (**Panel C**, arrow). The jailed struts were then deflected distally after respective Dx and LAD dilations **(Moving image 1)**. These struts protruding in the lumen distal to the Cx were subsequently reapposed after KBI (**Panel D**, arrows) but an area uncovered by stent struts remained proximally (triangles).

GW recrossing in the optimal distal cell leads to adequate side branch dilation and less incomplete stent apposition. GW recrossing in the proximal cell has been reported to cause protrusion of the jailed struts into the main vessel, and the present case suggests a potential risk of struts protruding distally into the main vessel after proximal rewiring. Malapposed struts in the bifurcation and incomplete apposition of the double-layered struts in complex stenting have been reported to increase the risk of stent thrombosis and restenosis. Three-dimensional OCT was useful to identify accurately GW recrossing and the cause of strut deformation and malapposition.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Supplementary data

Moving image 1. Final three-dimensional OCT.

The supplementary data are published online at: www.asiaintervention.org

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Unsuccessful confirmation of rewiring position with three-dimensional optical coherence tomography caused by thrombus formation on jailed struts

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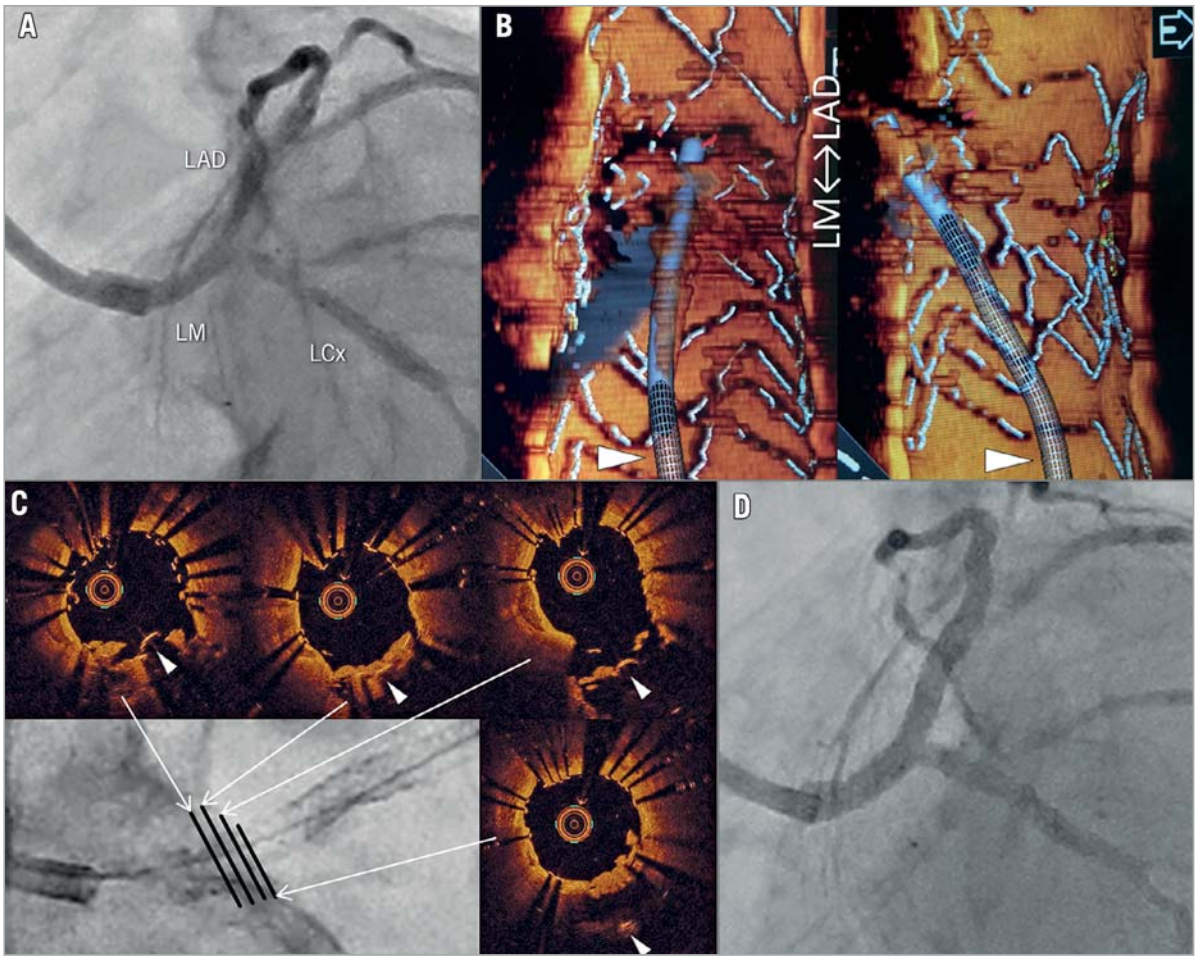

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An 80-year-old man had culotte stenting performed for a left main (LM) true bifurcation lesion **(Panel A)**. He underwent implantation of a first stent on the LM-left circumflex artery (LCx) with an Ultimaster® 2.5×18 mm (Terumo, Tokyo, Japan). After opening the jailed struts, he underwent a second stent implantation on the LM-left anterior descending artery (LAD) with an Ultimaster 3.0×24 mm. After rewiring to the LCx, using three-dimensional optical coherence tomography (3D-OCT) with the OPTIS™ Metallic Stent Optimization Software™ (St. Jude Medical, St. Paul, MN, USA), no links connecting to a carina were confirmed, but the guidewire recrossed to the LCx through some tissue on the LCx ostium, and the distal cell rewiring could not be confirmed **(Panel B)**. According to two-dimensional OCT (2D-OCT), the unsuccessful confirmation with 3D-OCT was caused by thrombus formation on the jailed struts, and the guidewire recrossed through the distal cell **(Panel C, Moving image 1)**. After final kissing balloon dilation, coronary angiography **(Panel D)**, 2D-OCT **(Moving image 2)**, and 3D-OCT **(Supplementary Figure 1)** showed a good result.

3D-OCT is useful for bifurcation PCI, but confirmation by 2D-OCT is also required.

Conflict of interest statement

The author has no conflicts of interest to declare.

Supplementary data

Supplementary Figure 1. Final 3D-OCT.

Moving image 1. 2D-OCT from LAD to LM, after second stent implantation followed by rewiring to LCx.

Moving image 2. Final 2D-OCT from LAD to LM.

The supplementary data are published online at: www.asiaintervention.org

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Angiographic and optical coherence tomography features of positive arterial remodelling causing very late thrombosis in a first-generation sirolimus-eluting stent

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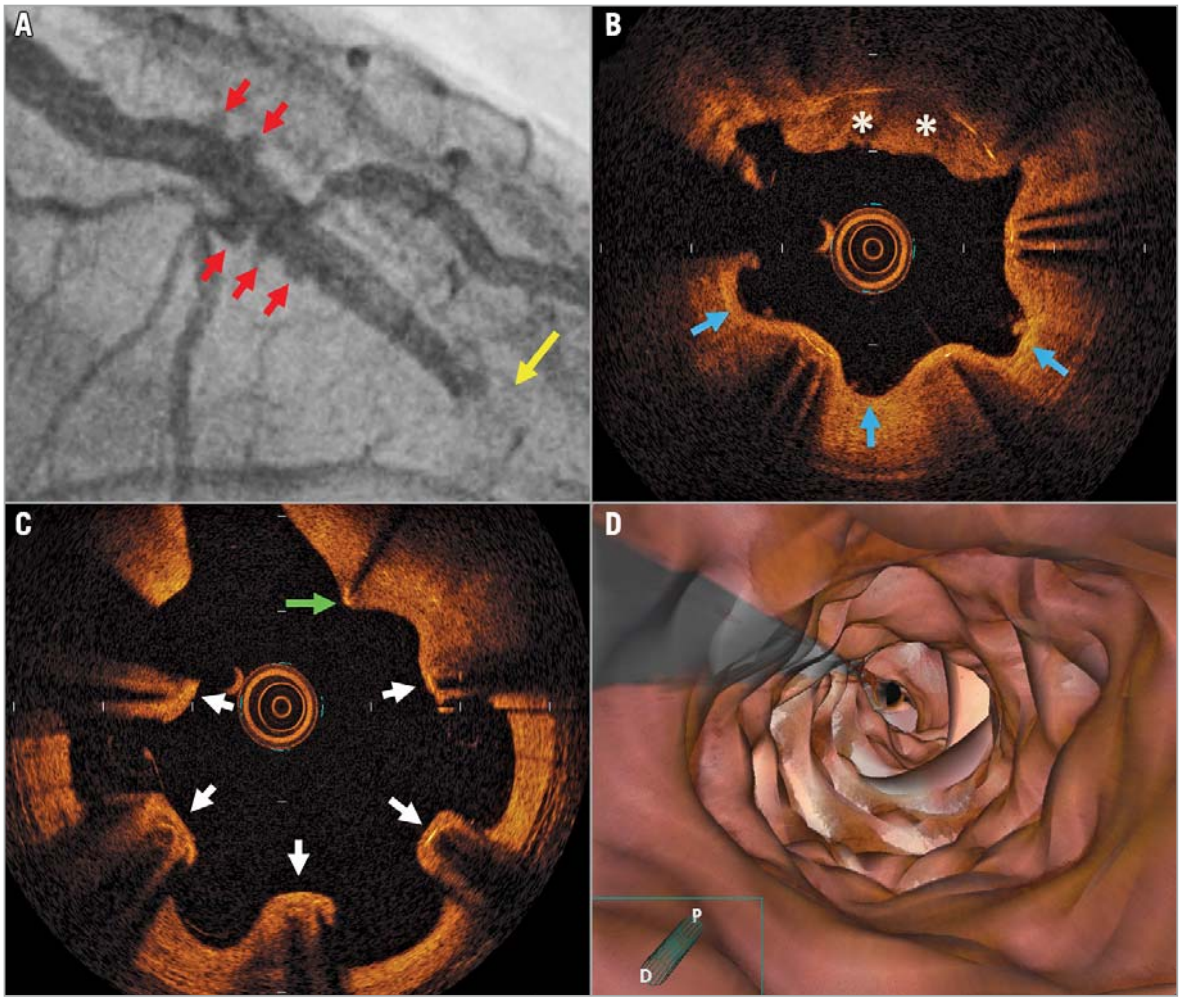

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A 45-year-old man presented with acute anterior ST-elevation myocardial infarction four years after the implantation of two 3.0 mm diameter first-generation sirolimus-eluting CYPHER® (Cordis, Johnson & Johnson, Warren, NJ, USA) stents in his left anterior descending coronary artery. Emergent angiography **(Moving image 1)** now revealed a thrombotic occlusion of the distal stented segment (**Panel A**, yellow arrow), with peri-stent contrast staining in the proximal stented segment (**Panel A**, red arrows). Following thrombus aspiration, optical coherence tomography (OCT) **(Moving image 2)** showed positive arterial remodelling throughout the previously stented segments causing vessel evaginations (**Panel B** [blue arrows], **Panel C**) and malapposed stent struts (**Panel B**, **Panel C** [white arrows]), with occasional uncovered stent struts (**Panel C**, green arrow) and residual thrombus (**Panel B**, *). Three-dimensional OCT reconstruction displayed a highly irregular luminal surface **(Panel D)**. He was successfully treated with stenting of the occluded segment with a third-generation drug-eluting stent.

Localised hypersensitivity and inflammation related to first-generation sirolimus-eluting stents may induce positive remodelling, leading to late stent malapposition. While first-generation sirolimus-eluting stents have been phased out of use in recent years, the clinical impact of very late stent thrombosis due to late stent malapposition and uncovered stent struts may continue to be seen in the coming years.

Conflict of interest statement

C.Y. Chin has received honoraria from ACIST Medical Systems. The other authors have no conflicts of interest to declare.

Supplementary data

Moving image 1. Emergency coronary angiogram.

Moving image 2. OCT pullback after thrombus aspiration.

The supplementary data are published online at: www.asiaintervention.org

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Intraprocedural rupture of neoatherosclerosis causing extensive neointimal dissection: use of optical frequency domain imaging to evaluate the mechanism and guide intervention

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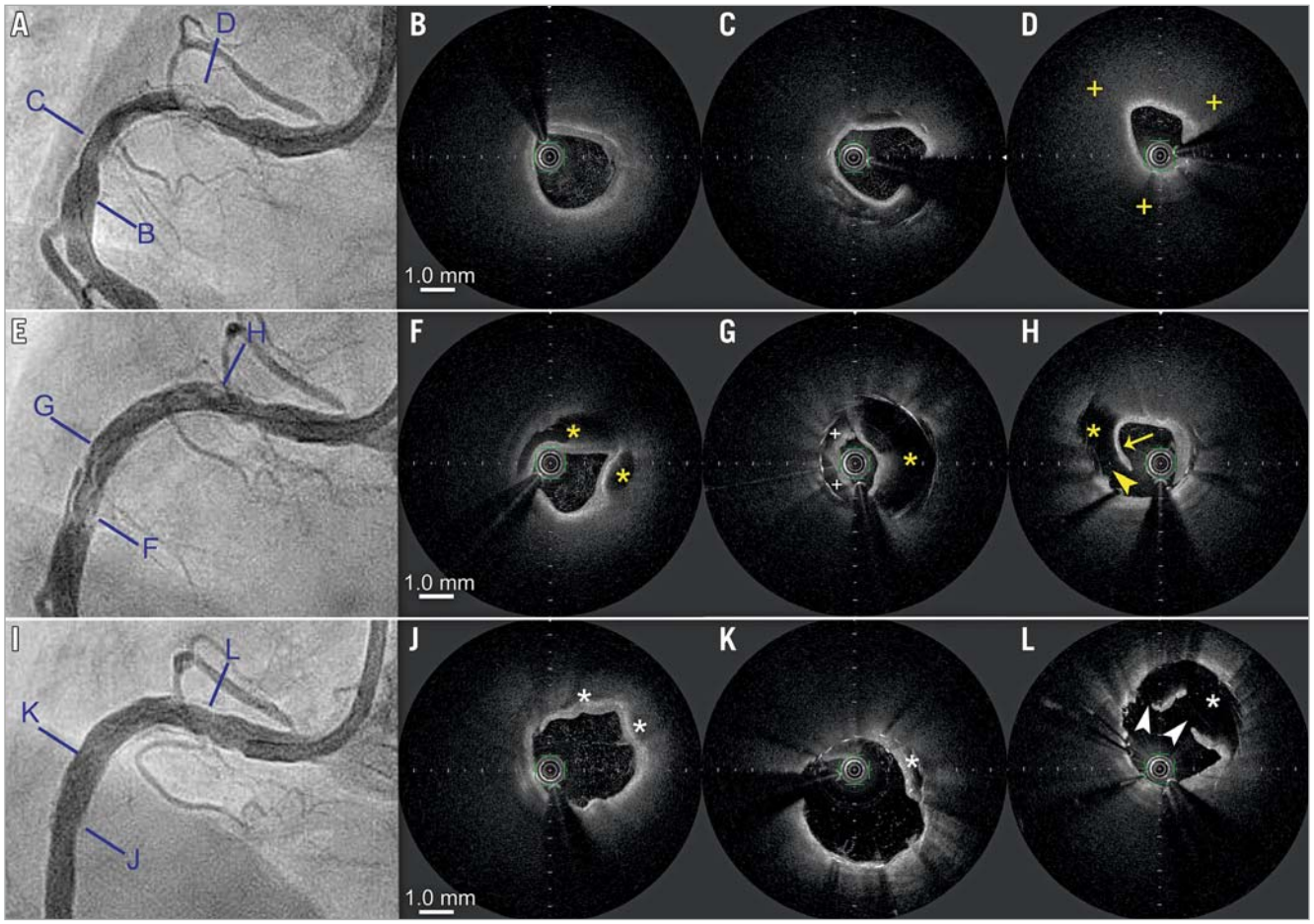

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A 75-year-old woman who was implanted with a 3.0×28 mm biolimus-eluting stent in the proximal right coronary artery two years previously presented with unstable angina due to focal in-stent restenosis **(Panel A)**. Optical frequency domain imaging (OFDI) (Terumo Corp., Tokyo, Japan) revealed a normal pattern of homogeneous neointimal hyperplasia **(Panel B, Panel C)** and neoatherosclerosis with a lipid-laden neointima and large lipid pool at the most stenotic lesion **(Panel D, Moving image 1)**. After excimer laser coronary angioplasty (1.4 mm concentric) with concomitant saline flushing, angiography revealed sudden extended multilayered haziness **(Panel E, Moving image 2)**. OFDI clearly demonstrated extensive neointimal dissection (**Panel F-Panel H**, yellow asterisks, **Moving image 3**), some mural thrombus (**Panel G**, plus signs), disruption of the neointima (**Panel H**, arrowhead), and a mobile flap at the lasing site **(Panel H**, arrow), confirming neoatherosclerosis rupture complicated by extensive neointimal dissection. After angioplasty with a 3.5×13 mm scoring balloon at 20 atm and a 3.5×30 mm paclitaxel-coated balloon at 12 atm, reentry between the true lumen and dissected lumen was successfully obtained **(Panel I, Moving image 4)**. OFDI revealed remarkable decompression of the dissected lumen (**Panel J-Panel L**, asterisks, **Moving image 5**) and several incisions (**Panel L**, arrowheads) created by scoring balloon angioplasty.

In-stent neoatherosclerosis has emerged as an important mechanism of drug-eluting stent failure, including delayed restenosis and very late stent thrombosis. To the best of our knowledge, this is the first report of OFDI for intraprocedural rupture of neoatherosclerosis causing extensive neointimal dissection. Although the process of this phenomenon remains unclear, the present case raises two important clinical issues: (1) some interventional procedures for neoatherosclerosis with a lipid-laden neointima and large lipid pool might carry a risk of neoatherosclerosis rupture, which can lead to extensive neointimal dissection; and (2) OFDI was crucial to elucidate the underlying mechanism and manage it successfully.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Supplementary data

Moving image 1. Baseline OFDI, showing development of in-stent neoatherosclerosis with a lipid-laden neointima and large lipid pool.

Moving image 2. Angiography after treatment with excimer laser coronary angioplasty, showing sudden development of multilayered haziness.

Moving image 3. OFDI after treatment with excimer laser coronary angioplasty, showing ruptured neoatherosclerosis complicated with extensive neointimal dissection, disrupted neointima, and mobile flap at the lasing site.

Moving image 4. Post-procedural coronary angiography, showing restored good coronary flow and improvement of neointimal dissection.

Moving image 5. Post-procedural OFDI, showing the incision on the dissected neointima, remarkable decompression of the dissected lumen, and successful fenestration between the true lumen and dissected lumen.

The supplementary data are published online at: www.asiaintervention.org

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Wire pull-through technique using a double lumen sheath during transapical transcatheter aortic valve implantation

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KEYWORDS

- aortic stenosis
- radial
- transapical
- transcatheter aortic valve implantation

Abstract

Transapical transcatheter aortic valve implantation (TA-TAVI) with the wire pull-through technique using a double lumen sheath via the brachial or radial artery is a new therapeutic approach to aortic stenosis patients having shaggy aortic arch. The risk of systemic embolisation of atherothrombotic material can theoretically be reduced by avoiding any manipulations of stiff guidewires or catheters across the diseased segments based on the "non-touch" method. We report a case series of three patients undergoing the wire pull-through technique during TA-TAVI using the SAPIEN XT transcatheter heart valve. The rationale, technical considerations and clinical implications of this technique are described.

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Introduction

Transcatheter aortic valve implantation (TAVI) has been developed as an alternative therapeutic approach to surgical aortic valve replacement (SAVR) for high-risk or inoperable patients with symptomatic aortic stenosis (AS). In patients with AS, shaggy aorta is frequently observed by ultrasonography or computed tomography (CT). It has been reported that the presence of shaggy aorta is associated with serious complications during surgical or endovascular procedures due to embolisation of atherosclerotic or thrombotic materials[1]. In patients undergoing endovascular aneurysm repair, atherothrombotic embolisation presenting with systemic organ ischaemia (e.g., brain, bowel, or limb) was observed in 5.0-7.8% of cases, but it might result in catastrophic consequences (in-hospital mortality: 50-80%)[2,3]. The transapical (TA) approach instead of the transfemoral (TF) is thus generally accepted as the optimal treatment strategy in patients having shaggy aorta. Despite the lack of evidence, however, the conventional TA-TAVI technique still has a potential concern in terms of disruption of atherothrombotic mass and subsequent systemic embolisation by manipulating stiff guidewires or catheters.

The current report presents three cases undergoing TA-TAVI with the wire pull-through technique using a double lumen sheath. The technical considerations and clinical implications of this technique are also discussed.

Rationale and procedural technique

A rationale of the wire pull-through technique – non-touch method – is to avoid manipulations of any devices into shaggy aortic arch. This approach could minimise the risk of atherothrombotic embolisation that may result in serious post-procedural complications. Using a double lumen sheath via the brachial or radial artery, a 0.035-inch wire and a pigtail catheter or a guiding catheter can be inserted simultaneously in a sheath.

Preparing for the wire pull-through technique, a double lumen sheath (Medikit, Tokyo, Japan) has to be inserted via the right brachial or radial artery. Following the needle puncture to the left ventricle (LV) wall, a hydrophilic soft wire with angle-shaped tip (Radifocus® Guidewire M Standard type; Terumo Corp., Tokyo, Japan) is advanced into the right subclavian artery (SCA) together with a coronary diagnostic catheter (e.g., Judkins right or multipurpose). After replacing the soft wire with a hydrophilic half-stiff wire (Radifocus® M Half stiff type; Terumo Corp.), it should be advanced distally to the snaring system (Indy OTW™ Vascular Retriever [Cook Medical, Bloomington, IN, USA]; EN Snare® [Merit Medical Systems, South Jordan, UT, USA]). The wire can be caught easily and retrieved through the sheath **(Figure 1)**. After establishing the pull-through system, the diagnostic catheter is removed and a pigtail catheter is introduced retrogradely through another port of the double lumen sheath. The following procedure after the insertion of a 24 Fr Ascendra+ sheath (Edwards Lifesciences, Irvine, CA, USA) is the same as that of conventional TA-TAVI using the SAPIEN XT (Edwards Lifesciences).

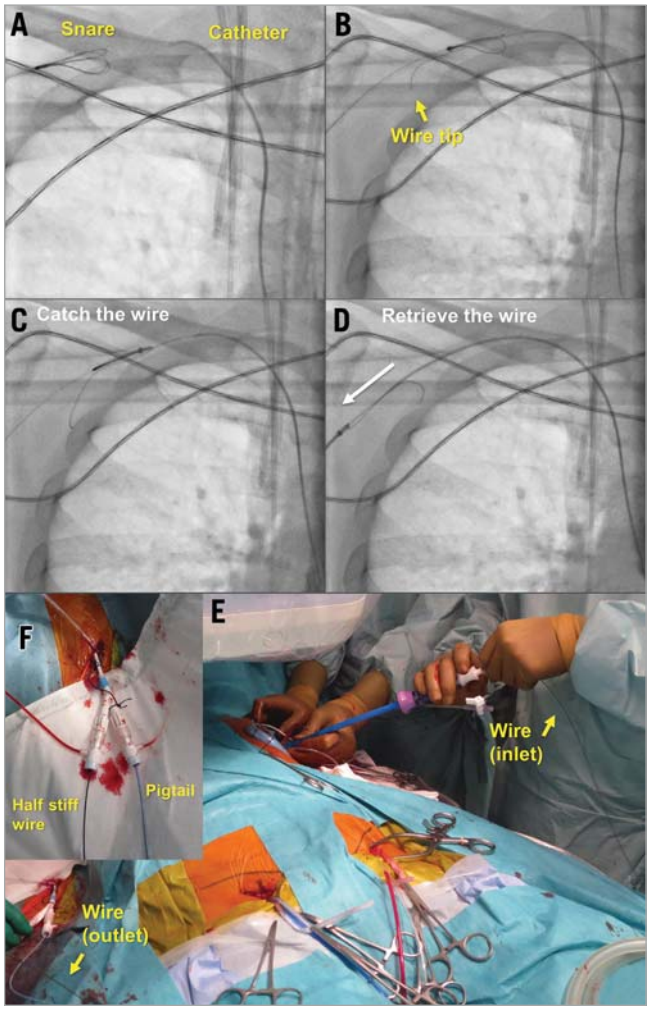

Figure 1. *Wire pull-through technique during TA-TAVI. A snaring system and a Judkins Right diagnostic catheter are placed in the right subclavian artery (A). The wire is advanced distally to the snaring system introduced through the double lumen sheath (B, yellow arrow). The wire can be grasped easily (C) and retrieved through the sheath (D). After establishing the wire pull-through system, the diagnostic catheter is removed (E), then a pigtail catheter is retrogradely introduced through another port of the double lumen sheath (F).*

Results

Three cases treated with the wire pull-through technique are summarised in **Table 1**. In brief, mean age was 86 and all patients were frail and male. Average STS score (30-day mortality) and logistic EuroSCORE were 8.3% and 14.3%, respectively. One patient (Case 2) was diagnosed as having classical low-flow low-gradient AS based on dobutamine stress echocardiography. Multidetector CT (MDCT) revealed significant shaggy aortic arch in all cases **(Figure 2)**. Regarding the double lumen sheath, an 8 Fr via brachial cut-down was used for our first two cases and a 6.5 Fr via radial puncture was used for the third case. Post-procedural paravalvular leak was acceptable (i.e., mild or trace) in all cases. Two patients were discharged 10 days after the procedure without any

Table 1. Clinical and procedural characteristics of three representative cases.

	Case 1	Case 2	Case 3
Demographics			
Age (years)	89	83	87
Sex	Male	Male	Male
Height (cm)	161	160	150
Weight (kg)	50	51	48
Body surface area (m^2)	1.50	1.51	1.40
Hypertension	Yes	Yes	Yes
Diabetes mellitus	Yes	No	No
Dyslipidaemia	No	No	Yes
Current smoking	No	No	No
Prior cerebrovascular accidents	No	No	No
Prior myocardial infarction	No	Yes	No
Prior PCI	No	No	No
Prior CABG	No	Yes	No
Preoperative risk assessment			
Atrial fibrillation	No	Yes	No
Chronic kidney disease	Yes	Yes	No
Chronic obstructive pulmonary disease	No	Yes	No
Peripheral artery disease	No	No	No
Steroid or immunosuppressant use	No	No	No
Estimated glomerular filtration rate (mL/min/1.73 m^2)	27.6	42.8	50.5
NT-proBNP (pg/mL)	10,152	1,918	5,226
STS 30-day mortality rate (%)	10.1	8.3	6.5
Logistic EuroSCORE (%)	10.1	23.9	9.0
CSHA frailty scale	5	5	4
Imaging assessment			
Aortic valve area (cm^2)	0.52	0.63	0.54
Mean pressure gradient (mmHg)	85	26	83
Peak velocity (m/s)	5.9	3.4	6.0
Left ventricular ejection fraction (%)	55	42	65
Preoperative aortic regurgitation	Trivial	Mild	Mild
Annulus perimeter (mm)	70.4	76.3	73.7

	Case 1	Case 2	Case 3
Imaging assessment			
Annulus diameter (mm)			
TTE	19.5	19.8	19.2
TEE	19.4	20.8	21.5
CT	21.9	24.3	22.8
Annulus area (mm^2)			
TEE	352	361	396
CT	360	440	407
Mean STJ diameter on CT (mm)	29.9	32.9	32.9
Mean diameter of sinus of Valsalva (mm)	33.9	33.8	30.6
Subannular calcification	No	Yes	No
Aortic aneurysm	No	Yes	Yes
Shaggy aorta	Yes	Yes	Yes
Penetrating aortic ulceration	Yes	No	No
Procedures			
Anaesthesia	General	General	General
Guidewire	extra-stiff	half stiff	half stiff
Size of double lumen sheath (Fr)	8.0	8.0	6.5
Vascular access site	Brachial	Brachial	Radial
Sheath insertion technique	cut-down	cut-down	puncture
Pre-BAV balloon size (mm)	20	skipped	20
SAPIEN XT THV size (mm)	23	26	26
Balloon inflation volume	Nominal	–1 mL	–2 mL
Postoperative paravalvular leak	Mild	Mild	Trace
Procedural complications	No	Worsening of interstitial pneumonia	No
Hospital stay after the procedure (days)	10	35	10

BAV: balloon aortic valvuloplasty; CABG: coronary artery bypass graft; CSHA: Canadian Study of Health and Aging; CT: computed tomography; PCI: percutaneous coronary intervention; STJ: sinotubular junction; STS: Society of Thoracic Surgeons; TEE: transoesophageal echocardiography; THV: transcatheter heart valve; TTE: transthoracic echocardiography

complications. Another patient (Case 2) who suffered from worsening of interstitial pneumonia was discharged 35 days after the procedure.

Discussion

To our knowledge, this is the first description of the wire pull-through technique using a double lumen sheath during the TA-TAVI procedure. Despite our early experience, the current report highlights the safety and feasibility of this technique specifically for patients having shaggy aortic arch.

The bottom line for applying this technique was that the majority of TAVI patients were elderly, usually above the age of 80, and probably with associated atherosclerotic disease of the aortic arch, in which this technique would be beneficial in reducing the thromboembolic risk. A previous study indicated that post-procedural magnetic resonance imaging revealed evidence of cerebral embolism in 84% of patients undergoing TF-TAVI[4]. Another study demonstrated that severe atheroma in the aortic arch and descending aorta appeared to be a predictor of cerebral infarction after TAVI, despite the fact that the majority of patients were clinically silent[5,6]. An embolic deflector device is expected to be an attractive solution and has been clinically tested in order to establish whether the risk of post-procedural cerebral infarction can be reduced[7]. Although the pathogenesis and origin of embolic materials have not been fully investigated, the TA-TAVI procedure without any device manipulations across diseased aortic segments might reduce the risk of systemic embolisation of atherothrombotic materials.

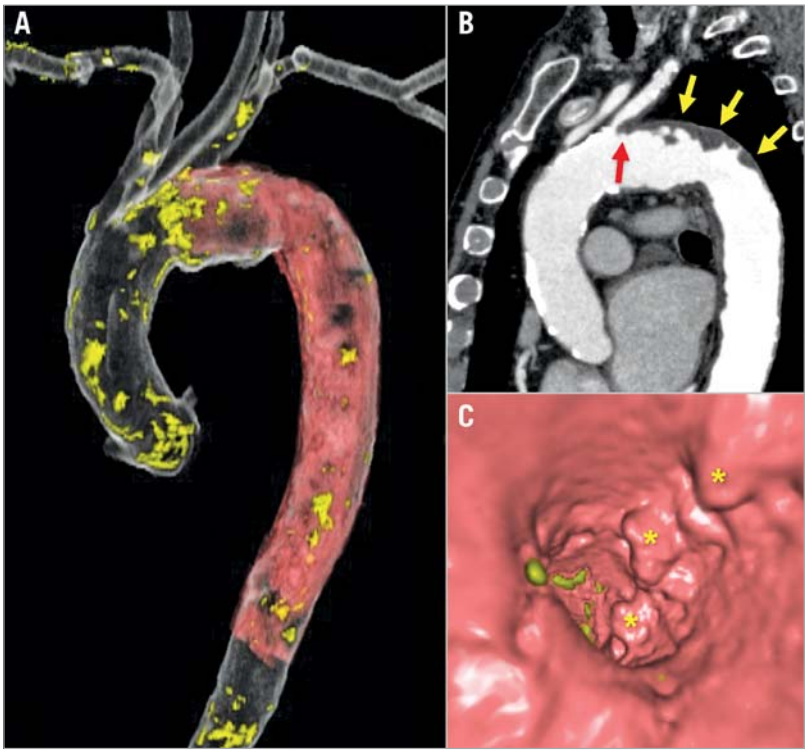

Figure 2. *Computed tomography assessment of shaggy aorta. Distribution of calcification is highlighted in yellow and atherothrombotic material is highlighted in red in a three-dimensional volume-rendered image (A). An irregular-shaped atheroma was diffusely observed in the aortic arch (B, yellow arrows) and the ostium of the left subclavian artery was also involved (B, red arrow). Upstream fly-through view indicated that the atheroma was protruding into the aortic lumen (C, asterisks).*

Toyota et al reported the wire pull-through technique via the femoral artery in a TA-TAVI case with kinked guidewire and unsuccessful passage of a THV system through the aortic valve[8]. Bagur et al reported the "no-touch" technique by placing a stiff wire distally into the right SCA during TA-TAVI[9]. A potential advantage of our wire pull-through technique is that it ensures substantial back-up force of the wire in order to deliver and stabilise the THV system. Furthermore, as the wire is grasped and retrieved, we will never have the problem of losing the wire or penetrating small side branches (i.e., wire perforation). It is quite easy for skilled interventional cardiologists to deliver the wire and diagnostic catheter to the SCA, while preoperative three-dimensional CT will be useful for wiring navigation.

A double lumen sheath offers another vascular access for a pigtail catheter or a guiding catheter when coronary protection or subsequent percutaneous coronary intervention (PCI) is needed. A 4 Fr pigtail catheter is compatible for a 6.5 Fr sheath, and a 6 Fr guiding catheter is compatible for an 8 Fr sheath in the setting of a 0.035-inch wire already inserted in the sheath. Although bilateral brachial/radial access is an alternative option, there are several concerns to be considered: 1) single vascular access rather than double is less likely to be associated with vascular complications, 2) single-side (right-side) approach does not interfere with the operators or anaesthesiologists (e.g., arterial blood pressure monitoring via the left radial artery), and 3) atheroma in the aortic arch sometimes involves the ostium of the left SCA as shown in **Figure 2**. It should also be noted that we were able to downsize the double lumen sheath from 8 Fr to 6.5 Fr during our experience, and a 6.5 Fr sheath could be introduced via the radial artery (Case 3). None of our cases entailed vascular complications, something which may also benefit patients by reducing the risk of nerve injury by brachial access.

Limitations

This technique has some potential limitations. First, the procedures require additional equipment/cost and procedural time compared to conventional TA-TAVI. In our experience, however, the pull-through system could be established within five minutes after introducing a 6 Fr sheath to the LV apex. In addition, our procedure became less invasive owing to the fact that we shifted from surgical cut-down to puncture for introducing the double lumen sheath as it was downsized from 8 Fr to 6.5 Fr. This may contribute to shortening the procedure time. Second, even in cases with THV migration into the ascending aorta, the THV will never be overturned because the wire is grasped outside the sheath. In this scenario, surgical retrieval of the migrated THV might be safer than percutaneous bail-out by implanting a THV in the descending aorta, which may result in catastrophic embolisation to systemic organs.

Conclusions

The wire pull-through technique using a double lumen sheath was safe and feasible in TA-TAVI for AS patients with shaggy aortic arch or penetrating aortic ulceration.

Impact on daily practice

The wire pull-through technique using a double lumen sheath could be an optional strategy during TA-TAVI when the Heart Team has a potential concern about embolic complications due to the presence of significant atherothrombotic mass detected in the aortic arch.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Balloon post-dilation of the mechanically expanded LOTUS transcatheter aortic valve

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KEYWORDS

- aortic stenosis
- balloon valvuloplasty
- miscellaneous
- transcatheter aortic valve replacement (TAVR)

Abstract

Aims: The aim of this study was to describe the technique and assess the feasibility of balloon post-dilation (BPD) within the mechanically expanded LOTUS transcatheter aortic valve.

Methods and results: Consecutive patients with severe aortic stenosis who underwent LOTUS valve implantation at a single centre were prospectively followed with pre-discharge and 30-day echocardiography. BPD was performed in limited cases of significant procedural paravalvular aortic regurgitation (AR) where mitigation by initial device repositioning had been unsuccessful. BPD success was defined as a reduction of paravalvular AR to a severity of mild or less. Safety was determined by 30-day occurrence of major adverse events defined according to VARC-2 criteria. BPD was performed in four patients for significant post-implant paravalvular AR (n=4) and/or prosthesis frame deformation (n=2). BPD was successful in achieving a reduction of procedural paravalvular AR in three out of four patients and in pre-discharge AR in all patients. There were no 30-day deaths, cerebrovascular events or new pacemaker requirement in patients who received BPD.

Conclusions: This is the first study to describe the technique of BPD within the mechanically expanded LOTUS transcatheter aortic valve. An acceptable success rate with no complications was observed with the use of BPD in a small number of LOTUS valve recipients.

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Abbreviations

AR aortic regurgitation
BPD balloon post-dilation
CHB complete heart block
LBBB left bundle branch block
LVOT left ventricular outflow tract
MDCT multidetector computed tomography
STS Society of Thoracic Surgeons
TAVR transcatheter aortic valve replacement
TOE transoesophageal echocardiography

Introduction

Residual significant paravalvular aortic regurgitation (AR) occurs in approximately 5-17% of all transcatheter aortic valve replacement (TAVR) recipients, and has been linked to poorer outcomes[1]. Patients found to have significant periprocedural paravalvular AR following TAVR can undergo balloon post-dilation (BPD) to expand the valve better and improve sealing of the paravalvular space. The potential risks of BPD include damage to the valve prosthesis leaflets, annulus rupture and increased risk of conduction abnormalities or cerebrovascular events.

In recipients of the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences Inc., Irvine, CA, USA) and the self-expanding CoreValve® (Medtronic, Minneapolis, MN, USA), BPD is utilised in approximately one quarter of patients[2-4]. In contrast, BPD has been discouraged in the mechanically expanded LOTUS™ valve system (Boston Scientific, Marlborough, MA, USA) and is generally only recommended to mitigate significant residual transprosthetic gradients due to severe frame distortion. The LOTUS valve's adaptive seal and fully repositionable and retrievable nature generally result in extremely low rates of moderate to severe paravalvular AR[5,6]. While the proportion of LOTUS recipients who develop AR remains small, increasing implantation rates worldwide will result in this complication being encountered more frequently. This is the first case series to describe the technique and preliminary efficacy of BPD following implantation of the LOTUS valve system.

Methods

Consecutive patients with severe AS at high or extreme surgical risk underwent TAVR with the LOTUS valve system at a single centre from April 2012 to October 2015. All patients underwent standard preprocedural TAVR work-up including transthoracic echocardiography, multidetector computed tomography (MDCT) and coronary angiography, as previously described[7]. Baseline, procedural, in-hospital and 30-day follow-up was prospectively collected for all patients and entered into a dedicated TAVR database. This was pre-approved by the institutional human research ethics committee and complies with the Declaration of Helsinki. Balloon predilation was routinely performed before valve implantation. After valve deployment, the presence, location and severity of AR were carefully assessed using aortography and/or transoesophageal echocardiography (TOE). Residual AR was defined as non-significant (none, trivial or mild) or significant (mild-to-moderate, moderate, moderate-to-severe, or severe).

BPD was performed in cases of significant paravalvular AR (defined as a severity of mild-to-moderate or higher) despite, where appropriate, an initial attempt to mitigate this by device repositioning being unsuccessful. Sizing of the post-dilatation balloon was at the operator's discretion; however, in keeping with the manufacturer's recommendation, the balloon did not exceed 3 mm less than the prosthesis diameter in order to avoid damaging the locking mechanisms. In addition, the left ventricular outflow tract (LVOT) dimensions and degree of calcification were considered in order to minimise the risk of annular injury. After BPD, the presence and severity of periprocedural AR was again carefully assessed using aortography or TOE. The BPD was considered successful if the degree of residual paravalvular AR was reduced to a severity of mild or less. Safety was determined by occurrence of procedural, in-hospital or 30-day major adverse events defined according to the Valve Academic Research Consortium-2 criteria[8]. Thirty-day echocardiography was also used to assess prosthesis valve leaflet deterioration or the haemodynamic impact of BPD.

Results

BPD was performed in a total of four (out of 104) patients during the time period stated above. The four patients who received BPD all received a 25 mm LOTUS valve via the transfemoral approach. The baseline and procedural characteristics for these four patients are shown in **Table 1** and **Table 2**, respectively. Cases 1, 3 and 4 underwent TAVR under conscious sedation and in case 2 general anaesthesia (GA) with TOE was utilised. Post-dilation was

Table 1. Baseline characteristics.

Variable	Case 1	Case 2	Case 3	Case 4
Age	87	80	89	98
Baseline creatinine (µmol/L)	73	421	136	115
STS Plus score	2.1	7.8	5.1	7.6
STS morbidity score	14.7	35.9	22.4	28.9
Echocardiographic			Bicuspid*	
Valve area (cm^2)	0.6	0.7	0.7	0.8
Peak/mean gradient (mmHg)	160/98	61/35	87/48	107/63
LVEF (%)	65	59	15	55
Baseline AR	mild	trivial	trivial-mild	mild
Annulus				
Min/max diameter (mm)	22/30	22/27	24/35	23/26
Perimeter (mm)/area (mm^2)	81/489	77/456	93/648	77/472
Left ventricular outflow tract				
Perimeter (mm)/area (mm^2)	82/481	79/479	103/813	74/426
Sinus of Valsalva				
Perimeter (mm)/area (mm^2)	99/769	100/747	129/1,244	102/775
Valve calcification	severe	mild	severe	severe

*Case 3 had a bicuspid native aortic valve. AR: aortic regurgitation; LVEF: left ventricular ejection fraction; STS: Society of Thoracic Surgeons

Table 2. Procedural characteristics.

Variable		Case 1	Case 2	Case 3	Case 4
Device size (mm)		25	25	25	25
Device/annulus perimeter ratio		0.97	1.02	0.84	1.02
Predilation balloon (mm)		18	18	22	18
Number of re-sheathings and repositioning		1	2	2	0
Pre balloon post-dilation	Severity of AR	Moderate	Moderate	Mild-mod	Moderate
	AR index	0.35	0.17	0.22	0.11
Size of post-dilation balloon		20	18	22	20
Post balloon post-dilation	Severity of AR	Mild	Mild	Mild-mod	Mild
	AR index	0.38	0.18	0.24	0.19
Periprocedural CHB		No	N/A*	Yes	Yes
New or worsened LBBB		Yes	Yes	Yes	No

*Case 2 had a pre-existing permanent pacemaker. AR: aortic regurgitation; CHB: complete heart block; LBBB: left bundle branch block

performed in each patient after the deployed prosthetic valve was crossed with a pigtail catheter and a super stiff wire positioned in the left ventricle (Amplatz Super Stiff™ 0.035 wire; Boston Scientific). In accordance with the manufacturer's recommendation, the BPD balloon was undersized by at least 3 mm to avoid damage to the prosthesis locking mechanism. The post-dilation balloon was filled with dilute contrast and expanded within the prosthetic valve under rapid ventricular pacing. Each case procedure is illustrated in **Figure 1**-**Figure 4**.

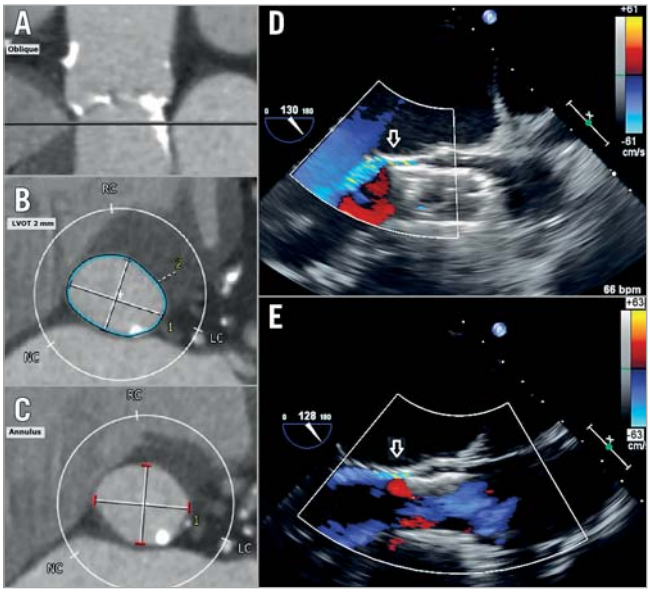

Figure 2. *Case 2. Transoesophageal imaging pre and post balloon post-dilation of the LOTUS valve. MDCT imaging demonstrates calcification of the native aortic valve, particularly at the site of the left coronary cusp (A-C). Transoesophageal echocardiogram shows moderate paravalvular AR immediately after LOTUS valve implantation, along the area of calcification, seen on long-axis view (D). The LOTUS valve was post-dilated with an 18×40 mm NuCLEUS-X™ balloon (B. Braun Interventional Systems, Bethlehem, PA, USA) with improvement in paravalvular AR to mild (E). Arrows indicate the paravalvular leak.*

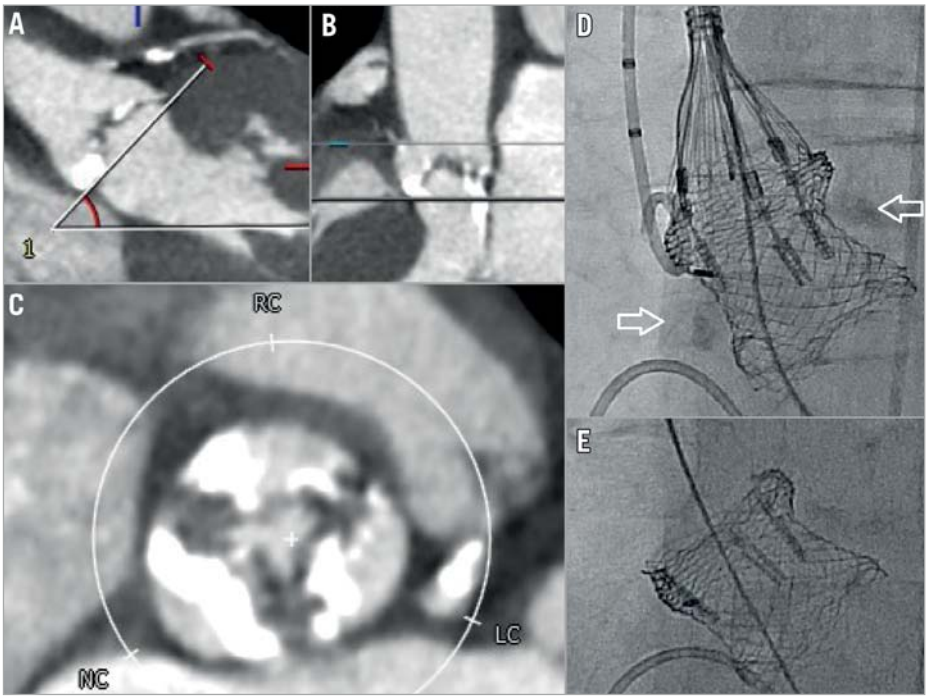

Figure 1. *Case 1. Severe native valve calcification with resultant device frame deformation and underexpansion. Severe native valve calcification is seen on MDCT and fluoroscopy (A-D). Following deployment of a 25 mm LOTUS valve system, deformation of the frame at the site of heavy calcification is seen (D, arrows). This patient underwent post-dilation with a 20×45 mm Cristal balloon (Balt Extrusion, Montmorency, France) with mildly improved frame expansion (E).*

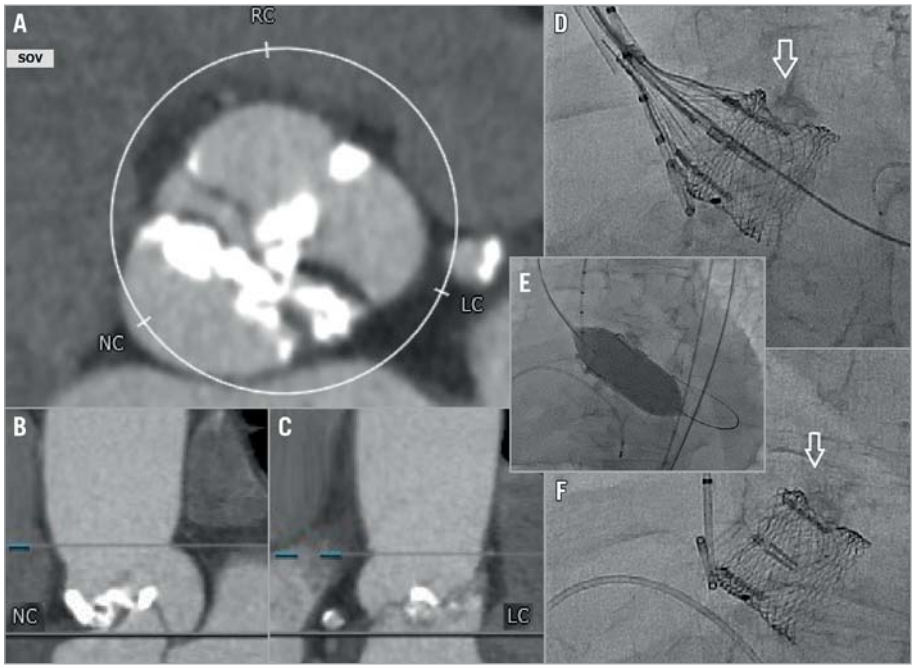

Figure 3. *Case 3. Severe native bicuspid valve calcification with resultant device frame deformation responding to BPD. Severe native valve calcification is seen on MDCT in a functionally bicuspid aortic valve (A-C). Following deployment of a 25 mm LOTUS valve system, deformation of the frame at the site of heavy calcification is seen (D, arrow) with mild-moderate paravalvular AR. This patient underwent post-dilation with a 23×40 mm Z-MED II-X™ balloon (B. Braun Interventional Systems) with improved frame expansion (E & F) but no reduction in severity of AR.*

There were no major procedural or in-hospital complications, including no annular rupture, strokes, myocardial infarction, major vascular or major bleeding events in the four patients who underwent BPD. No patients required new pacemaker implantation within 30 days. All four patients were alive at 30-day follow-up without any major cerebrovascular events. The echocardiographic outcomes are shown in **Table 3**.

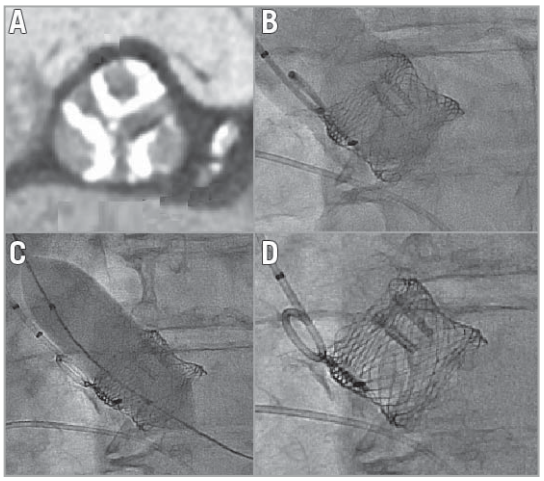

Figure 4. *Case 4. Severe native valvular calcification with deployment of a 25 mm LOTUS valve system (A & B). Following valve deployment, moderate paravalvular AR was seen on the aortogram. This patient underwent post-dilation with a 20×40 mm Z-MED II-X balloon under rapid ventricular pacing (C). Aortogram demonstrated AR improvement to mild with improvement in the AR index (D).*

Discussion

In the mechanically expanded LOTUS valve, use of BPD has typically been discouraged. This is due to the LOTUS valve's adaptive seal and fully repositionable nature, designed to minimise significant paravalvular AR[5]. As such, BPD has generally been reserved for cases of severe frame distortion with a high residual transprosthetic gradient.

Table 3. Echocardiographic results.

Echocardiogram	Case 1	Case 2	Case 3	Case 4
Pre-discharge				
Mean gradient (mmHg)	16	7	9	7
Aortic regurgitation	Trivial	Mild	Mild	Trivial-mild
Dimensionless index	0.40	0.59	0.36	0.55
LVEF	70	60	15	50
30-day				
Mean gradient (mmHg)	21	6	Not performed*	10
Aortic regurgitation	Trivial	Mild		Trivial-mild
Dimensionless index	0.48	0.55		0.49
LVEF	70	60		50

*Patient was re-admitted to another facility for an unrelated small bowel obstruction treated surgically with resultant missed 30-day echocardiographic follow-up. LVEF: left ventricular ejection fraction

This first case series describes BPD in four patients with mild-to-moderate or greater severity paravalvular AR immediately following LOTUS valve implantation. A reduction of paravalvular AR to mild or lesser severity was seen in three out of four patients. This success rate is similar to that seen following BPD within the Edwards SAPIEN or CoreValve, both prostheses that commonly require BPD to treat periprocedural AR[2,4]. Therefore, while BPD is rarely required following LOTUS valve implantation, it appears to be reasonably successful in the treatment of paravalvular AR.

In the current case series, two out of four patients undergoing BPD for significant AR had associated prosthesis frame underexpansion or deformation. This was related to the presence of significant native valve calcification. The successful use of BPD in this clinical scenario has been described in a single case study where underexpansion of the LOTUS valve was associated with a significant residual transaortic gradient[9]. In the current case series, BPD was utilised to treat frame deformation in two patients. This resulted in marked improvement of valve frame underexpansion in one patient and a mild improvement in the second patient **(Figure 1, Figure 3)**.

The presence of a heavily calcified aortic valve probably prevents complete sealing of the paravalvular space, and has been seen to predict paravalvular AR and the need for BPD[3,5,10]. The degree of valve calcification has also been seen to be the only independent predictor of BPD success[2]. In the current study, all patients requiring BPD had calcification of the native aortic valve. In addition, in the patient where BPD did not result in a reduction of periprocedural AR, severe valvular calcification was present.

Prosthesis-to-annulus undersizing is another factor associated with paravalvular leak and hence the need for BPD[4,11]. The LOTUS valve is sized according to the MDCT-derived annulus measurements, as well as consideration of the entire aortoventricular interface anatomy, degree of calcification and valve morphology. In cases 1, 2 and 4, the device to annulus ratio was 1:1 and the presence of severe prosthesis deformation and/or adequate waisting of the device supported adequate sizing. In these cases, upsizing the device was felt unlikely to result in improvement in AR while increasing the risk of annular injury; hence BPD was performed instead. In case 3 the presence of a bicuspid aortic valve resulted in the appearance of apparent device undersizing when basal plane dimensions were considered in isolation. However, as this was a bicuspid valve, further factors including the specific bicuspid morphology, intercommissural dimension and potential for supra-annular sealing were considered. While there are no specific sizing algorithms universally available for bicuspid valves, utilisation of a combination of these factors is widely accepted; however, it does result in apparent undersizing of the chosen prosthesis.

No studies have yet evaluated the safety of BPD following TAVR with the LOTUS valve. A safety concern with performing BPD is that further manipulation or expansion of the prosthesis in the annulus may be associated with higher rates of cerebral embolisation and new conduction abnormalities[2]. In our small case series, no cerebrovascular events or conduction abnormalities were observed following BPD. Another safety concern with BPD includes potential damage to the annulus or prosthesis leaflets, resulting in escalated deterioration of prosthetic valve function. In this small case series, we demonstrated no adverse impact of BPD on the prosthesis leaflets, with no deterioration of valve haemodynamics or occurrence of central AR at 30-day echocardiography. Due to the known increased mortality associated with residual AR[1], BPD could be considered in LOTUS valve recipients with significant residual AR.

Limitations

The main limitation of this study is the small patient number. Whilst patients were recruited from a high-volume TAVR centre, due to very low rates of paravalvular AR following LOTUS valve implantation, BPD was considered after valve repositioning in only a minority of patients. Further studies are required to evaluate the long-term efficacy and safety of BPD within the LOTUS valve. A further limitation is the use of aortography instead of TOE to assess periprocedural AR. However, routine use of conscious sedation for TAVR procedures with a resultant decline in TOE-guided TAVR probably reflects real-world practice.

Conclusions

This case series of four patients is the first to describe the technical feasibility of BPD for treatment of paravalvular AR and/or prosthesis frame underexpansion following implantation with the LOTUS valve system.

Impact on daily practice

Whilst BPD is rarely needed for the mechanically expanded LOTUS valve, this study demonstrates that it can be safely performed with acceptable success rates. In cases where repositioning or retrieval are not viable options, BPD allows an alternative management step to correct paravalvular AR or prosthesis frame deformation within the LOTUS valve.

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Conflict of interest statement

I. Meredith has received consultant fees and honoraria from Boston Scientific and Medtronic and proctor fees from Boston Scientific. R. Gooley has received proctor fees from Boston Scientific. The other authors have no conflicts of interest to declare.

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First-in-man study of transcatheter aortic valve implantations in aortic stenosis using the Hydra self-expanding bioprosthesis

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KEYWORDS

- aortic regurgitation
- femoral
- transcatheter aortic valve implantation (TAVI)

Abstract

Aims: The aim of this study was to document the initial experience with transcatheter aortic valve implantations with the Hydra self-expanding aortic bioprosthetic valve.

Methods and results: Implantation of the Hydra aortic valve was performed in patients with symptomatic, severe aortic stenosis at the King Chulalongkorn Memorial Hospital, Thailand. Surgical treatment was deferred based on Heart Team assessment of an estimated high surgical risk. The Hydra valve was implanted in 15 patients with mean STS score 6.2%, mean age 82 years, mean aortic valve area 0.68 cm^2, mean aortic pressure gradient 49 mmHg. All procedures were performed under general anaesthesia. Percutaneous transfemoral access was used in 13 patients, whereas the remainder had a transaxillary approach. There was one procedural death due to a major vascular complication. At 30-day follow-up, the median aortic valve area and pressure gradient were 1.53 cm^2 and 9 mmHg, respectively. The prevalence of more than mild paravalvular leakage and new permanent pacemaker implantation was 7.7% and 14.3%, respectively. No patient suffered from stroke or TIA.

Conclusions: The Hydra aortic bioprosthetic valve is useful for transcatheter treatment of severe aortic stenosis. Initial results indicate a high haemodynamic performance and complication rates similar to those reported for second-generation transcatheter aortic bioprostheses.

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Abbreviations

AR	aortic regurgitation
AVA	aortic valve area
CABG	coronary artery bypass grafting
COPD	chronic obstructive pulmonary disease
GFR	glomerular filtration rate
LVEDD	left ventricular end-diastolic dimension
LVEF	left ventricular ejection fraction
MR	mitral regurgitation
PCI	percutaneous coronary intervention
PVL	paravalvular leakage
SD	standard deviation
TAVI	transcatheter aortic valve implantation
TEE	transoesophageal echocardiography

Introduction

Transcatheter aortic valve implantation (TAVI) has become a part of the standard therapy for severe aortic stenosis in patients considered at high or prohibitive surgical risk[1-5]. A number of different transcatheter aortic valves are commercially available[6]. Recently, the Hydra Aortic bioprosthesis (Vascular Innovations Co., Ltd., Nonthaburi, Thailand) was developed as a self-expanding system with a mechanism for recapturing the prosthesis during deployment.

The preclinical study on the Hydra Aortic bioprosthesis was conducted in Rigshospitalet, Copenhagen, Denmark. The prostheses were implanted in sheep aortic valves and were explanted after three months. The procedure of implanting the valve is similar to that of TAVI in humans – using percutaneous access from the femoral artery, deployment of the valve at the aortic valve level under fluoroscopy guidance, and assessing the valve function using intracardiac echocardiography, angiography and haemodynamic measurements. The deployment of the valve was possible without any difficulties.

The histology of the eight explanted valves was performed at an independent lab - Innoheart Pvt Ltd, Singapore. The prosthesis showed an intact smooth and undulating morphology and good encapsulation after deployment in the sheep aorta. The materials remained closely integrated with the stent wire. There was a large surface area of the cusps with a smooth appearing surface that signifies good endothelialisation and good interaction of the materials with the circulatory elements. Fibrous and elastic filamentous materials were observed on the surfaces of the cusps and on the underlying surface denuded of endothelial layer, though no excessive fibrin network or thrombi were observed. The valve showed an overall good biocompatibility with the circulation system with limited cusps remaining uncovered by the endothelialisation process.

We report here the initial experience with implantations of the Hydra Aortic bioprosthesis in humans.

Methods

PATIENTS

Implantation of the Hydra Aortic valve was performed in 15 patients with symptomatic, severe aortic stenosis in the period from May 2014 to June 2015 at King Chulalongkorn Memorial Hospital, Thailand. In all cases, surgical treatment was deferred based on Heart Team assessment of an estimated high surgical risk. Patients were thoroughly informed and all gave written consent to the treatment. The study was approved by the ethics committee of King Chulalongkorn Memorial Hospital. The primary endpoint of the study was all-cause mortality at 30 days; secondary endpoints were myocardial infarction (MI), all stroke, bleeding, vascular access complications, and all TIA rates at 30 days.

Preprocedural examinations included transthoracic echocardiography, coronary angiography, and multislice ECG-gated computed tomography (CT) to measure the aortic annulus, aorta, and access vessels. For follow-up, patients had transthoracic echocardiography performed before discharge and at one month after the procedure. Any complications were documented at these time points.

HYDRA AORTIC BIOPROSTHETIC VALVE

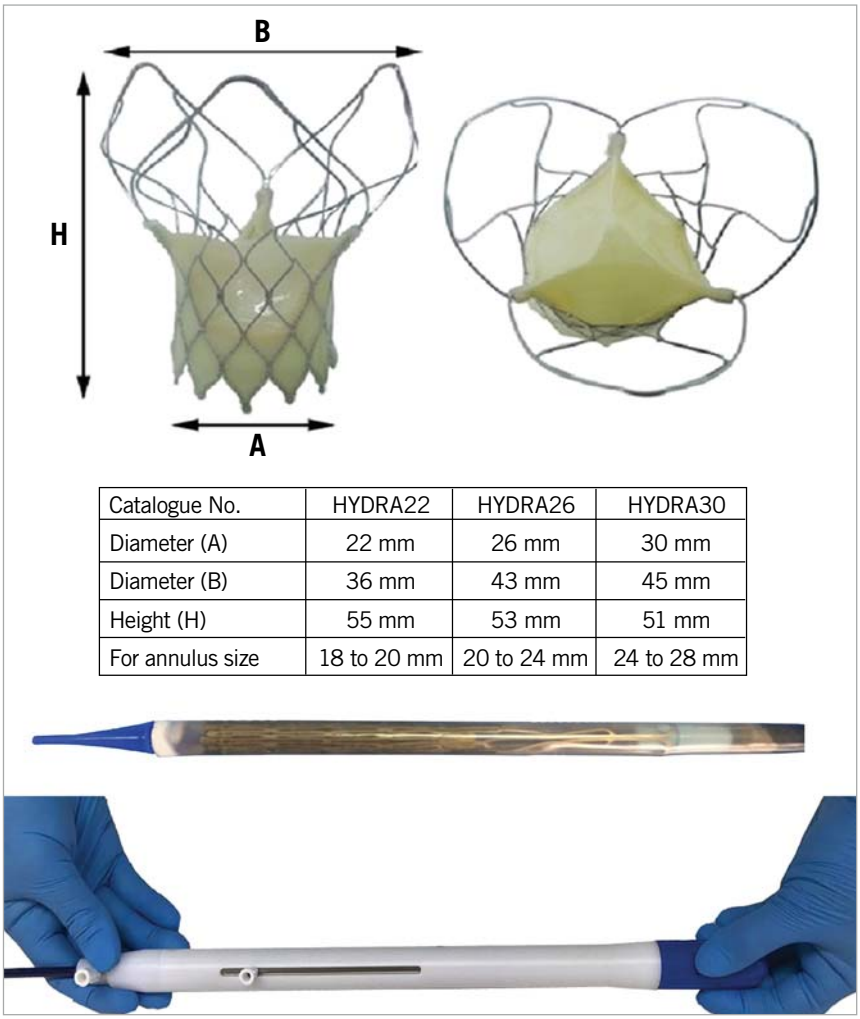
The Hydra Aortic valve consists of a self-expanding stent frame made of nitinol with three leaflets and a sealing cuff made of bovine pericardium **(Figure 1)**. The three tentacles (antennae) on the outflow part of the stent frame are used for fixation to the delivery system and, after deployment, provide flexible anchors at the outflow, which conforms to the shape of the aorta. The inflow section of the frame is non-flared, and exerts a higher radial force than the outflow portion to ensure attachment to the aortic annulus. The valve leaflets are positioned supra-annular of the native aortic valve, and the sealing cuff covers the proximal 12 mm of the inflow portion of the frame. The valve is produced in three sizes, 22, 26, and 30 mm, covering an annulus range of 18 to 28 mm **(Figure 1)**. The bioprosthesis can be fully recaptured, retrieved and repositioned until 80 to 90% of deployment.

DELIVERY SYSTEM

The Hydra valve is implanted using the Hydra Aortic valve delivery system **(Figure 1)**, which has a distal 18 Fr capsule for the Hydra valve and a 12 Fr shaft. The delivery system is introduced into an 18 Fr sheath along a 0.035” stiff wire. The prosthesis is crimped into the distal protective capsule using the single-operator Hydra Aortic valve loading system. The handle at the proximal end of the delivery catheter includes a turning knob for loading/re-sheathing and deploying the valve. Both the delivery system and the loading system are the same for all three valve sizes. The delivery system is suitable only for retrograde implantation.

IMPLANTATION TECHNIQUE

All procedures were performed under general anaesthesia using transoesophageal echocardiography (TEE) and fluoroscopy guidance. The transfemoral route was used in all but two cases, where the transaxillary access was chosen. An 18 Fr sheath was introduced into the access artery, and a pigtail catheter from the contralateral femoral artery was placed in the bottom of the non-coronary cusp for repeated aortic root angiograms during deployment. After



Catalogue No.	HYDRA22	HYDRA26	HYDRA30
Diameter (A)	22 mm	26 mm	30 mm
Diameter (B)	36 mm	43 mm	45 mm
Height (H)	55 mm	53 mm	51 mm
For annulus size	18 to 20 mm	20 to 24 mm	24 to 28 mm

Figure 1. *The Hydra Aortic valve and delivery system. The Hydra Aortic valve consists of a self-expanding stent frame made of nitinol with three leaflets and a sealing cuff made of bovine pericardium. The valve is produced in three sizes, 22, 26, and 30 mm, covering an annulus range of 18 to 28 mm.*

crossing the aortic valve and placement of a 260 cm long Amplatz Super Stiff™ 0.035" wire (Boston Scientific, Marlborough, MA, USA) with a J-tip manually shaped to acquire a pigtail configuration in the left ventricle, predilatation was performed under rapid pacing (160 bpm). The delivery system was then advanced over the stiff wire until the distal part of the valve frame had crossed the aortic valve. Deployment was then begun by rotating the knob clockwise aiming at an implantation depth of ideally 3-5 mm (sealing range 1-10 mm) below the native annulus. In case of a suboptimal position after opening the fully functional inflow portion of the valve, partial or complete re-sheathing and repositioning could be performed. Before final release, tension was released from the delivery system and the guidewire. Valve position, coronary patency, and paravalvular leakage (PVL) were examined with angiography. Deployment was then completed and the detachment of all three tentacles from the delivery system was checked fluoroscopically before withdrawing the delivery system. The function of the implanted valve was assessed with TEE and, in case of more than mild paravalvular leakage, post-dilatation was considered. If suboptimal high or low positioning of the fully deployed valve prosthesis was associated with more than mild paravalvular leakage, a second Hydra valve could be implanted within the first prosthesis. **Figure 2** provides fluoroscopic and angiographic images of the implantation procedure.

STATISTICAL ANALYSIS

Discrete variables are reported as proportions. Continuous variables are reported as mean (standard deviation).

Results

POPULATION

Fifteen patients with severe aortic stenosis were enrolled from May 2014 to June 2015 at King Chulalongkorn Memorial Hospital, Thailand. The clinical characteristics and imaging findings of patients are listed in **Table 1**. All patients were symptomatic; two patients (13.3%) had severe symptoms (NYHA Class III).

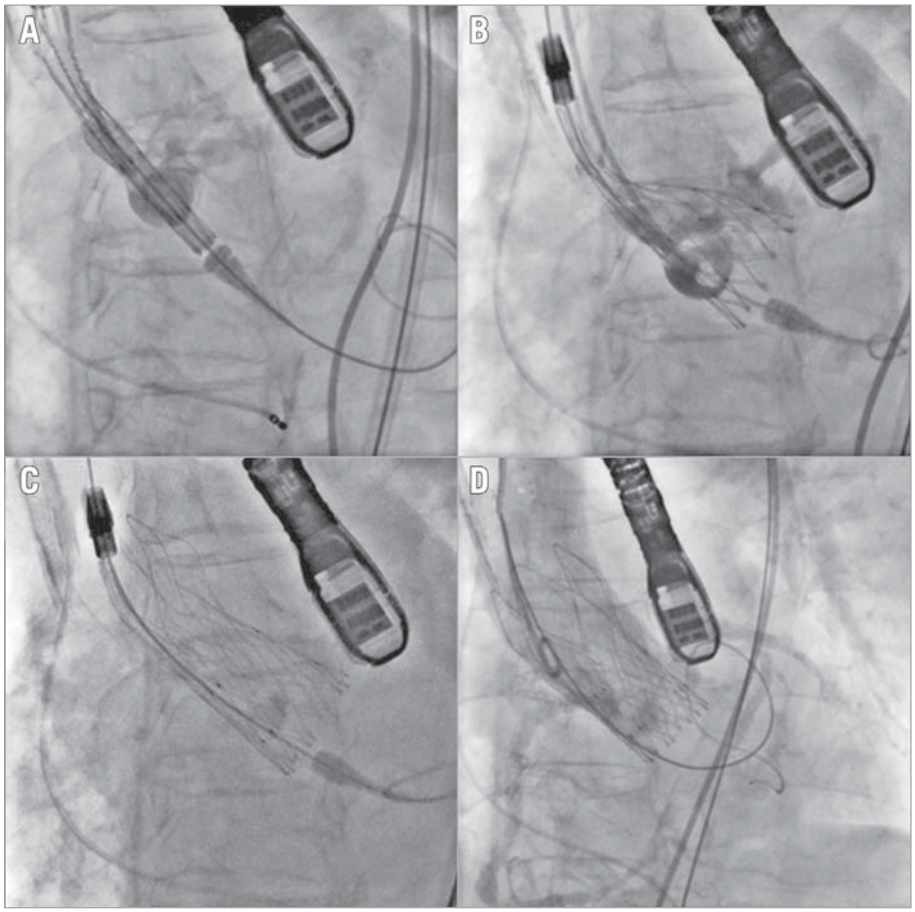


Figure 2. *Implantation of the Hydra Aortic valve. Fluoroscopic and angiographic images of the implantation procedure. A) Angiography in the LAO projection checking depth before deployment of the valve. B) Angiography during deployment. C) Fluoroscopic image at the time of tentacle release. D) Angiography after final release.*

OUTCOMES

Implantation of the Hydra valve was accomplished in all cases (**Table 2** for procedural details). There were no instances of delivery system failure. In five patients valve position was suboptimal after final release and a second Hydra valve was successfully implanted in a correct position. The presence of more than mild paravalvular leakage necessitated post-dilatation in seven cases. Two patients had major vascular complications related to the procedure according to VARC-2 definition. One patient was haemodynamically difficult to control during anaesthesia and systolic blood pressure was temporarily more than 350 mmHg, causing a dissection from the ascending to the descending aorta. This dissection was treated conservatively and the patient had an uneventful recovery. Another patient, treated by the transaxillary approach, required a valve retrieval in the subclavian artery, causing a fatal dissection and rupture of the aortic arch.

Thus, 14 patients survived the post-procedural period. Thirteen patients completed full echocardiographic assessment at 30 days **(Table 3)**. Prosthetic valve haemodynamics are listed in **Table 4**. The mean aortic gradient dropped from 49 mmHg pre-procedure to 9 mmHg. Paravalvular leakage graded more than mild was seen in only one patient and a permanent pacemaker implanted in two patients. Stroke or TIA did not occur in any patient.

Discussion

In this report, we describe the first experiences with the new self-expanding transcatheter Hydra Aortic valve for aortic stenosis in humans deemed ineligible for surgical aortic valve replacement.

SAFETY AND EFFICACY

The one mortality within the first 30 days was not related to the bioprosthetic valve but to the 18 Fr introducer sheath and the post-implantation evaluation of the access function. This complication underlines the need for careful preprocedural evaluation of the access vessels, and for gentle manipulation of sheaths and catheters in elderly and frail patients. Particularly in an Asian population, the vessel size is often smaller than in most reported TAVI studies. Other access-site complications encountered were comparable in frequency to those generally reported[6,7].

Post-procedural valve gradients demonstrated no significant obstruction to flow, and the values are in line with results from

Table 1. Preprocedural clinical characteristics and cardiac imaging findings (n=15).

Characteristic	All patients (n=15)
Sex, male, n (%)	8 (53.3)
Age, years (SD)	82 (4.5)
Body mass index, kg/m^2 (SD)	23.2 (4.4)
Hypertension, n (%)	10 (66.7)
Diabetes, n (%)	2 (13.3)
Previous myocardial infarction, n (%)	1 (6.7)
Previous PCI, n (%)	6 (40.0)
Previous CABG, n (%)	2 (13.3)
Peripheral vascular disease, n (%)	2 (13.3)
Atrial fibrillation, n (%)	2 (13.3)
Previous permanent pacemaker, n (%)	0 (0)
Stroke, n (%)	3 (20.0)
Chronic kidney disease, n (%)	6 (40.0)
e-GFR, mL/min (SD)	51.8 (20.8)
COPD, n (%)	1 (6.7)
STS score (SD)	6.2 (1.4)
EuroSCORE II (SD)	4.3 (1.9)
Echocardiography	
LVEF, % (SD)	60.0 (18.3)
LVEDD, mm (SD)	43.9 (9.2)
Peak aortic gradient, mmHg (SD)	71.8 (21.6)
Mean aortic gradient, mmHg (SD)	49.0 (16.3)
AVA, cm^2 (SD)	0.68 (0.19)
AR grade ≥moderate, n (%)	5 (33.3)
MR grade ≥moderate, n (%)	2 (13.3)
Multislice computed tomography	
Annulus mean diameter, mm (SD)	23.5 (3.4)

AR: aortic regurgitation; AVA; aortic valve area; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; e-GFR: estimated glomerular filtration rate; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; PCI; percutaneous coronary intervention; SD: standard deviation

Table 2. Implantation characteristics.

Implantation characteristic	
Transfemoral access, n (%)	13 (86.7)
Subclavian access, n (%)	2 (13.3)
Mean annulus diameter, mm (SD)	23.1 (3.3)
Mean annulus area, cm^2 (SD)	3.7 (0.9)
Mean annulus planimetry, mm (SD)	69.1 (8.1)
Coronary height – LCA, mm (SD)	11.9 (2.0)
Coronary height – RCA, mm (SD)	12.0 (1.6)
Hydra 26, n (%)	9 (60.0)
Hydra 30, n (%)	6 (40.0)
Predilatation, n (%)	15 (100)
Post-dilatation, n (%)	7 (46.7)
Need for 2nd valve, n (%)	5 (33.3)

Table 3. Clinical outcomes at 30 days post procedure (n=15).

Outcomes at 30 days		
Myocardial infarction, n (%)		0 (0)
Stroke, n (%)		0 (0)
Death, n (%)		1 (6.7)
Bleeding complication, n (%)	Minor	3 (20.0)
	Major or life-threatening	1 (6.7)
Vascular complication, n (%)	Minor	4 (26.7)
	Major	2 (13.3)
New permanent pacemaker, n (%)		2 (14.3)

other transcatheter aortic bioprosthetic valves[6]. In the present study, only one patient (7.7%) had more than mild paravalvular leak at 30-day follow-up. A second valve was needed in five cases; however, this may be due to our learning experience for this new valve technology.

The deployment technique for the Hydra valve is different from the CoreValve® (Medtronic, Dublin, Ireland). The CoreValve has a tendency to move downwards at the time of final release but the Hydra valve seems to be stable at the deployed position. The initial position of the Hydra valve may be a bit lower than that of the CoreValve, which helps to avoid valve pop-up into the aorta. The expanding force of the Hydra is slightly lower compared to the CoreValve. This may be a benefit in terms of less injury to the conduction system; however, in some cases this may require post-deployment balloon inflation to expand the valve, especially if the annulus is calcific.

Atrioventricular block requiring new pacemaker implantation was seen in two patients out of 14 (14.3%), which is in the same range as that reported for second-generation transcatheter aortic bioprosthetic valves. This is a reassuring result as a relatively high rate of pacemaker implantation has been a persistent feature of the most commonly used self-expanding aortic valves[8]. If confirmed in larger populations, this feature could potentially be attributed to the lack of flaring of the inflow end of the prosthesis.

Table 4. Valve performance at 30 days post procedure (n=13, one patient lost to echocardiography follow-up).

Follow-up echocardiography at 30 days		
LVEF, (SD)		69.3 (12.8)
Peak aortic gradient, mmHg (SD)		18.9 (8.7)
Mean aortic gradient, mmHg (SD)		9.4 (4.8)
AVA, cm^2 (SD)		1.53 (0.45)
AR grade, n (%)	None or trace	4 (30.7)
	Mild	8 (61.5)
	Moderate	1 (7.7)
	Severe	0

AR: aortic regurgitation; AVA: aortic valve area; LVEF: left ventricular ejection fraction; SD: standard deviation

Limitations

This is the first implantation of Hydra Aortic bioprosthetic valves in humans. The delivery system cannot retrieve the valve once it is completely deployed, which is not much different from the first generation of the CoreValve delivery system. The delivery system is under development to enable a perfect deployment.

Conclusions

The Hydra Aortic bioprosthetic valve is useful for transcatheter treatment of severe aortic stenosis. Initial results indicate that the haemodynamic performance of the implanted bioprosthesis is satisfactory, and complication rates are similar to those seen with other techniques. Further evaluation in a larger population is needed in order to assess the safety and efficacy of the Hydra Aortic valve more completely and to compare its performance to other treatment options.

Impact on daily practice

TAVI is now an acceptable treatment for symptomatic aortic stenosis patients who have an intermediate to high surgical risk. The Hydra self-expanding bioprosthetic valve may be an alternative device for this procedure.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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