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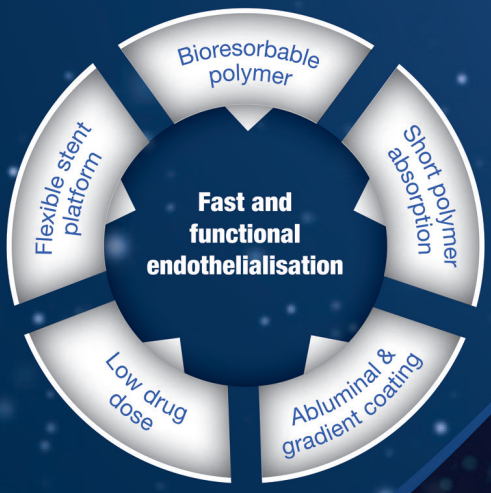

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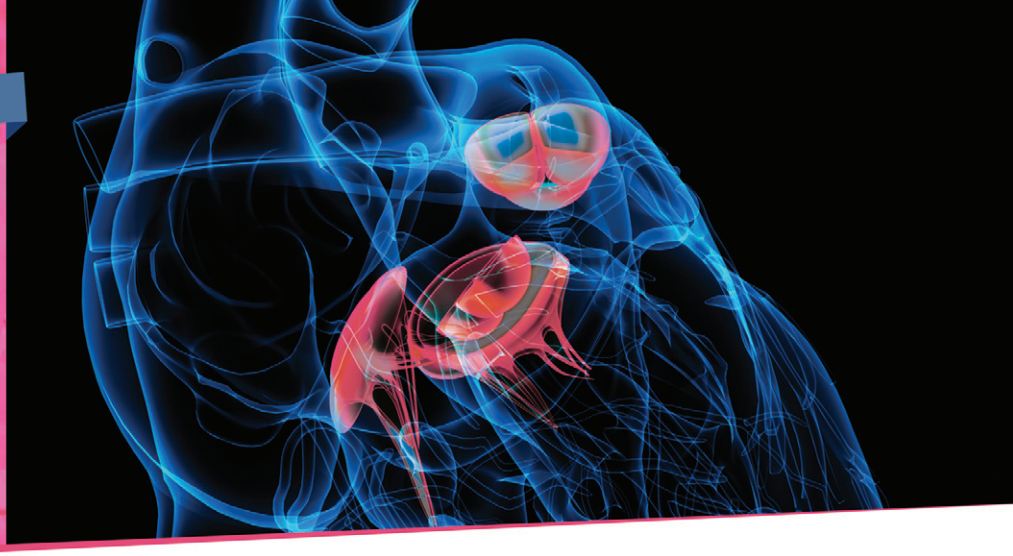

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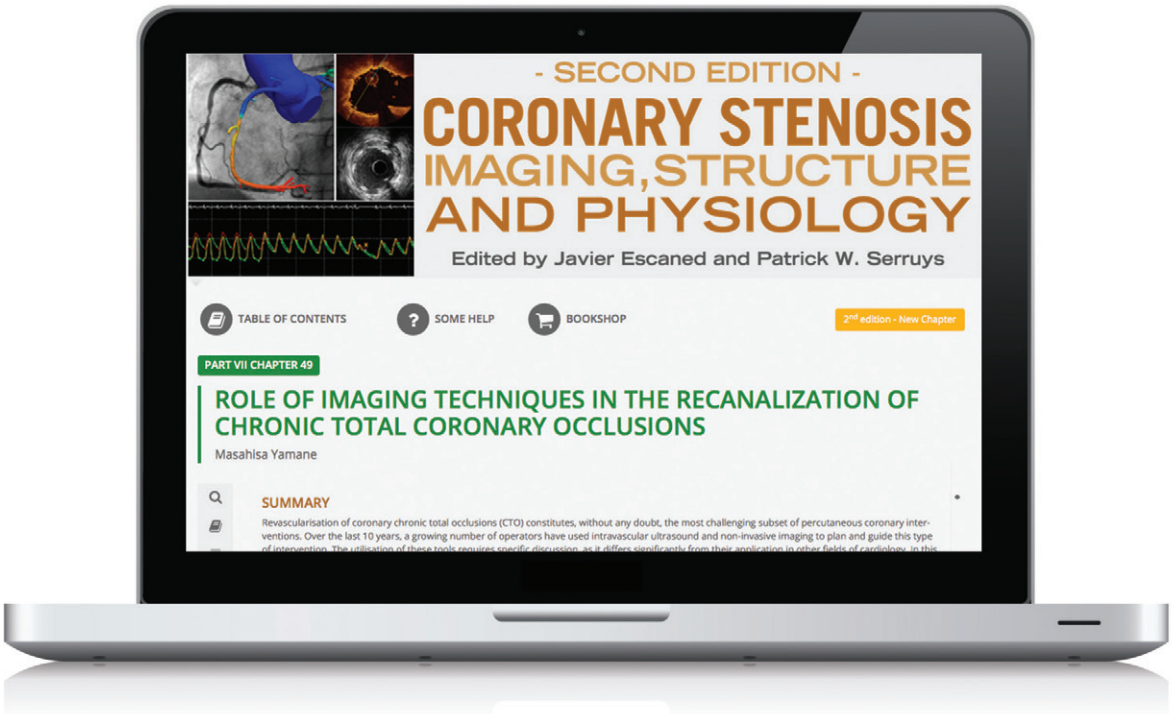

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PCR Innovation in education at work

AsiaIntervention 2016;2:7-9

Evolution and current status of interventional cardiology in India

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AsiaIntervention, a journal for our region, is a newcomer attempting to find a space in this wide area of readership, with so many established journals already being available. One of our objectives as editors is to make the readership aware of the developments which have occurred during the last four decades in countries of this region, which is the home for more than two thirds of mankind. Keeping this goal in mind, I thought of appraising our valued readers regarding the interventional cardiology scene in India.

Interventional cardiology, which is a subspeciality dealing with catheter-based treatment of structural heart disease, was conceptualised by Charles Dotter in 1964 and kick-started by Andreas Gruentzig more than a decade later. Soon after the pioneering work of Charles Dotter in peripheral artery dilatation, in 1966 Rashkind and Miller described a non-surgical procedure to create an atrial septal defect, using a balloon catheter in patients with transposition of the great vessels.

Non-surgical interventions have been progressively dominating the scene in the management of obstructive coronary artery disease, management of cardiac arrhythmias, and congenital heart disease, and are also encroaching on the field of valvular heart disease. Technological advances, innovative techniques, unique imaging techniques and increased operator experience have gone a long way to make these non-surgical procedures widely acceptable with high success and low complication rates. Percutaneous interventions have thus grown by leaps and bounds all over the world, India being no exception.

Era of interventional cardiology in India

As a stepping stone for the creation of an interventional cardiology programme, a cardiac catheterisation laboratory is a prerequisite. In 1962, Dr Sujoy B. Roy from the All India Institute of Medical Sciences, New Delhi, and Dr V. Lingam from the Christian Medical College, Vellore, started the first organised cardiac catheterisation programme in India. Selective coronary angiography was initiated in India in the late seventies. The coronary angioplasty programme in the country started in April 1985 with Dr B. Soma Raju from Hyderabad taking the lead.

Following this, several centres started performing coronary balloon angioplasty. In 1985, the National PTCA Registry of India was created by the author and his colleagues in order to document the number and type of procedures, operators and centres performing percutaneous coronary interventions (PCI). Publication of these data began in 1992. In that year, 3,398 PCI were performed in India by a total of 84 cardiologists in 103 centres. In 1993, the National

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PTCA Registry of India issued its first set of guidelines for performing percutaneous transluminal coronary angioplasty. The number of PCI procedures went on increasing steadily and at the last count had reached around 250,000, showing substantial growth.

Salient points of the PCI programme in India

1. More than 250,000 PCI are performed per year in nearly 600 centres.
2. More than half of the centres do not have on-site surgical capability.
3. Women constitute 25-30% of the total procedures performed.
4. 10% of the PCI are performed in patients younger than 40 years.
5. 20% of PCIs are primary PCI for STEMI.
6. PCI is performed in a single artery in about 60% of cases.
7. Radial route is used in about 50% of cases.
8. Reuse of material for procedures is common (about 95%).
9. The patient has to bear the cost of the procedure in at least 50% of instances.
10. 40% of the total stents used are indigenously produced.
11. 83% of the stents used are drug-eluting.
12. Rotablation is used in <1% of cases.
13. Fractional flow reserve (FFR) guidance is currently used in <5% of procedures.

(This information has been obtained through the National Interventional Council, a part of the Cardiological Society of India)

The practice of interventional cardiology

The practice of interventional cardiology is changing in India. Across India, there is an increase in the number of diagnostic and interventional coronary procedures. The number of centres and operators is steadily increasing. Coronary intervention, however, still remains the dominant procedure in vascular interventions in India (nearly 90% of all therapeutic catheter-based procedures), and the number of procedures is growing significantly.

The indications for PCI remain centred around acute coronary syndrome (ACS) in the majority of cases. This may be due to the phase of epidemiological transition in India, where ACS outnumbers chronic stable disease. This is a cause for concern. Most metropolitan cities have PCI facilities available and even smaller cities are acquiring these at a rapid rate. There has been an annual 20% growth in coronary procedures in India for the last five years compared to the western world where PCI numbers are stagnating due to better preventive measures and greater emphasis on appropriateness criteria. Lack of an organised uniform health insurance policy for these expensive procedures is a major drawback for the optimal utilisation of these facilities.

Non-coronary interventions in India

The volume of non-coronary interventions seems to be static. The catheter-based interventions in paediatric cardiology are increasing, but the numbers of percutaneous mitral valvotomies are steadily decreasing because of the decline in rheumatic heart diseases. Despite a high prevalence of diabetes mellitus, the interventions for peripheral vascular disease have very modest numbers. The programme of non-surgical aortic valve replacement is in its early stages and being performed only in selected centres in small numbers. The main reasons for this are the attitude of the very elderly patients and their families not keen on invasive procedures, non-reimbursement, and lack of structured training programmes for performing these procedures in sick patients.

Transcatheter therapy for aorto-arteritis (Takayasu's disease) was pioneered in India, and a number of techniques to dilate and stent the ischaemia-producing vessels which include the central aorta, arch vessels and branches from descending abdominal aorta, are being performed in several centres in the country.

Documentation of non-coronary interventions, however, has been sketchy. About twenty-five to thirty thousand non-coronary interventions are performed per year in India, with the number remaining fairly steady. Nearly half of these interventions are for valvular heart disease, predominantly for rheumatic mitral stenosis. Catheter-based interventions in congenital heart disease are showing a modest increase, although peripheral arterial interventions are on the decline for reasons difficult to explain.

Perspective

In the absence of any formal training in interventional cardiology the coronary intervention programmes have picked up in a big way, but structural heart disease interventions are lagging behind. Formal training programmes for general cardiology are available, and three-year courses after an MD (medicine or paediatrics) leading to a degree of DM or DNB (cardiology) are a prerequisite before being certified as a cardiologist and getting teaching jobs or jobs in non-government institutions. Most trained cardiologists prefer to go in for interventional cardiology rather than non-invasive cardiology. This is possibly because of the better emoluments offered to invasive cardiologists.

The initial interventional cardiology training experience in India involved the development of *ad hoc* unregulated programmes, mostly located at "high-volume" coronary interventional centres. Practising cardiologists desiring to develop interventional coronary skills would often temporarily leave from their practice and enrol in short-duration observational courses in India and overseas which were often facilitated by industry. In this regard the contribution of Dr Alain Cribier has been noteworthy. A large number of interventional cardiologists were trained in Rouen, France, under his guidance in short-term programmes of two to three months. An Indo-French foundation funded by the industry used to look after these cardiologists in the interventional cardiology teaching programmes.

Interventional cardiology requires multiple skills, including cognitive and procedural competencies, which cannot be gained in the absence of formal training and certification with quality assurance. Formal, defined, and measurable interventional cardiology certification and training is still in its initial stages in India, although the National Board of Examinations offers fellowships in interventional cardiology. SCAI-sponsored courses of a few days are also available from time to time. The constantly evolving nature of this

relatively young subspeciality presents a landscape with many challenges. The robust and sustained evolution of the pharmacological innovations and new medical devices in this field has dramatically changed the practice during the past three decades at a pace and complexity unmatched in most other medical fields. The evaluation and maintenance of procedural competence present an even more challenging issue with very little regulation or control.

Historically, procedural volume has been used as a surrogate for catheterisation laboratory procedural performance and is one of the benchmarks used for rating competence. The concept is that the more procedures an operator performs the better his/her skills become, which will finally result in better clinical outcomes. Formal evaluation processes in this regard are lacking.

In recent years, the practice of interventional cardiology in India has been increasingly scrutinised by patients, tax payers, price-regulatory authorities, and the media. However, there are no benchmarks, scorecards or publically displayed performance reports to grade physician performance and evaluation. It is hoped that the cardiac societies, the medical councils and the government will take a note of this and come out with guidelines. A comprehensive healthcare programme with insurance is available in some states but not in all. Health is a state subject in India with very few central regulations. It is desirable that in times to come a more structured healthcare system and credible training programmes will be available. This is a necessity which has to be realised.

Interventional cardiology has shown significant growth in India. There are challenges which need to be recognised and adequate measures taken to streamline the processes. The future is very bright and most growth in this area is going to come in our region.

Conflict of interest statement

The authors have no conflicts of interest to declare.

AsiaIntervention 2016;2:10-12

Tailoring TAVI in Asia: insights from MSCT

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Clinical outcomes from transcatheter aortic valve implantation (TAVI) have improved remarkably over the last decade and have the potential to surpass those associated with surgical aortic valve replacement (SAVR)[1,2]. Such success can be attributed to a number of key advances, including physician experience, device iteration, and patient selection. The latter infers choosing the most appropriate patient for the procedure and, more importantly, assumes the application of the optimal procedural strategy for each case. In this regard, the introduction of three-dimensional (3D) multislice computed tomography (MSCT) for transcatheter heart valve (THV) sizing and procedural planning has been revolutionary.

THV sizing with 2D transoesophageal echocardiography is suboptimal. This strategy increases the rates of significant paravalvular leak, post-implantation balloon dilatation, and yields longer and more complex procedures[3]. It has been suggested that 3D transoesophageal echocardiography can provide similar annular measurements to MSCT; however, our group's experience with this technique has been disappointing[4]. Moreover, MSCT provides much more than THV sizing alone. A good quality CT data set can determine the most appropriate vascular access route, provide crucial information on coronary height, sinotubular junction and sinus of Valsalva width, aortic root angulation, and implant plane. These elements impact on the selection of the type and size of the transcatheter prosthesis.

In this issue of AsiaIntervention, Watanabe et al present a retrospective observational comparison of the MSCT-measured dimensions of the aortovalvular complex between Asian (Japanese) and European (French) TAVI populations[5]. As expected, the authors confirm significantly smaller and more elliptical annular dimensions in the Asian cohort: short and long annulus diameter, perimeter and area were between 11 and 20% smaller in Japanese patients.

Article, see page 49

The height of the coronary arteries from the annular plane and both the sinotubular junction and sinus of Valsalva dimensions were similarly reduced in the Asian cohort. Consequently, Japanese patients required smaller Edwards THV (Edwards Lifesciences, Irvine, CA, USA) sizes than their French counterparts: the 23 mm Edwards SAPIEN valve was appropriate for 51.1% and 12.7% of the Japanese and French cohorts, respectively. The authors also found no between-group differences in the quantification of aortic valve calcification.

The authors of this Japanese-French collaborative should be commended for undertaking this important study that has considerable implications for both patient selection and valve development in Asia. What are these implications?

First, small anatomy (annulus, sinus of Valsalva, coronary height) has been associated with a higher incidence of serious complications

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such as annular rupture and coronary occlusion[6,7]. Thus, these adverse events could occur more commonly in Asian TAVI cohorts, particularly if the industry-recommended sizing parameters are not respected. In contrast, smaller annular sizes could be potentially advantageous in the longer term, as the incidence of more than mild paravalvular leak – a factor associated with poor long-term survival – is less frequently observed in smaller annuli[3].

Second, as demonstrated by Watanabe et al, annular size correlates well with body surface area, which is closely associated with femoral artery dimensions[8]. While the current study did not compare the dimensions of the peripheral vasculature between continents, it is intuitive that Asian patients have smaller iliofemoral anatomy than European or American patients. One could therefore speculate that there may be a higher risk of vascular complications in Asian TAVI candidates.

The smaller anatomy of Asian TAVI candidates has potential implications for THV development/proliferation in Asia. Smaller annuli will require smaller valve sizes and it remains to be seen whether established THV manufacturers will develop smaller device sizes for the Asian market. Unfortunately, the retrospective nature of the study by Watanabe et al resulted in the exclusion of patients with annular sizes that were deemed too small for TAVI during the enrolment period – the CoreValve (Medtronic, Minneapolis, MN, USA) and 20 mm Edwards SAPIEN XT valve were approved in Japan in March and May 2015, respectively – and therefore does not provide information on the true spread of annular sizes in Japanese patients. Nevertheless, two THV devices specifically developed in Asia have introduced valve sizes geared towards smaller anatomy, namely the J-Valve™ (JieCheng Medical Technology Co., Ltd., Suzhou, China) available in sizes 21, 23, 25, 27 mm, and the MicroPort (MicroPort Inc., Shanghai, China), available in sizes 21, 23, 27, 31 mm. Currently available Venus valve (Venus MedTech Inc., HangZhou, China) sizes are 23, 26, 29, and 32 mm. While reducing the calibre of THV delivery systems has been a real challenge, the recent availability of new-generation THVs with low-profile delivery systems bodes well for the development of TAVI in Asia. The 14 Fr CoreValve Evolut R (Medtronic) and Edwards eSheath (Edwards Lifesciences) systems will facilitate the treatment of a greater number of patients using transfemoral access[9,10].

The findings of the current study relating to aortic valve calcification are interesting. A recent analysis found significantly greater valve calcification in Chinese compared to US TAVI patients[11]. A similar analysis between Korean and European TAVI patients found no difference in calcium quantification[12]. Therefore, there may be regional differences in valvular calcification due to environmental factors, age profile of TAVI candidates, and perhaps the method of calcium quantification using MSCT. It is noteworthy that the construction of the Venus and MicroPort nitinol self-expanding prostheses has considerably greater inflow radial strength to accommodate greater calcification.

The findings of the study by Watanabe et al are important and thought-provoking. Procedural experience in many Asian nations is in its infancy but is on the cusp of rapid expansion in an enormous population. There remains great potential to progress the field of TAVI in Asia by learning from the experience gained internationally and tailoring this to the specific needs of the Asian population. The recent introduction of dedicated courses such as PCR-CIT China Chengdu Valves and PCR Tokyo Valves will facilitate the dispersion of important educative content. Concurrently, the development of home-grown THV technologies in Asia represents an exciting benchmark on the road to TAVI adoption in Asia.

Conflict of interest statement

D. Mylotte and N. Piazza are proctors and consultants for Medtronic and MicroPort. S. O'Connor has no conflicts of interest to declare.

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Opening the shell for better stent results

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Calcification is a hallmark sign of advanced atherosclerosis and increases with age. As age advances, the mean percent calcified area increases for plaques both with moderate and with severe narrowing[1]. In an autopsy study of patients with severe coronary disease, coronary calcification was present in 90% of men and women aged 50 to 60 and in 100% of men and women older than 60[2]. However, the distribution and magnitude of calcium are distinctly different in atherosclerotic plaques. Calcium can be fragmented or diffuse, different in thickness, arc, and distance from the lumen surface.

Whilst non-invasive coronary computed tomography angiography (CCTA) provides accurate measures of calcium score for more effective risk stratification of interventional procedures[3], the detection and quantification of coronary artery calcification in patients undergoing invasive angiography is problematic. Overall, angiography identifies calcium in less than half of the target lesions with ultrasound-detected calcification. In addition, angiography is not reliable for differentiating superficial from deep calcification[4]. If angiographic calcium is visible in multiple views, the arc of vessel involvement is probably larger.

Does calcification render a stent procedure more difficult or is it only a marker of advanced disease? Delivering a stent into a calcified lesion may be difficult, and full and symmetrical expansion of a stent may be impaired by extensive superficial calcification. Conversely, calcification deep within a plaque does not preclude effective stenting. Biomechanical studies based on computer models have suggested that calcium distribution within plaque could impact differently on stent expansion and apposition[5].

Distinguished patterns of calcification may require different treatment strategies for optimal coronary stent implantation. In the analysis of drug-eluting stents (DES) an arc of calcium ≥90 degrees or an area of calcium ≥1.58 mm^2 significantly reduced stent expansion[6]. In bioresorbable scaffolds (BRS), due to the limited radial force and the polymeric strut configuration not transfixing the coronary artery, significantly lower expansion and more scaffold eccentricity have been reported in the presence of superficial calcification (distance of calcified plaque to the lumen <180 microns), while the observed increase in the rate of malapposition correlates with the area of calcium[7,8].

Compared to intravascular ultrasound (IVUS), optical coherence tomography (OCT) has greater ability to provide accurate quantitative and qualitative evaluation of coronary artery calcifications[9]. Whilst OCT has been extensively used and promoted for lipid-rich plaque identification and characterisation, particularly in acute coronary syndromes, few studies have reported on OCT evaluation

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of calcification. In fact, light can more easily penetrate calcium compared with lipid, where light scattering might limit the signal penetration.

The manuscript of Ishida and colleagues, published in this issue of AsiaIntervention 2016, attempts to fill this gap in knowledge, bridging the current era of standard angiography-guided PCI to a novel one of pre-interventional OCT-based procedural planning[10]. The most salient OCT finding reported in this study is the predominance of superficial calcium, mainly located within 100 microns from the lumen surface, the most accurate range for light-based measurements. In addition, superficial calcium is the key OCT factor for predicting difficult stent expansion. In total, pre-stent OCT at the target lesion displaying calcium close to the lumen significantly impacts on the stent strategy. Are we ready for prime-time use of pre-intervention imaging planning in daily practice?

Article, see page 36

Despite incredible progress of current-generation OCT in terms of the speed of acquisition, on-line automatic lumen measures and co-registration with angiography, we definitely think we are not ready for such a similar, systematic approach. Technical issues and missing clinical data are responsible. From a technical point of view, the imaging catheter plays a pivotal role. It has to be robust enough to go back and forth in rigid vessels, to overcome spotty and speckled superficial calcification without trapping and/or generating artefacts, and finally not to become fatigued with multiple passes (before stent/scaffold for lesion type characterisation; post-stent/scaffold to optimise the implantation). This type of catheter is not available to interventional cardiologists as yet and must represent a true priority for all companies interested in PCI-guided procedures. Recently, OCT co-registration with angiography has been made available to interventional cardiologists, in order to project plaques immediately on the operative fluoroscopic monitor. If superficial calcium is so important for stenting and easy to detect by OCT, dedicated software for automatic identification, measures and display of calcified plaques along the artery has to be rapidly implemented into OCT systems.

From a clinical perspective, we are still missing convincing evidence of the benefit of pre-interventional imaging on PCI outcome. Prospective studies using intracoronary imaging for stent optimisation in different lesion types (ADAPT-DES, ILUMIEN I) have demonstrated the clinical benefit of a change of strategy guided by either IVUS or OCT, with pre-PCI imaging impacting more substantially on procedural planning and physician decision making compared to post-stent optimisation[11,12]. However, no large prospective, randomised studies comparing angiography versus intracoronary imaging stent guidance are available as yet.

Why do we need to continue to devote attention to accurate calcium detection and characterisation before PCI if there is still no clinical evidence and the optimal tools for imaging are not yet available? First, there is an exponential growth of all factors promoting calcium deposits in lesions undergoing PCI (age, diabetes, multivessel disease [MVD], chronic renal failure). Some of these factors (e.g., diabetes, MVD) are already heading the clinical profile of patients treated by PCI in the emerging countries. Second, calcium remains a major determinant of periprocedural complications and negative outcome. Third, the novel generation of fully bioresorbable scaffolds, when fully developed, will probably change the way we currently perform PCI. In complex, fibro-calcific plaques, accurate imaging-based interrogation and effective lesion preparation will maximise the potential of the scaffolds.

Finally, Ishida's article has major limitations that need to be considered. These data are based on too small a group of procedures conducted with OCT evaluation before and after stenting (only 8% of the total number of procedures), in the presence of essentially mild to moderate calcified lesions (mean arc of calcium 149°, the majority of cases with only one quadrant involved), without exploring alternative treatment strategies for plaque modification with athero-ablative devices (e.g., scoring balloons or rotational atherectomy).

Nevertheless, understanding the contents of the shell before opening with a permanent metallic cage or a more susceptible plastic scaffold will limit any unwelcome surprises for doctors (under-expansion) and patients (adverse events).

Conflict of interest statement

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Asia-Pacific Hotlines at TCT 2015: a prospective randomised trial of paclitaxel-eluting vs. everolimus-eluting stents in diabetic patients with coronary artery disease (TUXEDO)

Upendra Kaul*, MD; on behalf of the Taxus Element versus Xience Prime in a Diabetic Population (TUXEDO) INDIA Investigators

Escorts Heart Institute and Fortis Group of Hospitals, Okhla, New Delhi, India

What was your rationale for this study and what was known before?

The choice of a drug-eluting stent in diabetics has been the subject of debate for a decade. Based on a large meta-analysis, paclitaxel-eluting stents have traditionally been given an equivalent status to everolimus-eluting stents (possibly even favoured over them) in insulin-dependent diabetics. This position was challenged on the basis of a patient-based meta-analysis. In the absence of an adequately powered study, a definitive answer was not possible.

What is unique about this study in your country?

This Indian study is the largest international study to compare a paclitaxel-eluting stent (PES) versus an everolimus-eluting stent (EES) in a diabetic population[1]. In total, 1,830 patients with diabetes mellitus were included using a non-inferiority trial design. They received either a PES (TAXUS Element™; Boston Scientific, Marlborough, MA, USA) or an EES (XIENCE PRIME; Abbott Vascular, Santa Clara, CA, USA). The primary endpoint was target vessel failure defined as a composite of cardiac death, target vessel myocardial infarction, or ischaemia-driven target vessel revascularisation at one-year follow-up.

Did you experience any unexpected challenges?

Because of changes to the rules concerning clinical trials in India and slow recruitment due to regulatory issues, recruitment of cases was challenging.

How does the conclusion apply to your daily practice?

PES did not meet the non-inferiority criteria of target vessel failure against everolimus-eluting stents at one year (5.6% vs. 2.9%; relative risk=1.89; 95% CI: 1.20-2.99; pNI=0.38 for non-inferiority at 4% margin; treatment difference 95% CI: 0.78-4.48). There was a significantly higher one-year rate of target vessel failure (p=0.005), myocardial infarction (3.2% vs. 1.2%, p=0.004), stent thrombosis (2.1% vs. 0.4%, p=0.002), target vessel revascularisation (3.4% vs. 1.2%; p=0.002) and target lesion revascularisation (3.4% vs. 1.2%; p=0.002) in the PES group compared to the EES group.

In this trial, the largest conducted in a diabetic population undergoing percutaneous coronary intervention, PES failed to meet non-inferiority compared with EES and resulted in higher rates of target vessel failure, myocardial infarction, stent thrombosis, and target vessel revascularisation at one year. The study has resulted in a marked increase in the use of EES, even in diabetic patients.

Conflict of interest statement

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Asia-Pacific Hotlines at TCT 2015: Bioresorbable vascular scaffolds versus metallic stents in patients with coronary artery disease (ABSORB China trial)

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What was your rationale for this study and what was known before?

Outcomes with drug-eluting stents (DES) have improved progressively with the latest contemporary designs. However, the presence of a polymer-coated permanent metallic cage constrains the vessel with potential late (>1 year) deleterious consequences, including impaired cyclic pulsatility, abnormal vasomotion, loss of normal vessel curvature, strut fracture and neoatherosclerosis, etc.[1]. As a result, 2-3% of patients per year develop late serious adverse cardiovascular events arising at the stent site. To overcome this limitation, fully bioresorbable vascular scaffolds have been developed, with the potential to improve late outcomes compared to metallic DES. Whether these devices are as safe and effective as the best-in-class metallic DES within the first year of implant remains to be seen. As more than 100,000 everolimus-eluting Absorb bioresorbable vascular scaffolds (BVS) (Abbott Vascular, Santa Clara, CA, USA) have been implanted worldwide, this is an imperative issue.

Did you experience any unexpected challenges?

ABSORB China, presented as a late-breaking trial at TCT 2015 and simultaneously published online in the Journal of the American College of Cardioliology[2], is a 480-patient trial which randomised Absorb BVS 1:1 to the XIENCE cobalt-chromium everolimus-eluting stent (CoCr-EES) (Abbott Vascular), the DES with the best outcomes of all contemporary DES. This trial was designed for regulatory approval in China, and is the first randomised ABSORB trial with a powered primary endpoint of angiographic in-segment late loss at one year. The results revealed that the Absorb BVS was non-inferior to CoCr-EES in in-segment late loss at one year (0.19 mm vs. 0.13 mm, pnoninferiority=0.01). Absorb BVS reported comparable rates of one-year angiographic restenosis and clinical outcomes compared to CoCr-EES, with low rates of death (0.0% vs. 1.3%), myocardial infarction (2.1% vs. 1.7%) and scaffold thrombosis (0.4% vs. 0.0%), respectively, demonstrating the safety and effectiveness of BVS in treating *de novo* coronary lesions in a Chinese population.

The first-generation BVS has thicker struts and a larger crossing profile than contemporary metallic DES. Nevertheless, similar high rates of acute device and procedural success were achieved with Absorb BVS in the present and prior ABSORB studies, comparable to those of CoCr-EES in non-complex lesions. In the present study, aggressive predilatation was recommended, and post-dilatation was performed at a higher rate with BVS than CoCr-EES (63.0% vs. 54.4%, p=0.05), which may have helped achieve the high rates of acute procedural success with a bail-out rate of only 2.0%.

How does the conclusion apply to your daily practice?

Improvements in implantation technique (e.g., routine post-dilatation or more frequent use of intravascular imaging guidance, which was rarely used in the present study) and device iterations (thinner struts) may further improve deliverability and angiographic and clinical outcomes, especially in complex lesions.

Funding

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Conflict of interest statement

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Asia-Pacific Hotlines at TCT 2015: evaluation of initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis (The CURRENT AS registry)

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What was your rationale for this study and what was known before?

Surgical aortic valve replacement (AVR) is strongly recommended in symptomatic patients with severe aortic stenosis (AS) who are suitable candidates for surgery. However, the management of asymptomatic patients with severe AS remains controversial. A strategy of watchful waiting is generally recommended other than in several subgroups of patients, for example those with left ventricular dysfunction or very severe AS. However, this recommendation was based on previous small, single-centre studies evaluating symptoms and/or AVR, but not mortality as outcome measures.

What is unique about this study in your country?

To the best of our knowledge this is the first large-scale multicentre study comparing the long-term outcome of the initial AVR strategy versus the conservative strategy following the diagnosis of asymptomatic severe AS.

Did you experience any unexpected challenges?

The CURRENT AS registry is a multicentre, retrospective registry which enrolled 3,815 consecutive patients with severe AS (peak aortic jet velocity >4.0 m/s, or mean aortic pressure gradient >40 mmHg, or aortic valve area <1.0 cm^2) between January 2003 and December 2011[1]. Among 1,808 asymptomatic patients, the initial AVR strategy was chosen in 291 patients and the conservative strategy in 1,517 patients. The median duration of follow-up was 1,361 days with a 90% follow-up rate at two years. The propensity score-matched cohort of 582 patients (initial AVR group: 291 patients, conservative group: 291 patients) constituted the main analysis set for the current report. The primary outcome measures for the current analysis were all-cause death and heart failure (HF) hospitalisation.

Baseline characteristics of the two groups in the propensity score-matched cohort were largely comparable, except for the slightly younger age and greater AS severity in the initial AVR group. In the conservative group, AVR was performed in 41% of patients during follow-up. The cumulative five-year incidences of all-cause death and heart failure hospitalisation were significantly lower in the initial AVR group than in the conservative group (15.4% versus 26.4%, p=0.009, and 3.8% versus 19.9%, p<0.001, respectively). The results from the multivariable Cox models in the entire cohort were consistent with those from the propensity score-matched analysis. Among 492 patients with emerging symptoms related to AS during follow-up in the conservative group, AVR was performed in 239 patients (49%) with a median interval of 70 (IQR: 41-131) days after onset of symptoms. AVR was less frequently performed in patients who presented with NYHA Class III or IV than in those who presented with NYHA Class II (37% versus 63%). The mortality of patients who did not undergo AVR despite their symptoms was very high.

How does the conclusion apply to your daily practice?

The long-term outcome of asymptomatic patients with severe AS might be substantially improved by employing an initial AVR strategy since, in real-world clinical practice, when managed conservatively, outcomes are dismal.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Late angiographic and clinical outcomes of the novel BioMime™ sirolimus-eluting coronary stent with ultra-thin cobalt-chromium platform and biodegradable polymer for the treatment of diseased coronary vessels: results from the prospective, multicentre meriT-2 clinical trial

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KEYWORDS

- angiography
- complex lesions
- sirolimus-eluting stent

Abstract

Aims: We sought to investigate the performance of the novel BioMime™ sirolimus-eluting coronary stent system (SES), with an ultra-thin cobalt-chromium platform and a biodegradable polymer, in a "real-life", minimally selected, coronary artery disease patient population.

Methods and results: A total of 250 patients (355 *de novo* lesions) were prospectively enrolled between August 2009 and January 2012 at 11 Indian sites. Mean age was 56.8±10.6 years, 36% of patients had diabetes, 32% had prior myocardial infarction, and 63.4% of lesions were classified as type B2/C. Overall, 1.4 lesions per patient were treated, and angiographic/procedural success was achieved in 99.2%. There were no major adverse cardiac events (MACE) at 30 days. At eight-month angiographic follow-up (available in 87% of patients), median in-stent late lumen loss (primary efficacy endpoint) was 0.12 mm (0.04-0.30 mm), whereas in-stent and in-segment binary restenosis rates were 4.9% and 6.2%, respectively. At 12 months (follow-up completed in 99.6% of patients), the cumulative MACE rate was 6.0%, including 0.8% cardiac death, and 5.2% target lesion revascularisation (4.8% clinically indicated target lesion revascularisation). In addition, one patient (0.4%) presented with definite/probable stent thrombosis.

Conclusions: The BioMime SES demonstrated a high procedural success rate, low late lumen loss (a surrogate of neointimal hyperplasia), and sustained safety and efficacy up to 12 months.

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Abbreviations

DES	drug-eluting stent
DS	diameter stenosis
LLL	late lumen loss
MACE	major adverse cardiac events
MI	myocardial infarction
MLD	minimum lumen diameter
PCI	percutaneous coronary intervention
QCA	quantitative coronary angiography
RD	reference diameter
SES	sirolimus-eluting coronary stent
TLR	target lesion revascularisation

Introduction

Compared to first-generation drug-eluting coronary stents (DES), new-generation DES have attempted to improve safety, deliverability and overall performance, while maintaining efficacy by preventing neointimal hyperplasia (NIH), restenosis, and therefore the need for target lesion revascularisation (TLR) over a period of time in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI)[1-3]. In general, low-profile metallic stents, polymer-based drug carriers with enhanced bio-inertness (whether durable or biodegradable), and potent yet safe pharmacological agents from the "limus" family have commonly been incorporated into novel DES technologies[4-11]. The CE (Conformité Européenne) mark-approved BioMime™ sirolimus-eluting coronary stent system (Meril Life Sciences Pvt. Ltd., Gujarat, India) is a novel DES system which incorporates an advanced ultra-thin stent platform covered with a biodegradable polymer, which releases sirolimus as the antiproliferative drug to the vessel wall. In the first clinical evaluation, the BioMime sirolimus-eluting coronary stent (SES) demonstrated safety and efficacy in inhibiting NIH in a relatively small sample of patients with single *de novo*, non-complex coronary lesions treated at a single institution[11]. However, the results of the BioMime stent in a larger "real-life" population with complex coronary lesions have not been studied. We therefore assessed the performance and late angiographic and clinical outcomes of the BioMime SES in the treatment of a relatively large series of patients with obstructive coronary artery disease with very few exclusions at multiple clinical sites.

Methods

STUDY DESIGN AND POPULATION

The meriT-2 trial was a prospective, non-randomised, single-arm, multicentre, phase II clinical evaluation of the BioMime SES in the treatment of consecutive patients with coronary artery disease. The study objective was to evaluate the overall performance, safety and efficacy of the BioMime device in inhibiting NIH in a relatively large population with minimally selected coronary lesions. Inclusion criteria were: patients ≥18 years of age, symptoms or signs of ischaemic heart disease, the presence of a single or multiple *de novo* lesion(s) ≤35 mm in length with stenosis 50-100% in native coronary vessel(s) with a reference diameter (RD) between 2.5 mm and 3.5 mm, an acceptable candidate for coronary artery bypass graft (CABG) surgery, and agreement to undergo all protocol pre-specified evaluations, including angiographic follow-up. Triple-vessel disease was not an exclusion. Exclusions were: acute myocardial infarction (MI) <48 hours from index procedure, women with childbearing potential, renal insufficiency (baseline serum creatinine >2.0 mg/dL), history of cerebral vascular accident or transient ischaemic attack <3 months previously, left main, large thrombus, saphenous vein graft, left ventricular ejection fraction <30%, contraindication to dual antiplatelet therapy, or any other known illness or clinical condition with a life expectancy of <12 months.

The study complied with the Declaration of Helsinki regarding investigation in humans, and was approved by the local ethics committee at each participating clinical institution. All patients provided written informed consent prior to enrolment. The meriT-2 trial was registered at the National Institute of Medical Statistics, Indian Council of Medical Research (Clinical Trials Registry – India, CTRI) at www.ctri.nic.in/Clinicaltrials: REFCTRI-2009000505, and at the United States National Institute of Health at www.clinicaltrials.gov: NCT02406326.

STUDY DEVICE AND PROCEDURE

The specifics of the BioMime SES have been detailed elsewhere[11]. In brief, it is built on an ultra-thin L605 cobalt-chromium platform (65 µm) with a "hybrid" cell design, including a mix of open and closed cells **(Figure 1)**. The drug carrier is a thin (~2 µm) co-polymer formulation combining two biodegradable components (poly-L-lactic and poly-lactic-co-glycolic acids), which degrades in approximately 60 days after implantation. In addition, sirolimus is coated in a dosage of 1.25 µg per mm^2 of stent surface area (total drug dose ~121 µg for a 3.0×19 mm stent), given that the complete drug release is expected to occur in approximately 30-40 days after stent implantation.

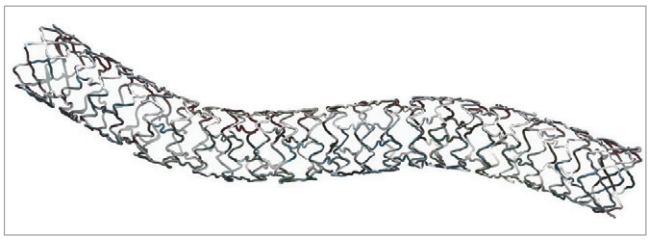

Figure 1. *The BioMime stent design showing its "hybrid" cell design with a mix of open (middle) and closed (end) cells.*

PCI procedures were performed according to current standard guidelines. Predilatation was recommended with a regular balloon catheter; post-dilatation was performed at the operator's discretion. Only one stent per lesion was allowed, even though an additional study stent could be implanted overlapping with the previous stent in case of a bail-out situation. Multiple stent implantation for multivessel PCI was allowed. The BioMime SES was available in 13, 16, 19, 24, 29, 32, 37, 40 mm lengths, and in 2.5, 3.0 and 3.5 mm

diameters. After discharge, all patients were prescribed aspirin (100-325 mg/day) indefinitely and clopidogrel 75 mg/day for at least 12 months.

ENDPOINTS, DEFINITIONS AND FOLLOW-UP

The primary safety endpoint was major adverse cardiac events (MACE) at 30 days after the procedure. The primary efficacy endpoint was in-stent late lumen loss (LLL), as determined by quantitative coronary angiography (QCA) analysis, at angiographic follow-up at eight months. Secondary endpoints were MACE and stent thrombosis (ST)[12] at all study time points up to 12 months, angiographic and procedural success, angiographic binary restenosis at eight-month angiographic follow-up, and clinically indicated TLR at 12 months. MACE was defined as the composite of cardiac death, MI or TLR. All deaths were considered cardiac unless a non-cardiac cause could be established clearly, either by clinical assessment or by pathological study. MI was classified as Q-wave or non-Q-wave, and according to its temporal and circumstantial occurrence (periprocedural, spontaneous or post-CABG), following standard definitions, as previously reported[11]. Clinically indicated TLR was considered under the following conditions at follow-up: a) stenosis ≥50% by QCA within the treated segment plus symptoms of (recurrent) angina and/or evidence of positive function test for ischaemia by either non-invasive or invasive methods, or b) the presence of stenosis ≥70% by QCA within the treated segment in the absence of the above-mentioned symptoms or signs of ischaemia. Angiographic success was defined as residual stenosis <20% plus final TIMI flow 3 after PCI with the study device. Procedural success was defined as angiographic success plus the absence of MACE during index hospitalisation. Clinical follow-up was scheduled at one, six, eight, 12, 36 and 60 months, either by medical visit or by telephone contact. All patients were assigned to angiographic re-evaluation at eight months. The study was managed by an independent clinical research organisation (SIRO Clinpharm Pvt. Ltd., Thane, India). In the current analysis, we report the baseline/index and clinical outcomes up to 12 months, and eight-month angiographic follow-up.

ANGIOGRAPHIC ANALYSIS

After intracoronary administration of nitroglycerine, serial angiographic studies were obtained in two orthogonal matching views at pre and post procedure, and eight-month follow-up. Angiographic analyses were performed off-line by experienced operators at an independent angiographic core laboratory (Cardiovascular Research Center, São Paulo, Brazil), using a validated 2D software for QCA analysis (QAngio XA® version 7.2; Medis medical imaging systems bv, Leiden, The Netherlands), as previously reported[11]. The minimum lumen diameter (MLD) and the mean RD, obtained by averaging 5 mm segments proximal and distal to the target lesion location, were used to calculate the diameter stenosis (DS=[1–MLD/RD]×100). Acute gain was the change in MLD from baseline to post-stent implantation. Late lumen loss (LLL) was the change in MLD from post-stent implantation to follow-up; the LLL index was LLL divided by acute gain. Binary restenosis was reported according to the Mehran classification[13]. QCA measurements were reported as "in-stent" within the stented segment, and "in-segment", spanning the stented segment plus the 5 mm proximal and distal peri-stent areas.

STATISTICAL ANALYSIS

Categorical data were presented as frequencies (percentages). Continuous variables were presented according to distribution pattern. In case of normal distribution, data were presented as mean values±standard deviation (SD). When non-normal distribution was evidenced, data were presented as median (interquartile). Cumulative frequency distribution (CFD) curves were used to illustrate the distribution of MLD. Time-to-event curves were reported according to the Kaplan-Meier method.

Results

A total of 250 patients with 355 *de novo* coronary lesions were enrolled between August 2009 and January 2012 at 11 sites in India. Mean age was 56.8 years, 36% of patients had diabetes, and the majority of patients presented with stable angina, followed by unstable angina **(Table 1)**. Baseline lesion characteristics are shown in **Table 2**. The left anterior descending (LAD) artery was the most prevalent target vessel, and a high complexity profile (ACC/AHA type B2/C) was found in 63.4% of patients. Overall, there were 1.4 lesions treated per patient. During the procedure, predilatation was performed in 90.1% of lesions, the study stent was implanted in all cases, 6.5% of lesions received >1 study stent, and more than half (60.8%) underwent post-dilatation. By intention-to-treat, procedural success was 98.6% (247/250). Considering only those

Table 1. Baseline demographics and clinical presentation.

Variable	n=250
Age, yrs	56.8±10.6
Female	42 (16.8)
Diabetes mellitus	91 (36.4)
Hypertension	123 (49.2)
Dyslipidaemia	26 (10.4)
Prior myocardial infarction	80 (32.0)
Prior PCI	15 (6.0)
Prior CABG	4 (1.6)
Prior CVA	2 (0.8)
History of CHF	5 (2.0)
Clinical presentation	
Asymptomatic (silent ischaemia)	28 (11.2)
Stable angina*	94 (37.6)
Unstable angina	68 (27.2)
Recent myocardial infarction¶	59 (23.6)

Values are expressed as mean±standard deviation or frequencies (percentages of the total). *According to the Canadian Cardiovascular Society classification. ¶Less than 30 days from index procedure. CABG: coronary artery bypass graft; CHF: chronic heart failure; CVA: cerebral vascular accident; PCI: percutaneous coronary intervention

Table 2. Baseline angiographic data.

Variable		n=250 (355 lesions)
Target vessel	LAD	169 (47.6)
	LCx	76 (21.4)
	RCA	110 (31.0)
Location	Ostial	13 (3.7)
	Proximal	102 (28.7)
	Mid	200 (56.3)
	Distal	40 (11.3)
Calcium (moderate/severe)		58 (16.3)
Ulcer		19 (5.4)
Tortuosity (moderate/severe)		19 (5.4)
Bifurcation		18 (5.1)
Lesion class*	A	16 (4.5)
	B1	114 (32.1)
	B2	165 (46.5)
	C	60 (16.9)
TIMI flow grade	0 or 1	23 (6.5)
	2	23 (6.5)
	3	309 (87.0)
QCA analysis		
Lesion length, mm		12.78 (8.79-18.66)
RD, mm		2.72 (2.40-2.97)
MLD, mm		0.74 (0.47-1.03)
% DS		71.4 (61.4-83.3)

Values are expressed as frequencies (percentages of the total) or median (25-75% interquartile range). *According to the modified American College of Cardiology/American Heart Association classification. DS: diameter stenosis; LAD: left anterior descending; LCx: left circumflex; MLD: minimum lumen diameter; RCA: right coronary artery; RD: reference diameter; TIMI: Thrombolysis In Myocardial Infarction

treated with the study device (n=249) (one patient died due to a haemorrhagic complication prior to PCI), procedural success was 99.2%, as two patients did not achieve angiographic success (final TIMI flow grade 2). In addition, there was no MACE reported up to 30 days.

QCA FINDINGS

Table 3 depicts QCA results post procedure and at follow-up. At eight months (follow-up available in 87% of patients), the median in-stent late lumen loss was 0.12 (0.04-0.30) mm. CFD curves for MLD are shown in **Figure 2**. **Figure 3** shows a case with complex multivessel PCI with patent stents at follow-up re-evaluation. Angiographic binary restenosis within the stent was found in 15 lesions (4.9%), whereas the in-segment rate was 6.2% (19 lesions). The majority of recurrences were focal, including type IC in 11 cases and type IB in four cases. Conversely, types ID, II, III and IV were found in one case each. Importantly, there was neither significant acute stent recoil (balloon-artery ratio 1.10 [1.06, 1.16]; final residual stenosis within the stent 7.6% [4.8, 11.8]) nor stent fracture/longitudinal deformation as assessed both at post procedure and at follow-up angiographic evaluation.

ONE-YEAR CLINICAL OUTCOMES

A total of 15 patients (6%) experienced MACE up to 12 months, including two cases of cardiac death (0.8%). In the first case, a 72-year-old female patient with multivessel disease and multiple comorbidities (diabetes, renal insufficiency, prior MI, prior CABG, congestive heart failure, mild anaemia) underwent PCI with the study device, but a second stent had to be implanted in order to cover a distal dissection. At post procedure, there was a suboptimal angiographic result (TIMI 2). After discharge, she was re-hospitalised due to progressive congestive heart failure and died on

Table 3. QCA analyses post-procedure and at eight-month follow-up.

QCA	In-segment	In-stent	Proximal edge	Distal edge
Post-procedure (n=355)				
RD, mm	2.84 (2.51-3.05)	–	–	–
Mean diameter, mm	–	2.92 (2.54-3.07)	2.82 (2.46-3.14)	2.49 (2.20-2.81)
MLD, mm	2.30 (2.20-2.61)	2.58 (2.30-2.87)	2.65 (2.29-2.97)	2.34 (2.04-2.66)
% DS	15.4 (10.4-22.3)	7.6 (4.8-11.8)	7.5 (3.6-13.1)	8.2 (4.2-15.8)
Acute gain, mm	1.59 (1.22-1.95)	1.85 (1.48-2.21)	–	–
Eight months (n=309)				
RD, mm	2.77 (2.45-2.99)	–	–	–
Mean diameter, mm	–	2.75 (2.48-2.98)	2.63 (2.35-3.03)	2.39 (2.09-2.71)
MLD, mm	2.09 (1.79-2.43)	2.36 (2.02-2.68)	2.45 (2.10-2.81)	2.17 (1.89-2.52)
% DS	21.4 (14.1-30.8)	12.2 (7.4-19.8)	11.1 (5.5-21.1)	12.6 (6.4-19.9)
LLL, mm	0.11 (0.04-0.29)	0.12 (0.04-0.30)	0.13 (0.03-0.30)	0.07 (0.03-0.19)
LLL index	0.07 (0.03-0.20)	0.06 (0.02-0.18)	–	–

Values are expressed as median (25-75% interquartile range). DS: diameter stenosis; LLL: late lumen loss; MLD: minimum lumen diameter; RD: reference diameter

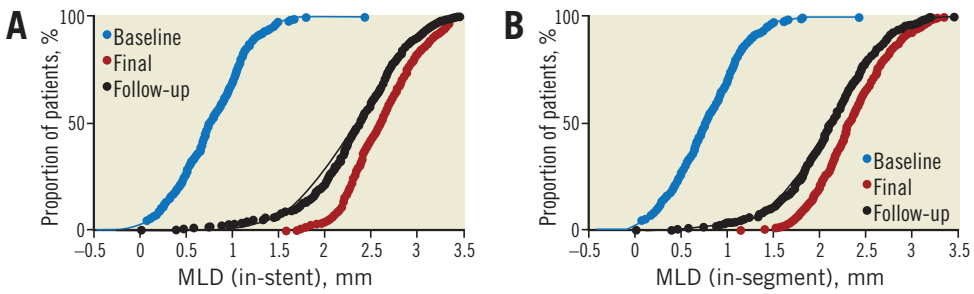

Figure 2. *Cumulative frequency distribution curves at pre-procedure, post-procedure and eight-month follow-up for in-stent MLD (A), and in-segment MLD (B).*

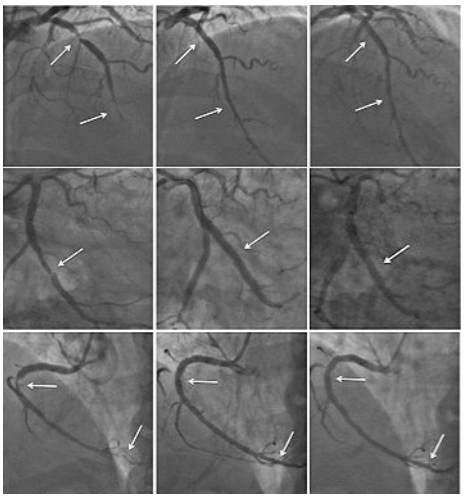

Figure 3. *Case example showing serial angiographic studies at pre-procedure (left column), post-procedure (centre column), and eight-month follow-up (right column) of a patient with multivessel disease treated with five BioMime SES in the mid and distal LAD (top row), mid LCx (centre row), and mid and distal RCA (bottom row).*

day 60. The second case was a 70-year-old patient, who had two target lesions successfully treated at the index procedure, developed cardiac heart failure and died at day 158. As for new revascularisation procedures, there were 13 cases of any TLR (5.2%), including 12 cases of clinically indicated TLR (4.8%) – 11 treated by PCI, one treated by CABG **(Table 4)**. The time-to-event curve for MACE is shown in **Figure 4**. Furthermore, there was only one case of definite/probable ST (0.4%) in a patient who presented with ST-elevation MI during the late follow-up. The angiographic study at the event evidenced occlusive thrombosis involving the study stent, which was successfully treated by PCI (also listed as MI and TLR for the individual event components).

Discussion

The results of the meriT-2 study demonstrated that the BioMime stent was associated with: a) high angiographic and procedural success among the treated population (99.2%); b) efficacy in inhibiting NIH at eight-month angiographic follow-up (median LLL 0.12 mm and binary restenosis rate <5% within the stented segment), despite

Table 4. Cumulative clinical events up to 12 months for patients receiving the study stent.

Outcome	30 days	6 months	8 months	12 months
MACE	0 (0)	6 (2.4)	8 (3.2)	15 (6.0)
All-cause death	0 (0)	2 (0.8)	2 (0.8)	2 (0.8)
Cardiac death	0 (0)	2 (0.8)	2 (0.8)	2 (0.8)
Non-cardiac death	0 (0)	0 (0)	0 (0)	0 (0)
MI	0 (0)	1 (0.4)	1 (0.4)	1 (0.4)
Any TLR	0 (0)	3 (1.2)	5 (2.0)	13 (5.2)
PCI	0 (0)	3 (1.2)	4 (1.6)	11 (4.4)
CABG	0 (0)	0 (0)	1 (0.4)	2 (0.8)
Clinically indicated TLR	0 (0)	3 (1.2)	5 (2.0)	12 (4.8)
PCI	0 (0)	3 (1.2)	4 (1.6)	11 (4.4)
CABG	0 (0)	0 (0)	1 (0.4)	1 (0.4)
Stent thrombosis (ARC)[12]				
Any	0 (0)	1 (0.4)	1 (0.4)	1 (0.4)
Definite/probable	0 (0)	1 (0.4)	1 (0.4)	1 (0.4)
Possible	0 (0)	0 (0)	0 (0)	0 (0)

Values are expressed as frequencies (percentages of the total).
ARC: Academic Research Consortium; CABG: coronary artery bypass graft; MACE: major adverse cardiac events (a composite of cardiac death, MI or any TLR); MI: myocardial infarction; PCI: percutaneous coronary intervention; TLR: target lesion revascularisation

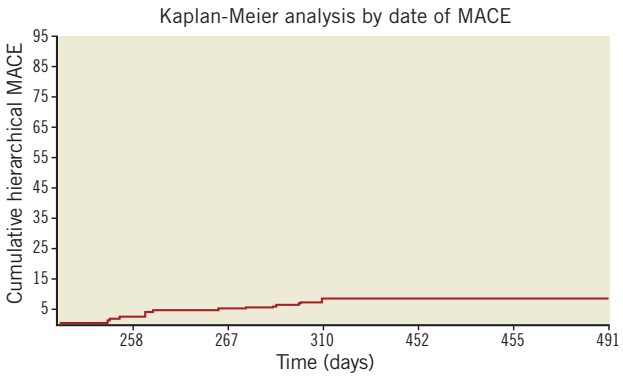

Figure 4. *Cumulative incidence of MACE up to 12-month follow-up (n=249).*

a high prevalence of small vessels (median RD <2.75 mm) and lesion complexity (63% type B2/C); and c) sustained safety and clinical efficacy (cardiac death 0.8%, ARC definite/probable ST 0.4%, clinically indicated TLR <5%) up to 12-month follow-up. Overall, these findings confirmed the results found in the first-in-human evaluation of BioMime SES (meriT-1)[11] despite the fact that the meriT-2 trial was a much larger trial involving a more complex population, with a high prevalence of diabetes and multivessel disease, enrolled at multiple sites. In addition, the performance, safety and efficacy demonstrated with the study stent appear to be comparable to those seen with the most effective new-generation low-profile DES used nowadays[5,7-10,14-16] **(Table 5)**.

Previous studies have demonstrated that strut thickness is a major determinant of local inflammation and NIH after stenting[17,18]. Moreover, thin-strut stent platforms offer enhanced flexibility and deliverability, thus facilitating PCI procedures, especially when targeting complex coronary anatomies. Still, a major concern about thinner devices may be their short- and long-term durability against axial and longitudinal stress in the coronary vessels[19,20]. In general, new advanced cobalt- or platinum-chromium DES platforms with thin struts (65-91 µm) have demonstrated the ability to preserve radial strength. They have also been associated with improved deliverability and procedural outcomes compared to DES with thicker struts[21-23]. Several reports with everolimus-eluting stents, zotarolimus-eluting stents, and other new SES systems have demonstrated high acute success and efficacy in the treatment of real-world patients, including complex subsets[21,24,25]. To our knowledge, the BioMime SES has the lowest profile among DES in current clinical use, with ultra-thin struts of 65 µm regardless of stent size. In addition, it has a thinner polymeric drug carrier (~2 µm). Interestingly, we did not observe direct evidence of mechanistic issues such as stent recoil, disruption or deformation that could be associated with acute or late stent failure in our study. This may be related to the innovative "hybrid" cell design combining open and closed cells in the BioMime **(Figure 1)**, which has been shown to preserve radial strength with minimal stent recoil (<3%) and without deformation in bench testing[11]. In fact, among 280 patients with 385 lesions (64% type B2/C) included in the combined meriT-1[11] and meriT-2 trials, there was neither unsuccessful PCI related to the study stent nor periprocedural MI. In terms of efficacy, BioMime SES demonstrated relatively low LLL at eight-month follow-up (0.12 mm), thus placing it within the range found

Table 5. Comparison of new-generation low-profile cobalt- or platinum-chromium DES trials.

Study	meriT-1[11]	meriT-2	SPIRIT I[5,14]	SPIRIT II[15,16]	RESOLUTE[7]	PLATINUM QCA[8]	EVOLVE FHU[9]	BIOFLOW-I[10]
No. (lesions)	30 (30)	250 (355)	27 (27)*	222 (260)*	139 (140)	100 (100)	94 (94)*	30 (30)
Device	BioMime™	BioMime™	XIENCE V®	XIENCE V®	Resolute®	Promus Element®	Synergy®	Orsiro®
Platform	cobalt-chromium	cobalt-chromium	cobalt-chromium	cobalt-chromium	cobalt-chromium	platinum-chromium	platinum-chromium	cobalt-chromium
Strut thickness	65 µm	65 µm	81 µm	81 µm	91 µm	81 µm	74 µm	71 µm¶
Polymer type	biodegradable	biodegradable	durable	durable	durable	durable	biodegradable	biodegradable
Polymer component(s)	PLLA/PLGA	PLLA/PLGA	acrylic/fluorinated polymers	acrylic/fluorinated polymers	C10/C19/polyvinyl pyrrolidinone	acrylic/fluorinated polymers	PLGA	PLLA
Polymer thickness	2 µm	2 µm	5-6 µm	5-6 µm	5.6 µm	5-6 µm	4 µm	7.5 µm
Drug	sirolimus	sirolimus	everolimus	everolimus	zotarolimus	everolimus	everolimus	sirolimus
Drug dose	1.25 µg/mm^2	1.25 µg/mm^2	100 µg/cm^2	100 µg/cm^2	1.6 µg/mm^2	100 µg/cm^2	100 µg/cm^2	1.4 µg/mm^2
Drug release	100% (30-40 days)	100% (30-40 days)	70-80% (30 days)	70-80% (30 days)	85% (60 days)	70-80% (30 days)	70-80% (30 days)	50% (30 days)
Diabetes mellitus	30%	36%	11%	23%	17%	19%	17%	23%
LAD	40%	48%	48%	41%	34%	–	42%	53%
Lesion class B2/C‡	77%	63%	59%	78%	81%	–	56%	47%
Lesion length, mm	15.51	12.78	10.1	13.0	15.61	15.40	13.41	11.71
RD, mm	2.94	2.72	2.61	2.70	2.81	2.72	2.60	2.75
Angio. FU (%)	8-mo. (87%)	8-mo. (87%)	6-mo. (85%)	6-mo. (91%)	9-mo. (96%)§	9-mo. (88%)	6-mo. (96%)	9-mo. (100%)
LLL, mm (in-stent)	0.15	0.12	0.10	0.12	0.22	0.20	0.10	0.05
ABR (in-segment)	0%	6.2%	0%	3.4%	2.1%	1.1%	2.3%	0%
Clinical FU (%)	1-yr (100%)	1-yr (99.6%)	1-yr (96.3%)	1-yr (99.1%)	1-yr (99.3%)	1-yr (100%)	6-mo. (100%)	1-yr (100%)
MACE◊	0%	6%	15.4%	2.7%	8.7%	1%	2.2%	10%
TLR	0%	5.2%	7.7%	2.7%	0.7%	1%	1.1%	6.7%
ST (ARC def./prob.)	0%	0.4%	0%	0%	0%	1%	0%	0%

*Number of patients (lesions) allocated in the corresponding device group in randomised trials with active control group. ¶For stents with nominal diameters ≤3.0 mm. ‡According to the modified American College of Cardiology/American Heart Association classification. §Pre-specified subset with late angiographic follow-up. ◊May also represent a similar composite endpoint. ABR: angiographic binary restenosis; ARC: Academic Research Consortium; FU: follow-up; MACE: major adverse cardiac (or clinical) events; RD: reference diameter; ST: stent thrombosis; TLR: target lesion revascularisation

with everolimus- and sirolimus-eluting stents reported in phase I and phase II studies (0.05-0.22 mm)[5,7-11,14-16] **(Table 5)**. In the first-in-human meriT-1 trial, there were no cases of binary restenosis reported at angio follow-up (26/30)[11]. However, restenosis rates were higher in meriT-2 (in-stent 4.9%, in-segment 6.2%) and directly associated with new revascularisation procedures (TLR 5.2%). A possible explanation may be found in the relatively high prevalence of diabetics in our population (36%), as TLR rates were numerically higher among this subset (8.8%). A similar trend has been demonstrated with first-generation SES and also with new-generation DES systems[26,27]. Overall, diabetes has historically been determined to be a major predictor of PCI failure, including ST[28,29].

Recent studies have suggested improved long-term safety associated with DES with a biodegradable polymer versus first-generation DES with a durable polymer[30,31]. However, whether this advantage would be superior to the newer-generation DES with durable polymers remains unclear. In the NEXT (NOBORI Biolimus-Eluting Versus XIENCE/PROMUS Everolimus-Eluting Stent Trial) trial, there were similar rates of death or MI (9.9% versus 10.3%, p=0.7) and target lesion revascularisation (7.4% versus 7.1%, p=0.8) at three years, when comparing biolimus-eluting stents with a biodegradable polymer versus everolimus-eluting stents with a durable polymer, respectively. Overall, the biocompatibility of the drug carriers used in DES systems has been demonstrated to impact significantly on their long-term performance. Polymer components, particularly those used in first-generation DES, may cause negative effects on vessel healing due to local inflammation and toxicity, which could lead to proliferative and thrombogenic responses[32]. Importantly, despite the unequivocal superiority of new-generation DES over first-generation DES in terms of biocompatibility and clinical outcomes, late and very late events may still occur[33,34]. Therefore, biodegradable polymer-based DES could offer, at least theoretically, additional advantages, such as avoiding the problems related to permanent polymeric residue (chronic inflammation and local toxicity over time), optimising vascular healing, potentially at an earlier stage, minimising the dependence on prolonged dual antiplatelet therapy and reducing bleeding events (without compromising safety, while maintaining efficacy in inhibiting NIH). Of note is the fact that a different clinical impact may be seen among the various DES systems with biodegradable polymer, as they vary greatly in terms of stent design, strut thickness, polymer type and degradation, and drug release, all components that have been shown to impact significantly on late and very late performance. In meriT-2, there were no safety concerns, and only one case of definite/probable ST reported. Nevertheless, larger comparative studies are needed to assess the impact of the BioMime SES technology with ultra-thin struts in comparison to contemporary new-generation DES with highly biocompatible durable polymers[35].

Limitations

A few limitations must be acknowledged in our study. First, the patient population mostly comprised patients with stable coronary artery disease or low-risk acute coronary syndrome. Therefore, caution should be exercised in extrapolating our results to patients with acute MI or high-risk ACS. Second, this was a non-randomised single-arm evaluation without an active control group. Therefore, even though our findings suggest favourable outcomes in terms of performance, safety and efficacy in a relatively large population with a representative prevalence of several high-risk subsets (diabetics, small vessels, complex lesions, total occlusions, etc.), no direct comparison can be drawn related to current "gold-standard" new-generation DES. In this regard, the randomised meriT-V trial comparing BioMime SES versus XIENCE EES (www.clinicaltrials.gov: NCT02112981) is currently recruiting patients. Third, one-year follow-up may be a relatively short time period for proper assessment of the long-term safety and efficacy of DES, as very late recurrences, including thrombotic events, may still occur after this time period, even with new-generation devices. Fourth, the sample size seemed appropriate for the evaluation of efficacy, using a surrogate endpoint of angiographic LLL (available in 87%), but is still limited for safety endpoints with a rare incidence, such as ST. Hence, larger trials with longer-term follow-up are warranted.

Conclusions

The novel BioMime SES with ultra-thin struts and a biodegradable polymer demonstrated a high procedural success rate, low late lumen loss (a surrogate of NIH), and sustained safety and efficacy up to 12 months in a relatively large patient population with a high prevalence of diabetes and multiple complex lesions treated at multiple clinical sites. Results from ongoing larger comparative studies are awaited.

Impact on daily practice

The BioMime SES is a novel DES technology, with ultra-thin struts and a biodegradable polymer which has demonstrated efficacy and sustained safety in the treatment of minimally selected patients with a relatively high prevalence of complex clinical and lesion characteristics. At eight-month angiographic follow-up, in-stent late lumen loss (the primary endpoint) was 0.12 mm. At 12-month clinical follow-up, cumulative rates for cardiac death and clinically indicated target lesion revascularisation were 0.8% and 4.8%, respectively. In addition, there was only one (0.4%) definite/probable stent thrombosis reported. Thus, in daily practice, the BioMime SES may offer an alternative for patients with an indication for percutaneous revascularisation procedures.

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Conflict of interest statement

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Impact of chronic lung disease after percutaneous coronary intervention in Japanese patients with acute coronary syndrome

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KEYWORDS

- acute coronary syndrome
- chronic lung disease
- chronic obstructive pulmonary disease
- percutaneous coronary intervention

Abstract

Aims: In Western countries, chronic lung disease (CLD) is a frequently encountered comorbidity in patients undergoing percutaneous coronary intervention (PCI). However, data are limited in Asians, where the prevalence of CLD is lower. We aimed to clarify the effects of CLD on in-hospital outcomes and discharge medications in ACS patients undergoing PCI in a multicentre registry.

Methods and results: We analysed 5,875 consecutive acute coronary syndrome patients undergoing PCI at 15 hospitals in Japan. Overall, 177 patients (3.0%) had CLD. The CLD patients were older, leaner, and had higher percentages of comorbidities. In-hospital mortality (7.3% vs. 3.8%, p=0.016) and post-PCI cardiogenic shock (7.9% vs. 3.0%, p<0.001) were higher in CLD patients; CLD was also an independent predictor of mortality after adjustment for baseline characteristics (OR 2.23; p=0.017). In-hospital cardiac deaths were not significantly different in the two groups; however, in-hospital non-cardiac deaths were significantly higher in the CLD group (3.4% vs. 2.8%, p=0.624, 4.0% vs. 1.0%, p<0.001, respectively). Notably, prescription rates of beta-blockers (65.5% vs. 73.1%, p=0.041) and statins (78.0% vs. 87.3%, p=0.049) were lower in CLD patients. Further, in a subgroup of ST-elevation myocardial infarction patients, door-to-balloon time (DBT) was longer in CLD patients (113 vs. 97.9 min, p=0.016), and CLD was an independent predictor of DBT >90 min (OR 3.05; p=0.002).

Conclusions: CLD was associated with high in-hospital mortality, post-PCI cardiogenic shock, and low adherence to performance indicators in patients undergoing PCI in Japan. Clinical attention is needed, given the increasing numbers of PCI patients with pulmonary conditions.

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Abbreviations

ACS	acute coronary syndrome
CLD	chronic lung disease
COPD	chronic obstructive pulmonary disease
DBT	door-to-balloon time
JCD	Japanese Cardiovascular Database
NCDR	National Cardiovascular Data Registry
PCI	percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction

Introduction

Chronic lung disease (CLD), including chronic obstructive pulmonary disease (COPD), chronic bronchitis, and emphysema, is a common comorbidity in coronary artery disease patients undergoing percutaneous coronary intervention (PCI). CLD and coronary artery disease share a common and significant risk factor: tobacco smoking. COPD is known to increase the risk of cardiovascular disease two- to threefold[1,2]. Systemic inflammation is present in patients with moderate-to-severe airflow obstruction and is associated with an increased risk of cardiac injury[3]. The World Health Organization stated that COPD is the fourth leading cause of mortality worldwide, and it could become the third leading cause by 2030.

The prevalence of CLD is lower in East Asian countries. Previous studies from Japan showed that CLD was present in only 2.4% of ischaemic heart disease patients[4], which is comparatively low compared to Western studies (ranging from 6.0% to 13.9%)[5,6]. However, the prevalence of COPD continues to increase in Japan and in many Asian countries[7] due to increases in cigarette smoking, air pollution, and the ageing population. In Japan, CLD is currently the ninth cause of mortality but is not widely recognised as an important comorbidity in patients with ischaemic heart disease[8].

However, the prognostic impact of CLD in acute coronary syndrome (ACS) has not been thoroughly investigated. Therefore, we aimed to clarify the effects of CLD on in-hospital mortality, post-procedural complications, and discharge medications in ACS patients undergoing PCI in a multicentre registry.

Methods

The Japanese Cardiovascular Database (JCD) is a large, ongoing, multicentre prospective cohort study designed to collect clinical background and outcome data on PCI patients. Data pertaining to approximately 150 variables are being collected. Participating hospitals were instructed to record data from hospital visits for consecutive PCI patients and to register these data in an internet-based database. The database system performs checks to ensure that the reported data are complete and internally consistent. PCIs performed using any coronary devices may be included.

The decision to perform PCI is made according to the attending physician's clinical assessments; the study does not mandate specific interventional or surgical techniques, such as vascular access, or the use of a specific stent or closure device. The majority of the clinical variables in the JCD were defined according to the National Cardiovascular Data Registry (NCDR), sponsored by the American College of Cardiology, to conduct comparative research and determine the factors which lead to disparities in PCI management[9,10].

In this study, all 5,875 consecutive ACS patients who underwent PCI from September 2008 to March 2014 in 15 Japanese hospitals participating in the JCD were included **(Figure 1)**. ACS was used to describe ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction, and unstable angina. STEMI was defined as myocardial infarction with ST elevation[9-11]. For the present analysis, the ACS patients were divided into two groups, the CLD group and the non-CLD group, and we assessed the baseline characteristics and in-hospital mortality and complications after PCI. CLD was identified by the trained clinical research coordinators when one or more of the following criteria were met: 1) information on CLD status (COPD, chronic bronchitis, emphysema) was obtained in a medical chart review; 2) forced expiratory volume in one second/forced vital capacity <70% on spirometry[12]; or (3) current use of bronchodilators prior to PCI. This definition was consistent with that of the NCDR. If there were any inconsistencies in the medical records, the local site investigator and/or a primary investigator (S. Kohsaka or I. Ueda) made the final judgement. In Japan, unlike in other countries, COPD is diagnosed using spirometry[13]. Patients with asthma or seasonal allergies were not considered to have chronic lung disease.

In the subgroup of patients with STEMI, we investigated the door-to-balloon time (DBT) of 1,725 STEMI patients who arrived at hospital with symptoms for less than 12 hours. The DBT was defined as the time from initial arrival at the PCI facility to the first balloon inflation of the culprit artery. In this sub-analysis, we excluded patients with a DBT over 240 minutes and culprit lesions of >2 arteries and transfer patients from other hospitals who underwent PCI from all the STEMI patients. We excluded patients with a DBT >240 minutes because they presumably did not receive PCI as a primary reperfusion strategy. We excluded patients with >2 culprit arteries since multiple culprit arteries affected DBT.

The study endpoints included in-hospital mortality, heart failure, cardiogenic shock, and other complications. Complications were

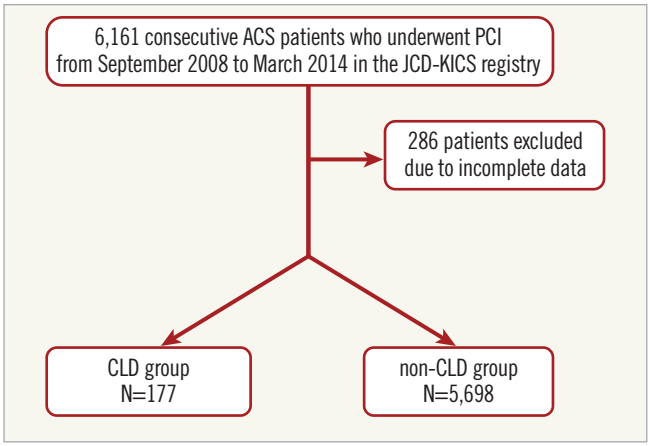

Figure 1. *Patient flow chart. JCD-KICS: Japan Cardiovascular Database-Keio Interhospital Cardiovascular Studies*

defined as a composite endpoint of severe dissection or coronary perforation, myocardial infarction after PCI, cardiogenic shock or heart failure, cerebral bleeding or stroke, and bleeding complications. Bleeding complications were defined as those requiring transfusion, prolonging hospital stay, and/or causing a decrease in haemoglobin of >3.0 g/dl[14]. Further, bleeding complications were subdivided into puncture-site bleeding, retroperitoneal bleeding, gastrointestinal bleeding, genitourinary bleeding, or other bleeding.

Statistical analysis

Continuous variables are expressed as means and standard deviations, and categorical variables are expressed as percentages. Continuous variables were compared using the Student's t-test, and differences between categorical variables were examined using a χ^2 test. Comparisons between groups were carried out with analysis of variance using general linear models. A multivariate logistic regression analysis was performed to determine the independent predictors of in-hospital mortality, in-hospital non-cardiac mortality and DBT >90 minutes for STEMI patients. Univariate logistic regression analysis was performed, and factors with a p-value <0.10 were included in the multivariate analysis. The covariates of univariate analysis for multivariate analysis were: female, previous myocardial infarction, previous heart failure, diabetes mellitus, diabetes mellitus with insulin, dialysis, cerebrovascular disease, peripheral artery disease, CLD, hypertension, cigarette smoking, dyslipidaemia, previous PCI, previous coronary bypass, cardiogenic shock at admission, cardiopulmonary arrest at admission, heart failure at admission, left main trunk stenosis, bifurcation lesion, type C lesion, STEMI, age >80, and BMI <21.6. All statistical calculations and analyses were performed using SPSS, Version 22 (IBM Corp., Armonk, NY, USA), and p-values <0.05 were considered statistically significant.

Results

Of 5,875 ACS patients, 177 (3.0%) had CLD **(Figure 1)**. The CLD patients were older and leaner than the non-CLD patients. Moreover, the CLD patients had a higher percentage of comorbidities, such as history of heart failure, cerebrovascular disease, peripheral artery disease, and heart failure symptoms on admission. Angiographically, the CLD group had a higher proportion of left main trunk stenosis and a lower proportion of three-vessel disease than the non-CLD group. The CLD group had a smaller proportion of STEMI patients than the non-CLD group; the two groups had similar incidences of cardiogenic shock on admission **(Table 1)**.

The post-PCI complication rate was significantly higher in the CLD group than in the non-CLD group; moreover, incidences of in-hospital death and post-procedural cardiogenic shock were significantly higher in the CLD group than in the non-CLD group. Cardiac death rates were not significantly different between the two groups. However, non-cardiac deaths occurred more frequently in the CLD group than in the non-CLD group. Pulmonary-related and neurologically related deaths were significantly higher in the CLD group **(Table 2)**. The results of the multivariable regression analysis are shown in **Table 3**. After adjustment for differences in the baseline comorbidities, CLD was found to be an independent predictor of in-hospital mortality (odds ratio [OR] 2.23, confidence interval [CI]: 1.16-4.29, p=0.017), and non-cardiac in-hospital mortality (OR 3.50, CI: 1.48-8.30, p=0.004).

Table 1. Baseline characteristics and procedural information.

	Chronic lung disease group n=177 (%)	Non-chronic lung disease group n=5,698 (%)	*p*-value
Age, years	73.6±7.8	67.2±12.0	<0.001
Age >80	43 (24.3)	907 (15.9)	0.003
Female	23 (13.0)	1,262 (22.1)	0.004
Previous myocardial infarction	27 (15.3)	861 (15.1)	0.958
Previous heart failure	21 (11.9)	330 (5.8)	0.001
Diabetes mellitus	59 (33.3)	2,130 (37.4)	0.273
Diabetes mellitus with insulin	16 (9.0)	365 (6.4)	0.175
Dialysis	5 (2.8)	220 (3.9)	0.479
Cerebrovascular disease	29 (16.4)	468 (8.2)	<0.001
Peripheral artery disease	22 (12.4)	310 (5.4)	<0.001
Hypertension	130 (73.4)	4,074 (71.5)	0.572
Smoking	78 (44.1)	2,246 (39.4)	0.213
Dyslipidaemia	106 (59.9)	3,525 (61.9)	0.594
Previous percutaneous coronary intervention	43 (24.3)	1,109 (19.5)	0.111
Previous coronary bypass	6 (3.4)	207 (3.6)	0.865
Heart failure on admission	40 (22.6)	865 (15.2)	0.007
Cardiogenic shock on admission	11 (6.2)	433 (7.6)	0.493
Cardiopulmonary arrest on admission	5 (2.8)	254 (4.5)	0.297
Left main trunk stenosis	13 (7.3)	240 (4.2)	0.043
2-vessel disease	58 (32.8)	1,829 (32.1)	0.851
3-vessel disease	27 (15.3)	1,253 (22.0)	0.033
Bifurcation lesion	52 (29.4)	1,559 (27.4)	0.553
Type C lesion	47 (26.6)	1,545 (27.1)	0.869
Intra-aortic balloon pump	28 (15.8)	745 (13.1)	0.398
Before procedure insertion of intra-aortic balloon pump	5 (2.8)	144 (2.5)	0.804
During/after procedure insertion of intra-aortic balloon pump	23 (13.0)	620 (10.9)	0.375
Radial artery approach	51 (28.8)	1,459 (25.6)	0.336
ST-elevation myocardial infarction	75 (42.4)	2,859 (50.2)	0.041
Balloon angioplasty	24 (13.6)	674 (11.8)	0.483
Bare metal stent	48 (27.1)	1,568 (27.5)	0.907
Drug-eluting stent	104 (58.8)	3,388 (59.5)	0.851
Rotablator	3 (1.7)	58 (1.0)	0.382
Body mass index	22.7±3.2	24.0±3.7	<0.001

Table 2. In-hospital mortality and complications, and discharge medications.

	Chronic lung disease group n=177 (%)	Non-chronic lung disease group n=5,698 (%)	*p*-value
All complications	34 (19.2)	754 (13.2)	0.022
Coronary dissection	3 (1.7)	56 (1.0)	0.349
Coronary perforation	2 (1.1)	41 (0.7)	0.528
Myocardial infarction	2 (1.1)	102 (1.8)	0.512
Cardiogenic shock	14 (7.9)	172 (3.0)	<0.001
Heart failure	7 (4.0)	189 (3.3)	0.642
Cerebral infarction	1 (0.5)	30 (0.5)	0.945
Intracranial haemorrhage	0 (0)	5 (0.1)	0.693
Cardiac tamponade	0 (0)	30 (0.5)	0.333
Dialysis	1 (0.5)	110 (1.9)	0.189
Transfusion	9 (5.1)	214 (3.8)	0.362
Bleeding all	12 (6.8)	247 (4.3)	0.119
Puncture-site bleeding	3 (1.7)	65 (1.1)	0.497
Haematoma	0 (0)	51 (0.9)	0.206
Peritoneal bleeding	0 (0)	8 (0.1)	0.618
Gastrointestinal bleeding	2 (1.1)	36 (0.6)	0.416
Genitourinary bleeding	2 (1.1)	11 (0.2)	0.009
Other bleeding	7 (4.0)	112 (2.0)	0.064
In-hospital mortality	13 (7.3)	216 (3.8)	0.016
Cardiac causes	6 (3.4)	158 (2.8)	0.624
Non-cardiac causes	7 (4.0)	58 (1.0)	<0.001
Pulmonary causes	3 (1.7)	9 (0.2)	<0.001
Infectious causes	0 (0)	9 (0.2)	0.597
Nephrological causes	0 (0)	8 (0.1)	0.618
Neurological causes	1 (0.5)	2 (0.03)	0.002
Vascular causes	0 (0)	7 (0.1)	0.641
Other causes	3 (1.7)	23 (0.4)	0.011
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker prescription at discharge	115 (65.0)	3,930 (69.0)	0.378
Beta-blocker prescription at discharge	116 (65.5)	4,168 (73.1)	0.041
Statin prescription at discharge	138 (78.0)	4,974 (87.3)	0.049

Further, CLD significantly impaired performance indicators such as medications on discharge and DBT in STEMI patients. Prescription rates of beta-blockers and statins on discharge were lower in the CLD group. In the subgroup analysis of STEMI patients, DBT was longer in the CLD group than in the non-CLD group (113 vs. 97.9 min, p=0.016). The clinical predictors of prolonged DBT are listed in **Table 4**. CLD was an independent predictor of DBT >90 min. In this subgroup analysis, CLD patients (N=43) had higher mortality rates than non-CLD patients (N=1,682; 11.6% vs. 4.9%, p=0.046). CLD patients indeed tended to have higher cardiac mortality rates than non-CLD patients (9.3% vs. 3.9%, p=0.072). The rates of non-cardiac death in patients with versus without CLD were not significantly different (2.3% vs. 1.0%, p=0.402). Furthermore, the proportion of patients with a DBT >90 min was significantly higher in the CLD group than in the non-CLD group (74.4% vs. 48.3%, p=0.001). Importantly, the patients with a DBT >90 min had higher mortality rates than those with a DTB ≤90 min (6.5% vs. 3.6%, p=0.006) and higher cardiac mortality rates (5.3% vs. 2.7%, p=0.006), but not higher non-cardiac mortality rates (1.2% vs. 0.9%, p=0.575).

Discussion

Although CLD was observed in only 3% of the Japanese PCI patients in a contemporary multicentre registry, we showed that it is an independent risk factor for in-hospital mortality in ACS patients, even after adjustment for confounding factors by multivariate analysis. Importantly, CLD was associated with high in-hospital mortality, especially due to non-cardiac causes.

Of note, the CLD prevalence was 3% in our study, which is consistent with other previous registry studies in Japan[4] and East Asia[15,16], and lower than that of ischaemic heart disease in Western countries (6.0%)[5]. Although pulmonary function tests were not mandated for all patients, this finding reflected real-world clinical practice. Since the prevalence of COPD may increase in Asian countries including Japan[7], COPD could worsen the in-hospital outcomes of patients with ACS.

Our study is in agreement with previous studies reporting the prognosis of coronary artery disease patients with CLD. Nishiyama et al concluded that COPD was an independent risk factor for long-term cardiac and cardiovascular mortality in patients with ischaemic heart disease after revascularisation (PCI or coronary artery bypass grafting)[4]. Another study revealed that myocardial infarction patients with COPD showed a significantly high one-year mortality rate, although the revascularisation rate in COPD patients was about 40%[5]. However, data on the relative impact on the short-term outcomes of acute cardiac conditions such as ACS and the cause of death remain unclear. In our study, in-hospital mortality (7.3% vs. 3.8%, p=0.016) was significantly higher in the CLD group than in the non-CLD group, and CLD was an independent predictor of in-hospital mortality after adjustment for baseline comorbidities (OR 2.23; p=0.017).

In recent years, studies have focused on performance indicators for optimised therapy. Some of the performance indicators in ACS patients include the application of reperfusion therapy within 12 hrs, DBT in STEMI patients, optimal medications including beta-blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and antiplatelet therapy[17]. Optimal medications could improve in-hospital events[18]. Although the present study and a previous study[19] demonstrated that CLD could affect DBT for STEMI patients as well as the use of beta-blockers and statins, we were unable to show that key performance indicators could affect in-hospital cardiac mortality. We suspected that a prolonged DBT for CLD-STEMI patients could cause a significantly

Table 3. Univariate and multivariate analysis for in-hospital mortality.

	Univariate		Multivariate	
Variable	**OR (CI)**	***p*-value**	**OR (CI)**	***p*-value**
Female	1.22 (0.90-1.66)	0.197		
Previous myocardial infarction	1.31 (0.94-1.85)	0.114		
Previous heart failure	4.54 (3.23-6.38)	<0.001	2.56 (1.68-3.91)	<0.001
Diabetes mellitus	1.36 (1.07-1.82)	0.014	1.29 (0.93-1.81)	0.29
Diabetes mellitus with insulin	1.63 (1.05-2.54)	0.029	0.72 (0.40-1.30)	0.277
Dialysis	4.21 (2.80-6.35)	<0.001	5.23 (3.10-8.84)	<0.001
Cerebrovascular disease	2.33 (1.63-3.33)	<0.001	1.85 (1.22-2.80)	0.004
Peripheral artery disease	1.83 (1.16-2.88)	0.008	0.92 (0.54-1.57)	0.749
Chronic lung disease	2.01 (1.13-3.60)	0.016	2.23 (1.16-4.29)	0.017
Hypertension	0.94 (0.70-1.25)	0.668		
Smoking	0.680 (0.51-0.90)	0.007	0.84 (0.61-1.17)	0.312
Dyslipidaemia	0.44 (0.34-0.57)	<0.001	0.53 (0.39-0.72)	<0.001
Previous percutaneous coronary intervention	0.95 (0.67-1.33)	0.747		
Previous coronary bypass	1.50 (0.82-2.72)	0.182		
Cardiogenic shock at admission	14.1 (10.6-18.7)	<0.001	3.99 (2.64-6.04)	<0.001
Cardiopulmonary arrest at admission	14.5 (10.6-19.8)	<0.001	5.52 (3.46-8.80)	<0.001
Heart failure at admission	4.66 (3.55-6.12)	<0.001	2.47 (1.78-3.41)	<0.001
Left main trunk stenosis	5.03 (3.46-7.30)	<0.001	2.29 (1.44-3.64)	<0.001
3-vessel disease	1.61 (1.21-2.15)	0.001	1.25 (0.90-1.74)	0.190
Bifurcation lesion	1.15 (0.86-1.53)	0.348		
Type C lesion	1.97 (1.50-2.57)	<0.001	1.48 (1.08-2.02)	0.014
ST-elevation myocardial infarction	2.40 (1.80-3.20)	<0.001	2.19 (1.55-3.10)	<0.001
Age >80	2.94 (2.23-3.90)	<0.001	2.43 (1.71-3.44)	<0.001
BMI <21.6	2.03 (1.55-2.67)	<0.001	1.35 (0.98-1.87)	0.071

Table 4. Multivariate analysis for door-to-balloon time >90 min in the subgroup analysis of ST-elevation myocardial infarction patients.

	Multivariate	
Variable	**OR (CI)**	***p*-value**
Women	1.13 (0.88-1.46)	0.330
Age >80	1.27 (0.94-1.71)	0.124
Previous percutaneous coronary intervention	1.77 (1.11-2.82)	0.017
Previous coronary bypass	2.07 (0.79-5.45)	0.139
Previous myocardial infarction	0.79 (0.49-1.28)	0.343
Previous heart failure	1.06 (0.59-1.92)	0.851
Diabetes mellitus	1.20 (0.96-1.51)	0.112
Diabetes mellitus with insulin	1.11 (0.63-1.96)	0.730
Hypertension	1.04 (0.85-1.28)	0.700
Smoker	0.89 (0.72-1.09)	0.260
Peripheral artery disease	1.66 (0.96-2.87)	0.072
Heart failure at admission	1.50 (1.11-2.01)	0.007
Intra-aortic balloon pump	1.12 (0.86-1.45)	0.391
Left main trunk stenosis	1.71 (0.67-4.38)	0.264
Type C lesion	1.14 (0.90-1.44)	0.278
Chronic lung disease	3.09 (1.53-6.25)	0.002

higher mortality rate and a trend towards a higher cardiac mortality rate; however, we could not definitively state that this would affect all CLD patients.

Previous studies investigated the reason why optimal medications were not prescribed[20], and this was true even in our study. There is a concern that beta-blocker therapy may produce life-threatening bronchial constriction in COPD patients. In our study, a high rate of cardiogenic shock after PCI was another reason for the low prescription rate of beta-blockers. On the other hand, the reason for the low prescription rate of statins in CLD remains unclear. Statins have previously been shown to provide beneficial effects in COPD as well as ACS patients[21,22].

Bronchial inflammation and elevated C-reactive protein levels are associated with an increased risk of cardiac injury[3] and play a role in plaque formation and rupture[23]. Hypoxia and increased work of breathing can worsen cardiac ischaemia and arrhythmia[24]. A previous study reported the incidence of cardiogenic shock after PCI in STEMI patients[25]. Wakabayashi et al speculated that left ventricular dysfunction might cause an increase in the right ventricular overload owing to hypoxia and pulmonary vasoconstriction. Therefore, pulmonary hypertension might have impaired systemic circulation in our patients as well. In our study, the CLD group had

a higher rate of cardiogenic shock after PCI, even though the complication rates and intra-aortic balloon pump insertion rates were similar between the groups. These burdens on the heart might be the reason for the high rates of cardiogenic shock. Man et al also showed that elevated C-reactive protein levels in COPD patients were associated with cardiovascular events including stroke[26], and another study showed an association between inflammation in COPD patients and myocardial infarction and pneumonia[27].

A higher in-hospital non-cardiac mortality rate was observed in the CLD group. Previous studies showed that COPD was an independent predictor of in-hospital non-cardiac death for heart failure patients[28,29]. Another study revealed that patients with ACS and a lower BMI had a higher proportion of COPD and a higher non-cardiac death rate[30]. However, to the best of our knowledge, no data have shown that COPD was an independent predictor of in-hospital non-cardiac death for patients with ACS who underwent PCI. Although we performed a multivariate logistic regression analysis to adjust for possible confounding variables, the heterogeneity of the CLD patients, such as lower BMI and higher age, may have affected the non-cardiac in-hospital mortality rate as shown in a previous study[30] , and we could not account for all confounding factors.

Despite the existence of confounding factors, we believe that the higher non-cardiac in-hospital mortality rate of CLD patients requires clinical attention. To prevent comorbidities, CLD patients need early cardiac rehabilitation, which is effective for acute myocardial infarction patients[31], to avoid bed rest, and to increase their physical activity[32]. A previous report showed that transradial PCI could facilitate early rehabilitation for elderly patients with acute myocardial infarction[33] and might have a beneficial effect for CLD patients.

Limitations

There were several limitations in this study. First, pulmonary function tests and interventional therapy for CLD were not performed in our study. In previous studies, the severity of COPD was a predictor of long-term mortality[6]; however, we could not investigate the relationship between the severity of CLD and in-hospital mortality. A previous study revealed that corticosteroid inhalation could reduce bronchial inflammation and ischaemic cardiac events[34]; however, this study did not include data on the use of corticosteroid inhalation therapy. Although pulmonary function tests were not mandated for all patients, our findings reflected real-world clinical practice. Second, we did not examine the symptoms in all patients. Diagnosis delay could not be calculated because of atypical presentations, which might be one of the reasons for a longer DBT in STEMI patients with CLD. Third, this analysis was performed on registered PCI patients, and therefore the ACS population without PCI was not investigated. It is possible that a portion of the CLD patients may not have been treated conservatively without PCI[19], but, given the high percentage of an invasive strategy that is applied to ACS patients in Japan (97.2% of all STEMI patients underwent PCI in the J-AMI registry)[35], the percentage of conservatively treated patients was probably low. Finally, since we did not have post-PCI prescription rate data, we could not include beta-blockers in our multivariate analysis of in-hospital mortality.

Conclusions

In conclusion, CLD is observed in 3% of Japanese ACS patients and should be recognised as a significant risk factor for in-hospital mortality and complications. Higher incidences of non-cardiac deaths might be the reasons for the poor prognosis of CLD. Clinical attention is needed, given the increasing number of PCI patients with multiple comorbidities including pulmonary conditions.

Impact on daily practice

Although CLD prevalence was 3% in this contemporary PCI multicentre Japanese registry, it should be recognised as a significant risk factor for in-hospital mortality and morbidity. Higher incidences of non-cardiac deaths deserve clinical attention.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Distribution characteristics of coronary calcification and its substantial impact on stent expansion: an optical coherence tomography study

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KEYWORDS

- cobalt-chromium stent
- coronary artery disease
- optical coherence tomography

Abstract

Aims: The aim of this study was to evaluate the spatial distribution and magnitude of coronary calcification and to investigate the relationship between measurable components of calcification and stent expansion.

Methods and results: Quantitative OCT analysis was performed in 66 consecutive patients who were successfully treated with OCT-evaluated stenting. Three representative measurements of calcium deposit, including thickness, arc, and depth (distance between lumen surface and calcium), as well as lumen and stent dimensions were assessed and compared. In our study, coronary calcification was detected in 66.7% of patients. The distribution of depth indicated that superficial calcium predominantly existed (mainly located within 0.010 mm from the intima). A positive correlation was observed between thickness and arc ($p<0.05$, $r=0.303$), and negative correlations were found between depth and thickness ($p<0.0001$, $r=-0.548$) and depth and arc ($p<0.005$, $r=-0.444$). Among the measurements of calcifications, depth positively correlated with relative stent expansion ($p=0.0051$, $r=0.406$), whereas thickness and arc did not.

Conclusions: Superficiality is most important for the assessment of coronary calcification, which is associated with the size of coronary calcification (arc and thickness) as well as expandability by stenting procedures. OCT, which allows accurate evaluation of coronary calcification, may be useful for the prediction of the resultant stent expansion of calcified lesions.

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Introduction

According to previous studies, the presence of coronary calcification was associated with worse clinical outcomes due to plaque fracture after angioplasty[1] and stent underexpansion[2]. It remained the biggest issue even after the emergence of drug-eluting stents (DES)[3-6]. Intravascular ultrasound (IVUS) played an important role in the evaluation of coronary calcification during percutaneous coronary intervention (PCI). However, due to limited resolution and inevitable artefacts such as acoustic shadowing and side lobes, only the arc or the "approximate" degree of superficiality of coronary calcifications could be assessed[3,7]. Currently, optical coherence tomography (OCT), another intravascular imaging technique with a higher spatial resolution, has become applicable in the clinical setting. It can visualise and delineate coronary calcification without attenuation or side lobe artefacts[8,9]. Thus, unlike IVUS, we can measure thickness, depth and the arc of the cluster of calcium as well as accurate luminal dimensions[10] using this modality. Considering such performance and superiority[11,12], detailed investigations regarding coronary calcification and its substantial impact on lumen expansion by PCI can be performed and have been demanded. Therefore, the present study was designed to: 1) evaluate geographic and morphological features of coronary calcification, and 2) investigate the relationship between measurable components of calcification and stent expansion in a consecutive series of patients. The results obtained will give us new insights into coronary calcification and vessel expansion.

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Methods

STUDY POPULATION

From August 2011 to May 2013, a total of 818 PCI procedures were performed at our institution. From these, 68 patients who underwent coronary stenting of the native coronary artery as well as OCT evaluation before and after stenting, were consecutively recruited. All patients underwent PCI without IVUS guidance according to the operators' own judgement. Since the purpose was to evaluate the adverse impact of coronary calcification on stent expansion by conventional PCI, two patients who underwent rotational atherectomy before stenting were excluded from the analysis. Three patients underwent OCT-evaluated stenting for two coronary vessels. Thus, 69 lesions were included in the present study.

Patient characteristics, and pre- and post-procedure characteristics were recorded for analysis. Chronic kidney disease was defined by an estimated glomerular filtration rate (eGFR) <60 ml/min^{-1}/1.73 m^{-2}. eGFR was calculated by the Modification of Diet in Renal Disease equation[13], with coefficients modified for Japanese patients as follows: eGFR (ml/min^{-1}/1.73 m^{-2})=194×Cr$^{-1.094}$×age$^{-0.287}$ (×0.739 if female).

OCT IMAGING AND STENTING PROTOCOLS

The C7 XR™ imaging system with the C7 Dragonfly™ imaging catheter (St. Jude Medical, St. Paul, MN, USA) was used in the present study. The imaging catheter was carefully advanced distal to the culprit lesion under fluoroscopic guidance just before PCI. In case the imaging catheter did not cross the target lesion, predilatation using a 1.5 mm balloon and intracoronary nicorandil or isosorbide dinitrate was given. Contrast media was flushed continuously through the guiding catheter during image acquisition, and motorised pullback OCT imaging was performed at a pullback rate of 20 mm/s throughout the lesion. At the discretion of the operator, type of stent, adequate stent diameter, adequate stent length and the endpoint of post-dilation were determined by angiography and OCT imaging. Number of stents, diameter, stent, maximum balloon diameter, maximum inflation pressure and non-compliant balloon usage were recorded. In the present study, the operator made an effort to expand the stent(s) by using a non-compliant balloon when the minimal stent area (MSA) was under 5.0 mm^2, which was a functional threshold for the prediction of DES restenosis[14].

QUANTITATIVE ANGIOGRAPHY

Serial quantitative coronary angiography (QCA) was obtained at pre- and post-intervention assessment. The target lesion was analysed using QCA on a QCA-CMS system, version 7.1 (Medis medical imaging systems bv, Leiden, The Netherlands). Using the external diameter of the contrast-filled guiding catheter as the calibration standard, % diameter stenosis was calculated as minimal lumen diameter divided by the reference diameter.

QUANTITATIVE OCT ANALYSIS

OCT analysis was performed using LightLab OCT imaging proprietary software (LightLab Imaging/St. Jude Medical, Westford, MA, USA) by an independent observer. The assessment range of pre- and post-procedural OCT images was from 5 mm proximal margin to 5 mm distal margin of the stent zone and the corresponding segment to the stent zone prior to stenting. Cross-sectional image analyses by OCT were performed using the measurement software echoPlaque 4 system (INDEC Medical Systems, Santa Clara, CA, USA) as in previous reports[15]. Quantitative OCT analyses included minimal lumen area (MLA), external elastic membrane area (EEMA) at the MLA site, lumen, plaque burden ([EEMA minus lumen] divided by EEMA), minimal stent diameter (MSD) and MSA. Manufacturer-predicted stent diameters and area were derived from the manufacturers' compliance charts. Coronary calcification was defined as a signal-poor or heterogeneous region with a sharply delineated border[16]. In patients with coronary calcification, quantitative assessment of coronary calcification focused on minimum depth (distance from the intima to the surface of calcification), largest arc, and maximum thickness of coronary calcification **(Figure 1)**. In cases with multiple coronary calcifications, the largest coronary calcification was exclusively selected for the analyses. Stent expansion was evaluated in various ways, including relative stent expansion, absolute stent expansion and stent symmetry index. In the present study, it was sometimes difficult to evaluate the reference lumen diameter from the OCT images because of attenuation or limitation of the penetration depth. In addition, all EEMAs could be evaluated at the MSA site. For our purpose, for simple evaluation, relative stent expansion was defined as MSA divided by EEMA at the MSA site. Axial stent symmetry was calculated as the

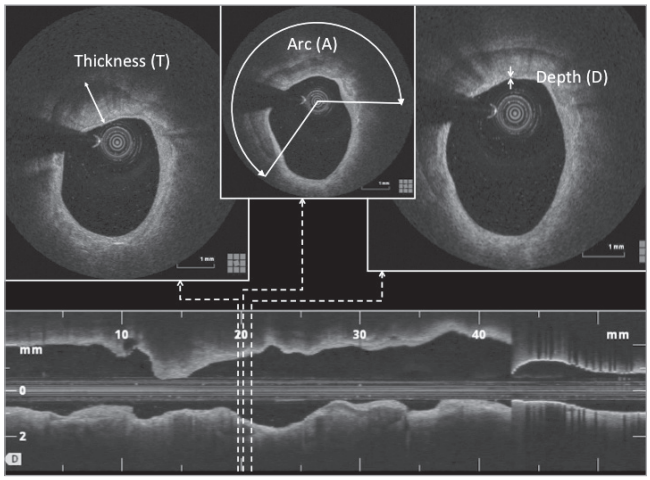

Figure 1. *Quantitative assessment of calcification. A: the arc of coronary calcification; D: the distance from intima to calcification surface; T: thickness of coronary calcification*

minimum stent diameter divided by the maximum stent diameter[17]. Because the difference of MSA was small between IVUS assessment and OCT assessment[10], the absolute stent expansion in the present OCT study was defined as an MSA of over 5.0 mm^2, which was previously reported as a functional threshold for the prediction of DES restenosis from IVUS assessment[14]. Furthermore, malapposition, defined as the axial distance between the strut's surface and the luminal surface, was greater than the strut thickness.

STATISTICAL ANALYSIS

All data were statistically analysed using GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) and are presented as means±standard deviation, or as medians (25th and 75th percentiles) when the distribution was non-normal. Continuous variables were compared by the unpaired Student's t-test or Mann-Whitney U test. Categorical variables were compared using Fisher's exact test. Correlations between variables were analysed by Spearman's rank correlation coefficient. Statistical comparisons among four groups were performed by one-way analysis of variance (ANOVA) and *post hoc* multiple comparison using Tukey's test. Values of $p<0.05$ were considered significant.

Results

INCIDENCE OF CORONARY CALCIFICATION AND UNDERLYING PATIENT AND LESION CHARACTERISTICS

Coronary calcification, as defined in this study, was detected in 46 cases out of 69 lesions (66.7%). We divided the cases by prevalence of coronary calcification into two groups and compared patient and lesion characteristics between the two groups (with coronary calcification versus without coronary calcification) **(Table 1)**. The mean age of the patient population was 68 years and the majority of the patients were male. Patients with coronary calcification had a lower prevalence of acute coronary syndrome and dyslipidaemia than patients without coronary calcification. Coronary calcification

Table 1. Baseline characteristics of the patients.

	Without CC (n=23)	With CC (n=43)	*p*-value
Age, years	68±11	68±10	0.89
Male, n (%)	19 (82.6)	32 (74.4)	1.0
MI or UAP, n (%)	10 (43.5)	6 (14.0)	0.017
Multivessel disease, n (%)	11 (47.8)	28 (65.1)	0.20
Hypertension, n (%)	19 (82.6)	35 (81.4)	1.00
Dyslipidaemia, n (%)	21 (91.3)	28 (65.1)	0.036
Diabetes mellitus, n (%)	6 (26.1)	18 (41.9)	0.28
CKD, n (%)	6 (26.1)	10 (23.3)	1.0
Current smoker, n (%)	5 (21.7)	5 (11.6)	0.30
Angiographic findings			
LAD/LCX/RCA, n	10/0/13	32/3/11	0.017
Reference diameter, mm	2.5±0.6	2.5±0.6	0.73
MLD, mm	0.4±0.2	0.5±0.2	0.15
% diameter stenosis	86.2±8.0	80.8±8.4	0.013
ACC/AHA class (B2, C), n	22	42	0.66
OCT findings			
MLA, mm^2	1.07 [0.79-1.45]	1.64 [1.26-2.18]	0.0064
EEMA at MLA site, mm^2*	11.1±3.7	10.9±3.1	0.76
Plaque burden,% *	88.9 [86.3-91.9]	83.2±6.3	0.0066

All variable data are presented as mean±standard deviation, or as medians (25th and 75th percentiles) when the distribution was non-normal. *Four lesions with calcified nodules were excluded from analysis for EEMA at the MLA site and plaque burden because of poorly delineated borders of EEMA. CC: coronary calcification; CKD: chronic kidney disease; EEMA: external elastic membrane area; LAD: left anterior descending artery; LCX: left circumflex artery; MI: myocardial infarction; MLA: minimal lumen area; MLD: minimal lumen diameter; OCT: optical coherence tomography; RCA: right coronary artery; UAP: unstable angina

was predominantly observed in the left anterior descending artery. There were significant differences in some quantitative parameters, including % diameter stenosis and MLA. Lesions with coronary calcification had less plaque burden and larger MLA compared with those without coronary calcification.

DETAILED ASSESSMENT OF CORONARY CALCIFICATION

We measured thickness, arc, and depth of coronary calcification by quantitative assessment of OCT images **(Figure 1)**. **Figure 2** shows the distribution of these three representative parameters. Distribution types were different among the three parameters. Depth and arc demonstrated non-normal distribution, whereas thickness appeared to demonstrate mostly normal distribution. Distribution of depth indicated that superficial calcium predominantly existed (mainly located within 0.010 mm from the intima). The arc had wider variation compared to the other parameters: 30.4% were more than 180 degrees.

The relationship among these three parameters was investigated **(Figure 3)**. The depth of coronary calcification had a moderate negative correlation with the thickness of coronary calcification ($p<0.0001$, $r=-0.548$) and with the arc of coronary calcification ($p<0.005$, $r=-0.444$). A weak positive correlation was observed between the thickness of coronary calcification and the arc of coronary calcification ($p<0.05$, $r=0.303$).

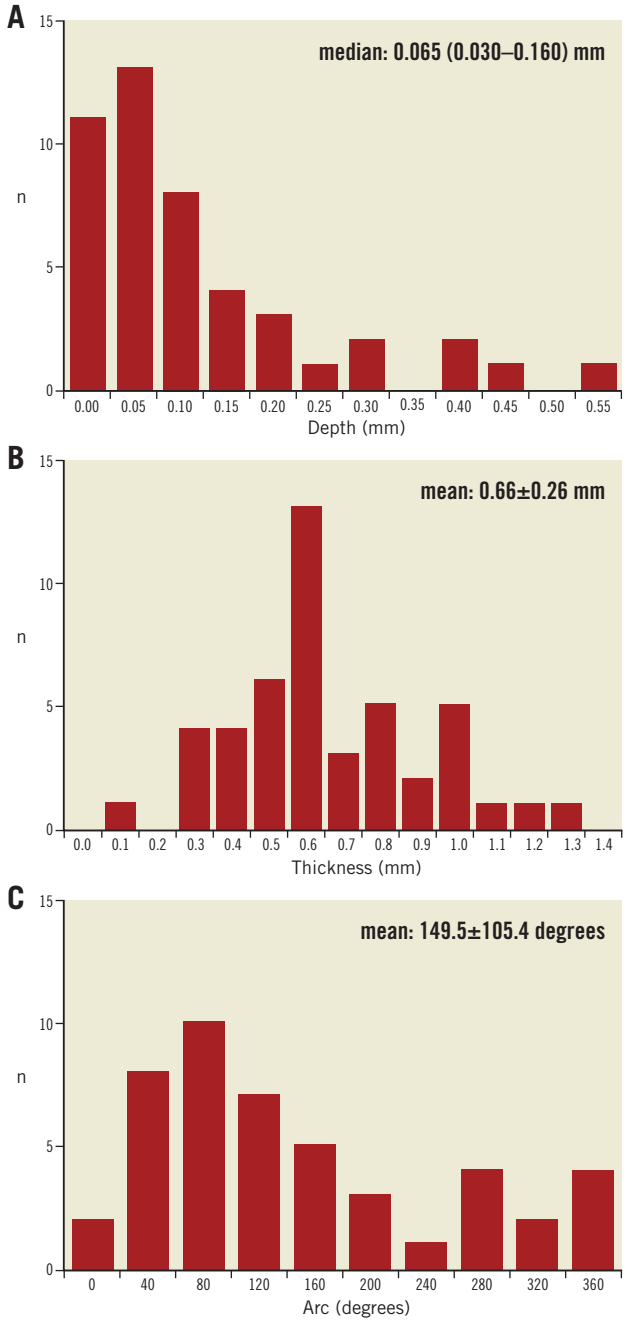

Figure 2. *Distribution of the three representative parameters of calcification in coronary arteries evaluated by OCT.*

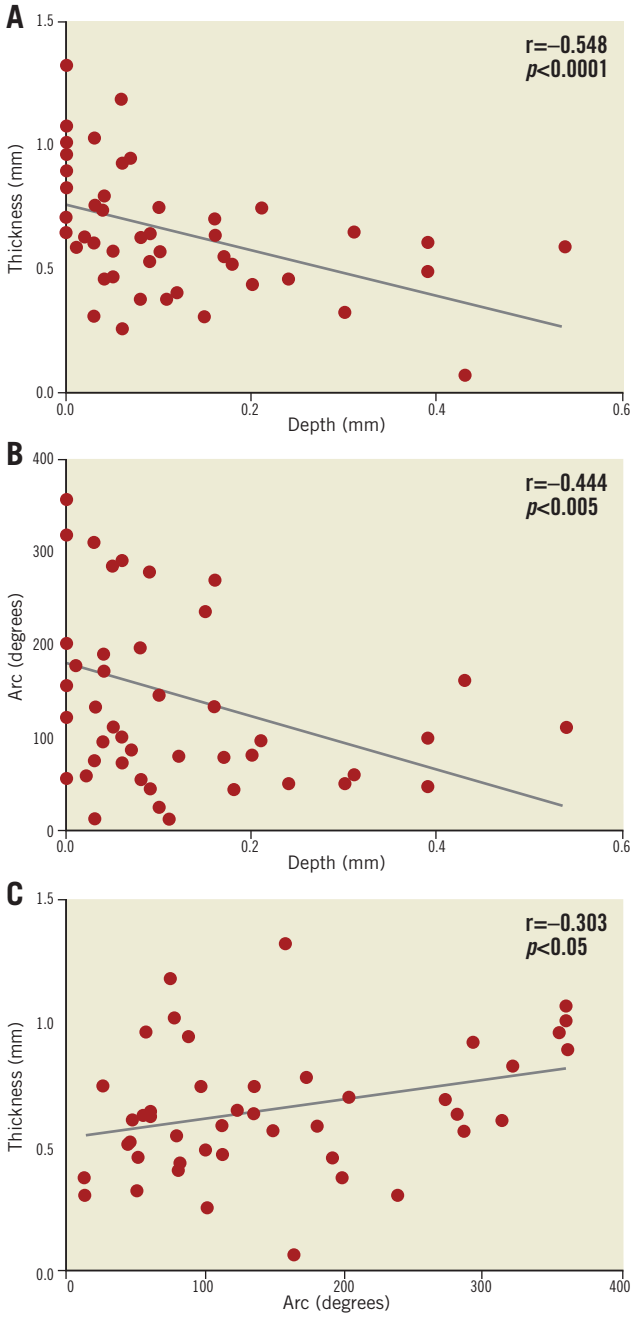

Figure 3. *Relationship between the three parameters of coronary calcification.*

IMPACT OF CORONARY CALCIFICATION ON STENT EXPANSION

Procedural characteristics and parameters of resultant expansion were compared between the two groups **(Table 2)**. Despite similarity in maximum balloon diameter and inflation pressure, the lesions with coronary calcification were more frequently treated with a non-compliant balloon. No significant differences were observed in the OCT-derived parameters of stent expansion except relative stent expansion, which tended to be smaller in those with coronary calcification.

Correlations among the three representative parameters of coronary calcification and relative stent expansion were investigated **(Figure 4)**. A positive correlation was observed between depth and relative stent expansion ($p<0.01$, $r=0.406$). However, no correlation was observed between the thickness and the arc and relative stent expansion.

The cases were categorised into three tertile groups by depth (T1: <0.04 mm, T2: 0.04-0.11 mm, T3: >0.11 mm) for further assessment. **Figure 5** demonstrates the comparison of relative stent expansion between each tertile category and the group without coronary calcification. Although no differences were observed in axial stent symmetry, relative stent expansion was different in each depth group. The shallowest group (T1) had significantly lower relative stent expansion than the group without coronary calcification (0.43 vs. 0.49,

Table 2. Procedural characteristics and results.

	Without CC (n=23)	With CC (n=46)	*p*-value
Average/total stent number	1.1/26	1.2/55	0.74
Average stent diameter of each stent, mm	3.1±0.3	3.1±0.4	0.82
Average stent length of each stent, mm	19.4±7.7	20.5±8.1	0.57
Stent			0.35
XIENCE V/PROMUS, n	7	10	
XIENCE PRIME/MULTI-LINK 8, n	11	19	
Others, n	8	26	
Maximum balloon diameter, mm	3.4±0.4	3.4±0.4	0.63
Maximum inflation pressure, atm	13.7±3.8	14.7±3.7	0.31
Non-compliant balloon usage, n (%)	2 (8.7)	15 (32.6)	0.039
MSD, mm	2.6±0.5	2.6±0.6	0.72
MSA, mm^2	6.3±2.1	6.1±2.2	0.74
OCT/manufacturer-predicted stent diameter ratio,%	0.84±0.13	0.83±0.20	0.51
OCT/manufacturer-predicted stent area ratio,%	0.81±0.21	0.78±0.19	0.96
Relative stent expansion	0.50±0.10	0.46±0.07	0.05
Absolute stent expansion, n (%)	17 (73.9)	29 (63.0)	0.43
Symmetry index	0.89 [0.86-0.91]	0.87 [0.80-0.92]	0.35
Stent malapposition, n (%)	3 (13.0)	14 (30.4)	0.11

All variable data are presented as mean±standard deviation, or as medians (25th and 75th percentiles) when the distribution was non-normal. Absolute stent expansion was defined as MSA >5.0 mm^2. Stent malapposition, defined as the axial distance between the strut's surface and the luminal surface, was greater than the strut thickness. Stent symmetry index was defined as minimum stent diameter/maximum stent diameter.
CC: coronary calcification; MSA: minimal stent area; MSD: minimal stent diameter; OCT: optical coherence tomography

p<0.05). A similar tendency was observed in absolute stent expansion; however, these differences were not statistically significant.

Discussion

The results obtained from this OCT study focusing on the nature of coronary calcification and resultant stent expansion can be summarised as follows. In terms of its prevalence or patient characteristics, coronary calcification was: 1) differentiated in two thirds of consecutive PCI cases, 2) observed less frequently in the cases with acute coronary syndrome and dyslipidaemia, and 3) observed more frequently in LAD vessels. Regarding its distribution or lesion characteristics, coronary calcification was located superficially in the majority of cases, and its thickness showed normal distribution. Distribution of the arc varied, but those of <180 degrees were predominant. Furthermore, the lesions with coronary calcification had less plaque burden and larger MLA compared with those without. In terms of relationships among the representative quantitative parameters of coronary calcification, there was: 1) an inverse correlation between its depth and thickness/arc, and 2) a weak positive correlation between its arc and thickness. As seen in the descriptive summary thus far, coronary calcification in the native coronary artery has unique geographic and morphological features. Finally, taking into consideration the impact of coronary calcification on stent

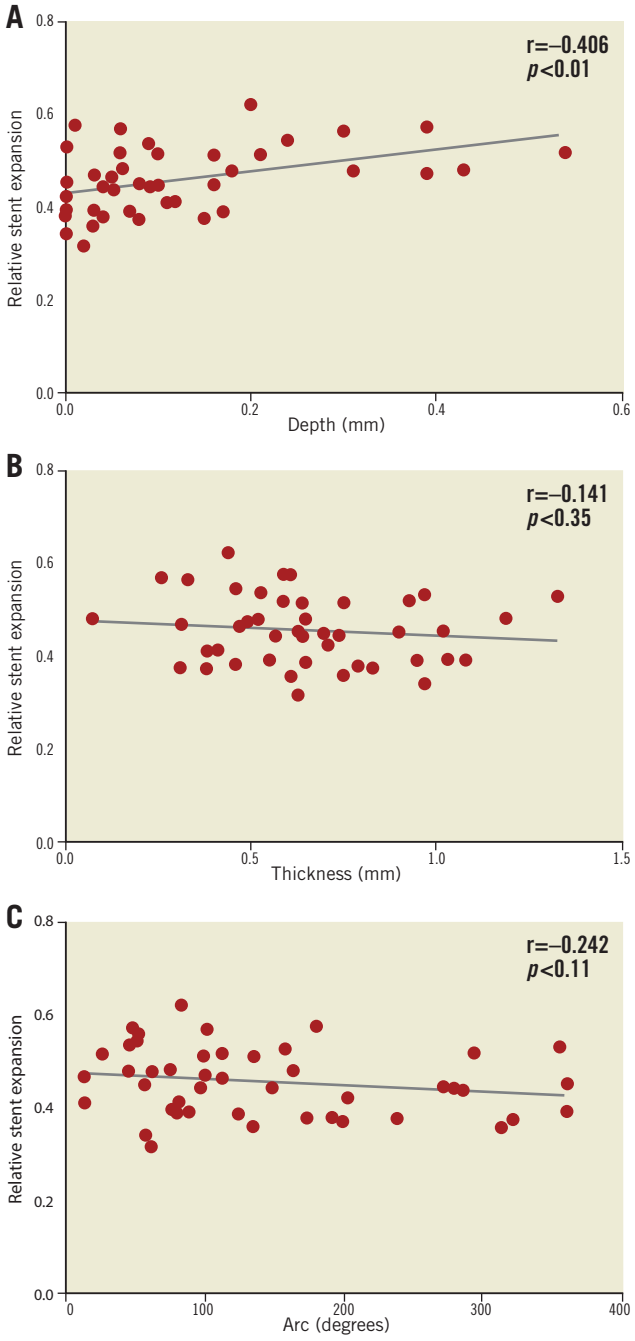

Figure 4. *Correlation between the three parameters of coronary calcification and relative stent expansion.*

expansion, very importantly among the three representative parameters (thickness, arc, depth) of calcification by OCT assessment, depth is the only parameter which is associated with resultant stent expansion. Thickness and arc, which have been considered as potential causes of insufficient expansion for a long time, did not relate to actual stent expansion in our consecutive data set analyses, if we exclude some severely calcified lesions impossible for OCT catheter insertion. These inherent characteristics of coronary calcification and its potential impact on resultant stent expansion should be taken into consideration for the purposes of prediction during OCT-evaluated

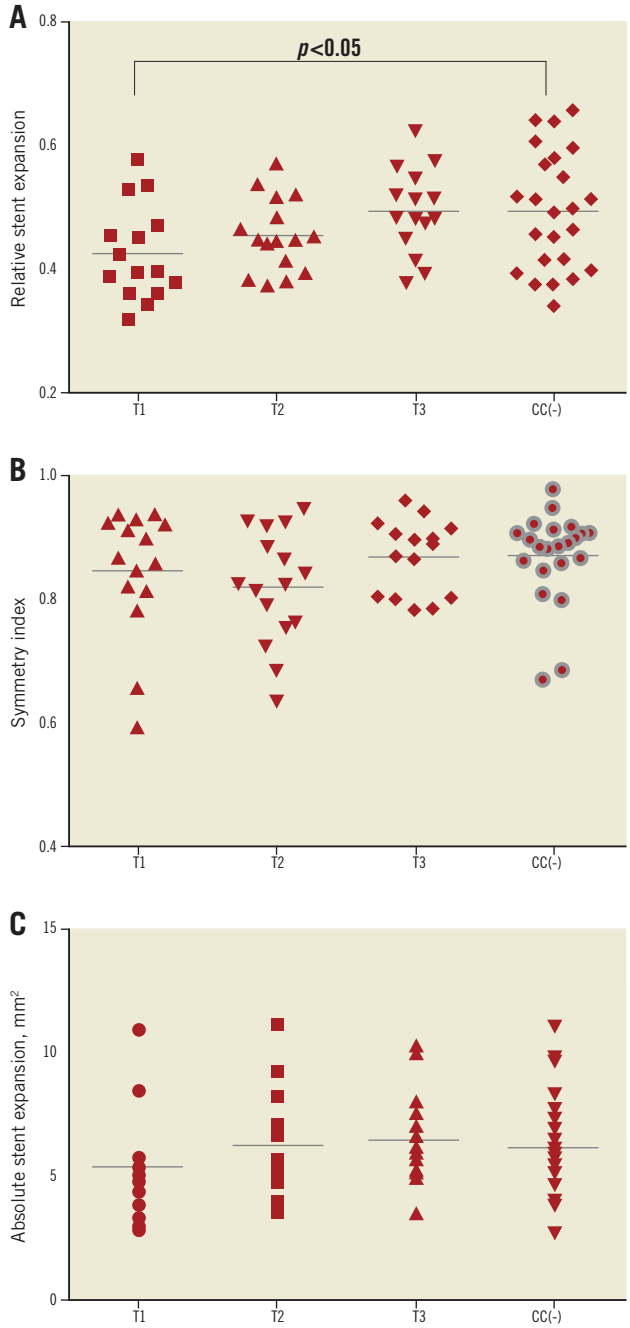

Figure 5. *Comparison of relative stent expansion between each tertile category and the group without coronary calcification. Patients were divided into tertile category (T) according to the distance from the intima to the calcified nodule (T1: <0.04 mm, T2: 0.04-0.11 mm, T3: >0.11 mm). CC (-): without coronary calcification*

stenting. In terms of clinical implications, this result means that the operator should avoid stenting consecutively and should use a scoring balloon or rotational atherectomy before stenting.

CONSISTENCY WITH PREVIOUS RESEARCH

As seen from the results of this study, coronary calcification has unique features. After the development of initial calcification, medial calcification related to vascular smooth muscle cell apoptosis[18] progresses to the intima layer, and occurs preferentially along the elastic lamina[19]. Accordingly, the potential formation processes of coronary calcification, elucidated by previous research, were well supported and explained by the actual findings observed in the current study. In fact, this study clearly demonstrated that the depth of coronary calcification inversely correlated to the arc or the thickness. Such features might confirm that coronary calcification extends inwardly (into the luminal centre) from the media and is distributed like a fan. Shallow calcification tended to be larger compared with deep calcification, a relationship which was clearly proved in this study.

IMPACT OF CORONARY CALCIFICATION ON STENT EXPANSION

As we have described, this study suggested that the "depth" of coronary calcification from the intimal surface is the key factor to predict stent expansion. In other words, lesions with superficial calcium are more difficult to expand. Several potential explanations for this phenomenon can be proposed. First, the depth of calcification could be considered as soft expandable space between the intima and the calcium surface. Thus, deeper calcium tends to have more soft tissue space inside the calcium, which can be expanded more. Second, superficial calcium tends to be thicker and axially wider. The absolute volume of calcium must enhance expandability. However, the thickness and the arc did not independently impact on actual stent expansion. Thus, the first explanation might be fundamental and the primary one as being the mechanism of stent expansion in lesions with coronary calcification.

COMPARISON OF THE PRESENT STUDY WITH OTHER STUDIES

Although many IVUS studies concerning coronary stenting have reported the impact of coronary calcification on clinical outcome, only simple comparisons between two groups that were defined by the presence or absence of coronary calcification were performed in most studies. From a previous IVUS study which assessed coronary calcification in detail and stent expansion, it was suggested that the arc of calcium, calcium location (deep or superficial) and calcium length had no relationship with the stent expansion index[7]. However, it was difficult to compare this IVUS study with the present study. Since procedural protocols (undergoing only direct stenting and avoiding the use of non-compliant balloons) were quite different from the present study, the impact of calcification regarding stent expansion might have been underestimated.

In contrast, another OCT study reported that the amount and extent of coronary calcification were associated with stent expansion[20]. Although these findings were similar to our findings, the mean MSA of another OCT study was smaller than that of the present study (4.96 mm^2 vs. 6.2 mm^2), and the depth of coronary calcification was not evaluated in another OCT study. For these reasons, careful comparison is required between other OCT studies and the present study.

STUDY LIMITATIONS

The present study has several inherent limitations. First, this study was conducted retrospectively and enrolled a relatively small

number of patients. Lack of a prospective protocol might have allowed a variety of endpoints of stent expansion among the operators; a uniform stent expansion protocol might be ideal for this type of investigation. Potentially compensating for this, detailed baseline characteristics regarding stent expansion were introduced as much as possible. Second, any long-term clinical events were not observed. This study clearly focused on "acute" results during the primary procedures. Insufficient stent expansion is known to relate to late adverse events[14,21], which can generally be considered as surrogate endpoints. Post-intervention MSA, recognised as a surrogate marker of a major cardiac event, was exclusively measured in this study. Third, the lesion of severe and complex coronary calcification which was suitable for rotational atherectomy had to be excluded from our analysis. These limitations of studies using catheter-based intravascular imaging devices seem inevitable. Fourth, the calcification buried in lipid-rich plaque had a potential to be missed. Because of attenuation, the presence or absence of coronary calcification could not easily distinguish the severity of calcification in our OCT study. Finally, our definition for measuring the arc of coronary calcification, using the centre of the OCT imaging catheter as reference, was different from that used in a previous IVUS study[22], which adopted the lumen centre as reference for calcium arc measurement. For OCT-based analysis, considering its limited penetration depth[23], we do not believe that the latter method is always good. If you use the lumen centre for arc measurement, you have to determine the lumen centre prior to arc measurement every time. The method we introduced in this study is surely more practical, not time-consuming, and reproducible for OCT-evaluated stenting.

Conclusions

Superficiality is most important for the assessment of coronary calcification, which is associated with the size of coronary calcification (arc and thickness) as well as expandability by stenting procedures. OCT, which allows the accurate evaluation of coronary calcification, may be useful for the prediction of the resultant stent expansion of calcified lesions.

Impact on daily practice

Our results show that shallow coronary calcification might relate to insufficient stent expansion. In daily practice, when pre-stenting OCT images show shallow coronary calcification within the zone recommended to implant the stent, the operator should avoid stenting consecutively and should use a scoring balloon or rotational atherectomy before stenting.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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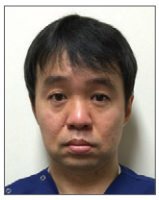
Smooth arterial healing after paclitaxel-coated balloon angioplasty for in-stent restenosis assessed by optical frequency domain imaging



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KEYWORDS

- in-stent restenosis
- optical frequency domain imaging
- paclitaxel-coated balloon

Abstract

Aims: Our aim was to evaluate visual and qualitative changes of intimal tissue by optical frequency domain imaging (OFDI) after paclitaxel-coated balloon (PCB) angioplasty.

Methods and results: We conducted a prospective observational study of 38 Japanese patients undergoing PCB angioplasty for in-stent restenosis at a single institute from February 2014 to June 2015. The scheduled follow-up coronary angiography (CAG) was performed six to nine months after PCI. Intravascular imaging assessment was performed twice, immediately following PCB angioplasty and during follow-up CAG, using an OFDI system. During the study period, PCB angioplasty was performed on 38 patients and OFDI assessment was performed in all 38 cases at the time of angioplasty. Follow-up CAG was performed in 22 patients and qualitative OFDI assessment was performed in 12 patients. The average follow-up period was 6.3±1.4 months. The minimum lumen area measured by OFDI immediately following balloon angioplasty and at follow-up was 4.8±1.5 mm^2 and 4.2±1.9 mm^2, respectively. The neointimal area immediately following angioplasty and at follow-up was 2.7±1.6 mm^2 and 2.9±0.9 mm^2, respectively. Late luminal loss six months after angiography was 0.6 mm^2. In the 22 follow-up patients, repeat ISR was seen in four patients (18%). Qualitative OFDI assessment at six months showed smooth healed neointimal tissue with a homogeneous appearance, which had been an uneven surface at the time of angioplasty.

Conclusions: After PCB angioplasty, the arterial healing process, as assessed by OFDI, shows smooth neointimal tissue by six months.

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Introduction

The paclitaxel-coated balloon (PCB) is a useful device for percutaneous coronary intervention (PCI). PCB angioplasty is performed mainly to ISR lesions and in small vessel disease. Previous studies have shown its favourable clinical outcomes and arterial healing process[1]. However, the visual changes of the arterial healing process in real-world patients have not yet been examined. We therefore sought to assess changes of the intima after PCB angioplasty using the high-resolution optical frequency domain imaging (OFDI) system.

Methods

STUDY DESIGN

We conducted a prospective observational study of 38 Japanese patients undergoing PCB (SeQuent® Please; B. Braun, Melsungen, Germany) angioplasty for ISR at a single institute from February 2014 to June 2015. All ISR lesions were predilated using the Lacrosse NSE balloon (Goodman Co. Ltd., Aichi, Japan). The scheduled follow-up CAG was performed at six to nine months after PCI. When patients reported chest pain, a follow-up CAG was performed earlier than the scheduled date.

METHODS OF OFDI ACQUISITION

Intravascular imaging assessment was performed twice, just after PCB angioplasty and at the time of follow-up CAG, using the OFDI system (Terumo Corp., Tokyo, Japan). OFDI imaging uses a non-occlusive technique at an image acquisition rate of 158 frames/s during an automated pullback at a speed of 40 mm/s. The pullback was performed during continuous intracoronary injection of contrast medium through the ≥6 Fr guiding catheter using an injection pump at a flow rate of 3.0 ml/s for the left coronary artery and 2.5 ml/s for the right coronary artery for four seconds.

STATISTICAL ANALYSIS

Discrete data are presented as frequencies and/or percentages and continuous variables are presented as mean±SD.

Results

From February 2014 to June 2015, PCB angioplasty was performed on 38 patients with ISR, and OFDI assessment was performed in all 38 cases at the time of angioplasty. Baseline data of the study participants are shown in **Table 1**. For the 38 patients with ISR, the rate of previously implanted stents that were bare metal stents (BMS) was 26.3% (n=10), first-generation DES was 7.9% (n=3), and second-generation DES was 65.8% (n=25). Next, follow-up CAG was performed in 22 patients and qualitative OFDI assessment was performed in 12 patients. The average follow-up period was 6.3±1.4 months. The minimum lumen area measured by OFDI immediately following balloon angioplasty and at follow-up was 4.8±1.5 mm^2 and 4.2±1.9 mm^2, respectively. The neointimal area following angioplasty and at follow-up was 2.7±1.6 mm^2 and 2.9±0.9 mm^2, respectively **(Table 2)**. Late luminal loss at six months after angiography was 0.6 mm^2. In the 22 follow-up patients, repeat ISR was seen in four patients (18%). Over a six-month period, qualitative OFDI assessment showed a smoothened surface of healed neointimal tissue with a homogeneous appearance in all 12 cases. This surface was jagged and uneven in appearance at the time of angioplasty **(Figure 1A, Figure 1B)**.

Table 1. Patient characteristics.

Number of patients		38
Number of lesions		38
Mean age, years		70.6±9.9
Male		34 (89.5%)
Coronary risk factors	HTN	35 (92.1%)
	DM	29 (76.3%)
	Dyslipidaemia	27 (71.1%)
	Smoking	15 (39.5%)
	Haemodialysis	5 (13.2%)
Multiple ISR history		14 (36.8%)
Target vessels	LAD	18 (47.4%)
	LCX	6 (15.8%)
	RCA	14 (36.8%)
Previous stents	BMS	10 (26.3%)
	1st DES	3 (7.9%)
	2nd DES	25 (65.8%)

BMS: bare metal stents; DES: drug-eluting stents; DM: diabetes mellitus; ISR: in-stent restenosis; HTN: hypertension; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery

Discussion

Drug-coated balloon (DCB) angioplasty is mainly performed for small vessel disease and in-stent restenosis. Previous studies have shown favourable clinical outcomes using DCB for in-stent restenosis when compared with plain balloon angioplasty and drug-eluting stents[1]. Long-term safety has also been shown. PCB angioplasty showed similar favourable clinical outcomes to DES implantation for the treatment of DES restenosis in complex situations[2]. We sought to assess the healing process of PCB angioplasty by OFDI, as this process is key for a favourable clinical outcome.

In our study, predilatation using the Lacrosse NSE balloon was performed in all cases. This balloon catheter contains three triangular nylon elements (width, 0.014″, height, 0.015″) which are free-floating on the outside of the balloon surface, and attached proximal and distal to a 13 mm balloon length[3]. Dilatation using the Lacrosse NSE balloon creates a scoring effect into the intimal tissue through

Table 2. Quantitative OFDI findings.

	Pre PCI	Post PCB	6-month follow-up
Minimal lumen area (mm^2)	1.1±0.5	4.8±1.5	4.2±1.9
Minimal stent area (mm^2)	6.0±2.3	7.5±2.7	7.2±2.5
Neointimal area (mm^2)	4.9±2.2	2.7±1.6	2.9±0.9

OFDI: optical frequency domain imaging; PCB: paclitaxel-coated balloon; PCI: percutaneous coronary intervention

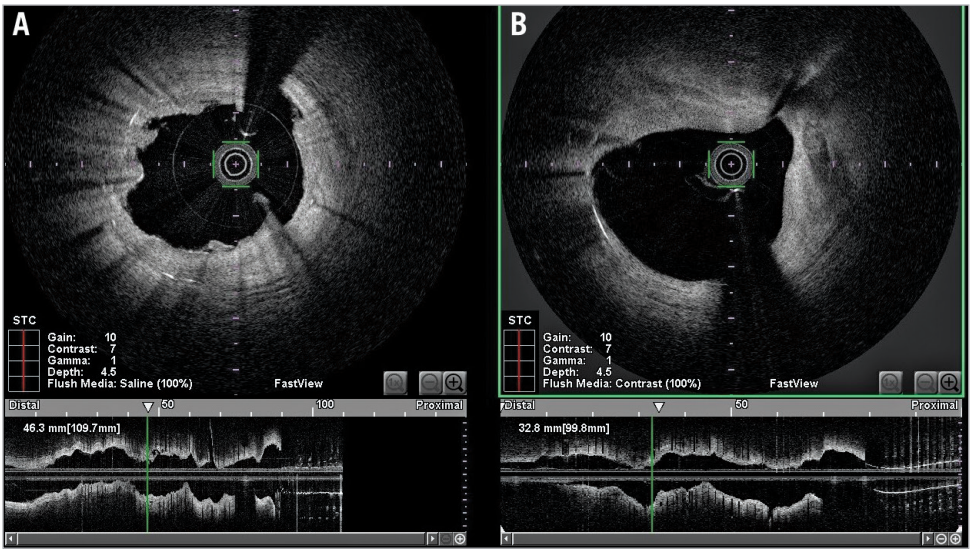

Figure 1. *Examples of qualitative findings by OFDI. A) OFDI image shows a jagged and uneven surface at the time of balloon angioplasty. B) Six months after balloon angioplasty, OFDI image shows a smoothened surface of healed neointimal tissue with a homogeneous appearance.*

a focused transmission of force through the elements. Several types of scoring balloon are available, and the scoring effect is useful for predilatation of calcified or hard plaque lesions. Because we used this balloon for predilatation in all ISR cases, OFDI showed a jagged, uneven surface at the time of PCB angioplasty. However, over six months this surface smoothened and a homogeneous neointima covered the stent strut very well in all cases. To our knowledge, this is the first study to evaluate visually how the intimal tissue changes following PCB angioplasty in real-world patients. Treatment of BMS ISR with PCB leaves significantly fewer stent struts uncovered at nine-month follow-up[4]. A previous study evaluated the PCB healing process by counting the number of covered or uncovered stent struts, and measuring the thickness of the intima[5]. However, our study focused on visual evaluation using a high-resolution OFDI system, which has been developed to overcome the limitations of conventional time-domain optical coherence tomography[6]. It enables the precise measurement of the vasa vasorum area in coronary arteries[7]. Our findings are in agreement with previous reports[8], which show that even dissection and intimal injury by scoring balloon inflation can be smoothly healed after PCB angioplasty.

Study limitations

This study has limitations related to study design and methods of data collection. First, the sample size was relatively small. It was a non-randomised study where all confounding factors and biases could not be eliminated. There is a possibility of substantial selection bias with regard to patient selection, as well as the experience and dedication of the operators.

Conclusions

After PCB angioplasty for ISR, the arterial healing process assessed by OFDI results in a smooth surface by six months.

Impact on daily practice

Paclitaxel-coated balloons have been widely used for treatment of in-stent restenosis. The present study showed a smooth arterial healing process after angioplasty. This finding might be applicable to native coronary artery disease, e.g., coronary dissection. Paclitaxel-coated balloons might help to avoid unnecessary metal stent implantation.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Mediastinal haematoma complicating percutaneous coronary intervention via the radial artery

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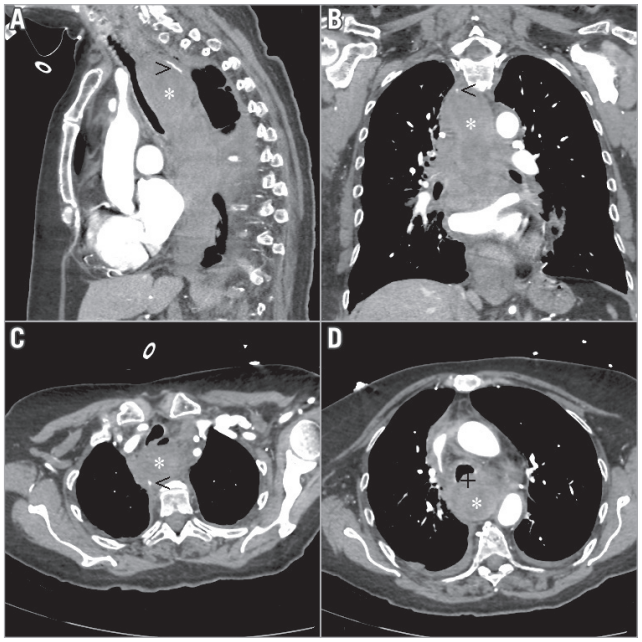

The radial artery has been increasingly used worldwide as the preferred access site for diagnostic coronary angiography and percutaneous coronary intervention (PCI), owing to increased patient comfort and reduced risk of haemorrhagic complications when compared to the femoral approach. Despite being rare, catastrophic haemorrhage can occur and should be promptly recognised. We present an example of a case complicating coronary intervention from the radial approach resulting in a large mediastinal haematoma.

An 87-year-old female underwent PCI to the LAD via the right radial artery, on aspirin, clopidogrel and bivalirudin. A hydrophilic Glidewire® (Terumo Corp., Tokyo, Japan) was required to negotiate the tortuosity of the subclavian artery during passage of the 6 Fr EBU 3.5 guiding catheter (Medtronic, Minneapolis, MN, USA), with there being transient passage of the Glidewire into a branch of the right subclavian artery. The PCI procedure subsequently proceeded without any apparent complication.

The patient experienced severe right-sided chest pain and nausea three hours post procedure. There were no ECG changes. A CT aortogram demonstrated a large posterior mediastinal haematoma (**Panels A-D**, asterisk) at the thoracic inlet extending inferiorly to the diaphragm with significant mass effect on the trachea (**Panel D**, cross). Contrast extravasation was seen through a vessel originating from the subclavian artery (**Panels A-C**, arrowheads).

Two units of packed red cells were transfused following a drop in Hb from 100 g/L to 84 g/L. The patient declined an open surgery, and an endovascular intervention with a covered stent across the culprit subclavian branch was not performed due to there being no haemodynamic instability and no further drop in haemoglobin. The patient experienced an acute deterioration two days post procedure and suffered a cardiac arrest. Re-bleeding or mediastinal mass effect was suspected on the basis of the rhythm being pulseless electrical activity. Cardiopulmonary resuscitation was unsuccessful. An autopsy was not performed.

The radial artery is increasingly favoured as the primary access site for both diagnostic and interventional coronary procedures owing to the reduced risk of access-site complications. This case depicts a potentially catastrophic complication and highlights the need for caution with the use of hydrophilic wires. The case also demonstrates an important differential diagnosis of chest pain following cardiac catheterisation by the radial route.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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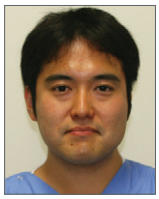
Comparison of aortic annulus dimensions between Japanese and European patients undergoing transcatheter aortic valve implantation as determined by multi-detector computed tomography: results from the OCEAN-TAVI (Optimised transCathEter vAlvular interveNtion) registry and a European single-centre cohort



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KEYWORDS

- aortic annulus measurement
- multi-detector computed tomography
- transcatheter aortic valve implantation

Abstract

Aims: This study sought to compare precise measurements of the aortic valve complex in Japanese and European patients undergoing transcatheter aortic valve implantation (TAVI) using multi-detector computed tomography (MDCT).

Methods and results: Between October 2013 and July 2014, 90 patients undergoing TAVI were prospectively included in the OCEAN-TAVI registry from three Japanese centres. Between March 2009 and December 2012, 181 patients undergoing TAVI at a single French centre were prospectively included in the European cohort. Female sex was more frequently observed in the Japanese cohort (74.4% vs. 44.2%, p<0.01). All MDCT-measured annulus dimensions including annulus area (375.9 cm^2 [IQR 333.8-410.7] vs. 472.5 cm^2 [IQR 415.3-536.6], p<0.01), left coronary ostium height (13.6 mm [IQR 12.0-15.0] vs. 15.1 mm [IQR 13.5-17.2], p<0.01), right coronary ostium height (15.9 mm [IQR 14.5-17.5] vs. 17.7 mm [IQR 16.0-19.7], p<0.01), and the sinus of Valsalva (27.2 mm [IQR 25.6-29.5] vs. 32.0 mm [IQR 29.7-34.0], p<0.01) were smaller in the Japanese patients.

Conclusions: Japanese patients had a smaller aortic valve complex than European patients. A smaller prosthesis is required for Japanese patients undergoing TAVI. The risks related to these anatomical characteristics should be considered.

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Abbreviations

AS	aortic stenosis
BSA	body surface area
IQR	interquartile range
LCC	left coronary cusp
MDCT	multi-detector computed tomography
NCC	non-coronary cusp
OCEAN-TAVI	Optimised transCathEter vAlvular interveNtion-TAVI
RCC	right coronary cusp
SOV	sinus of Valsalva
TAVI	transcatheter aortic valve implantation

Introduction

Transcatheter aortic valve implantation (TAVI) is evolving rapidly with an exponential growth in the number of procedures in European countries[1,2]. However, TAVI has just started to be used in some Asian countries[3,4], and its efficacy and safety in Asian patients has not been thoroughly investigated. Furthermore, Asians have a smaller body size and, consequently, a smaller aortic annulus size and vascular access than their European counterparts. The risks related to these anatomic differences have raised serious concerns about the safety of TAVI in Asian patients.

Editorial, see page 10

This study sought to examine the anatomic features of Asian patients undergoing TAVI and to compare aortic annulus dimensions, determined by multi-detector computed tomography (MDCT), with European patients undergoing the same procedure.

Methods

STUDY POPULATION AND DESIGN

OCEAN-TAVI REGISTRY

The OCEAN-TAVI (Optimised transCathEter vAlvular interveNtion) registry is a Japanese multicentre prospective registry. This registry was initiated to observe and document procedural results and post-procedural outcome of TAVI. The OCEAN-TAVI registry is independent of any industry influence.

Between October 2013 and July 2014, a total of 90 consecutive high-risk Japanese patients with symptomatic severe AS undergoing TAVI using the Edwards SAPIEN XT prosthesis (Edwards Lifesciences, Irvine, CA, USA) at the Teikyo University School of Medicine (Tokyo, Japan, n=20), Keio University School of Medicine (Tokyo, Japan, n=45) and Toyohashi Heart Center (Toyohashi, Japan, n=25) were prospectively included in the OCEAN-TAVI registry. All patients gave written informed consent before the procedure. Inclusion criteria were the presence of symptomatic degenerative AS with a New York Heart Association (NYHA) Class II or greater, a mean gradient >40 mmHg or a jet velocity greater than 4.0 m/s or an aortic valve area <1.0 cm^2 (or an effective orifice area index <0.6 cm^2/m^2). Patients for whom TAVI was deemed to be the best treatment option were selected based on the clinical consensus of a multidisciplinary team consisting of cardiac surgeons, interventional cardiologists, anaesthetists, and imaging specialists. Primary exclusion criteria were the following: bicuspid or non-calcified aortic valve, aortic annulus diameter (echo measurement) <18 mm or >25 mm, severe left ventricular dysfunction (left ventricular ejection fraction <20%), severe aortic regurgitation or dialysis dependence. All 90 patients underwent pre-procedural ECG-gated MDCT scans before TAVI.

THE EUROPEAN SINGLE-CENTRE COHORT

Between March 2009 and November 2012, a total of 545 consecutive high-risk patients with symptomatic severe AS treated with TAVI at the Institut Cardiovasculaire Paris Sud (Massy, France) were prospectively included in the study group designated as the European single-centre cohort. Of these, 181 patients in whom ECG-gated MDCT data were available were finally included in the study.

Patients with severe symptomatic AS (valve area ≤1.0 cm^2) were considered candidates for TAVI if they had a logistic EuroSCORE >20%, if surgery was deemed to be excessively risky due to significant comorbidities, or if other risk factors not captured by these scoring systems (e.g., porcelain aorta) were present. The decision to proceed with TAVI was discussed by a dedicated Heart Team including experienced clinical and interventional cardiologists, cardiovascular surgeons and anaesthesiologists. All patients agreed to participate in the study, and written informed consent was obtained in all cases.

MDCT IMAGE ACQUISITION

THE OCEAN-TAVI REGISTRY

All examinations were performed with multi-detector row CT scanners consisting of 64 rows or greater. The thickness of the reconstructed image was 0.8 mm in the Japanese cohort. Data acquisition, image post-processing, and data interpretation were performed according to the guidelines of the Society of Cardiovascular Computed Tomography[5].

THE EUROPEAN SINGLE-CENTRE COHORT

All examinations were performed using a Philips Brilliance 64-slice MDCT scanner (Philips Medical Systems, Best, The Netherlands). Standard technical parameters were used: gantry rotation time 300 ms, axial coverage 40 mm (64×0.625 mm), 120 kV tube voltage, 850-900 mAs intensity with our modulation, temporal resolution 165 ms. Retrospective ECG gating was performed. Contrast enhancement was achieved using 50-80 ml of Iomeprol 400 mg/ml (Iomeron®). In order to achieve optimal synchronisation, a bolus tracking method was used in the descending aorta. Additional beta-blockade was not administered in any case due to potential haemodynamic instability in severe AS.

MDCT ANALYSIS

All MDCT data from the European and Japanese cohorts were transmitted to an independent core laboratory (Japan Cardiocore, Tokyo, Japan) and assessed by experts blinded to patient data. The MDCT images of the aortic root were determined with dedicated software for aortic valve assessment (the automated 3mensio™ Valves 5.1, sp1, 3mensio; Pie Medical Imaging BV, Maastricht, The Netherlands). All MDCT measurements have been performed at 30% of the RR interval. The annulus surface area was then manually traced and the orthogonal long annulus diameter, short annulus diameter, and the

height of the coronary ostia were measured. The valve eccentricity index was calculated as: (1 – short annulus diameter/long annulus diameter)×100, according to the method previously described by Blanke et al[6]. Aortic root calcification volume was measured using the algorithm of 3mensio software, which has been described previously[7]. The Hounsfield unit threshold is defined by individually adjusting the calcification area measurements obtained by 3mensio imaging. Contrast agent was used in this procedure. The term aortic root refers to the aortic valve from its insertion at the left ventricular outlet to the sinotubular junction. The CT annulus assessments were performed by three experienced cardiac CT observers (Y. Watanabe, T. Tsunaki, and F. Yashima). All observers were highly experienced in MDCT valvular assessments (level of proficiency 3) according to the American College of Cardiology/American Heart Association statement on competency in cardiac CT imaging[8].

INTEROBSERVER AND INTRAOBSERVER AGREEMENT

Retrieved from 14 randomly selected data files, aortic annulus diameters were re-measured by another observer to determine interobserver agreement and by the same observer subsequently to determine intraobserver agreement. All observers were blinded to previous measurements.

STATISTICAL ANALYSIS

Quantitative variables were assessed for normal distribution with the Shapiro-Wilk test and are expressed as mean±standard deviation or as median and interquartile range (IQR: 25-75%), as appropriate. Qualitative variables are expressed as numeric values and percentages. Comparison of quantitative variables was performed using the unpaired Student's t-test or the Wilcoxon rank-sum test, depending on the variable distribution. The chi-square test or Fisher's exact test was used to compare qualitative variables. Pearson correlations were used to compare between the aortic annulus area, or perimeter and body surface area (BSA) in both the Japanese and European cohorts. In addition, intraobserver and interobserver agreement was evaluated for the aortic annulus measurement by calculating the intraclass correlation coefficients (ICCs), with excellent agreement defined as an ICC >0.8. The data were analysed with PASW statistics, Version 19.0 (IBM Corp., Armonk, NY, USA).

Results

PATIENT CHARACTERISTICS

The baseline characteristics of the two study groups are presented in **Table 1**. Female sex was more frequently observed in the Japanese cohort (74.4% vs. 44.2%, p<0.01). Body size area (BSA) and body mass index (BMI) were significantly smaller among Japanese patients than those in the European cohort (1.40±0.15 vs. 1.76±0.19 m², p<0.01; 22.5±3.1 vs. 25.8±4.0 kg/m², p<0.01, respectively). The rate of NYHA Class III or IV and previous pacemaker placement were significantly lower among the Japanese patients (47.8% vs. 88.4%, p<0.01; 5.6% vs. 15.2%, p<0.02, respectively). Higher rates of previous percutaneous coronary intervention and cerebrovascular disease were observed in the Japanese patients

Table 1. Baseline characteristics of the study population, Japanese registry vs. European study group.

	Japanese	European	*p*-value
No. of patients	90	181	
Age, years	85 (82.5-87.5)	84 (80.5-87.5)	0.83
Male sex	23 (25.6%)	101 (55.8%)	<0.01
Height, cm	147.6±9.5	164.2±8.4	<0.01
Weight, kg	49.0±8.1	69.8±13.2	<0.01
BSA, m²	1.40±0.15	1.76±0.19	<0.01
BMI, kg/m²	22.5±3.1	25.8±4.0	<0.01
Diabetes	28 (31.1%)	40 (22.1%)	0.11
Hyperlipidaemia	49 (54.4%)	87 (48.1%)	0.32
Hypertension	65 (72.2%)	124 (68.5%)	0.53
NYHA Class III/IV	43 (47.8%)	160 (88.4%)	<0.01
Previous pacemaker	5 (5.6%)	15 (15.2%)	0.02
Coronary artery disease	42 (46.7%)	98 (54.1%)	0.25
Previous MI	10 (11.1%)	12 (6.7%)	0.21
Previous PCI	35 (38.9%)	43 (23.8%)	0.01
Previous CABG	7 (7.8%)	17 (9.4%)	0.65
Peripheral artery disease	23 (25.6%)	60 (33.5%)	0.18
Cerebrovascular disease	14 (15.7%)	14 (7.8%)	0.05
COPD	19 (21.1%)	37 (20.7%)	0.93
eGFR	46.5 (35.8-57.3)	56.2 (41.7-70.8)	<0.01
Logistic EuroSCORE, %	16.4 (9.5-23.3)	15.5 (7.7-23.3)	0.53
STS score, %	6.9 (4.6-9.2)	5.6 (3.1-8.2)	<0.01
Aortic valve area, cm²	0.60 (0.47-0.73)	0.63 (0.52-0.74)	0.62
Mean pressure gradient, mmHg	42.0 (29.9-54.2)	45.0 (36.5-53.5)	0.11
LVEF, %	65.0 (59.9-70.1)	56 (43.5-68.5)	<0.01

Values are expressed as n (%) or mean±SD or median and interquartile range. BMI: body mass index; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PVL: paravalvular leak

(38.9% vs. 23.8%, p<0.01; 15.7% vs. 7.8%, p=0.02, respectively). The value of the estimated glomerular filtration rate, STS score, and left ventricular ejection fraction were higher among the Japanese patients (46.5 [IQR 35.8-57.3] vs. 56.2 [IQR 41.7-70.8], p<0.01; 6.9 [IQR 4.6-9.2] vs. 5.6 [IQR 3.1-8.2], p<0.01; 65.0% [IQR 59.9-70.1%] vs. 56.0% [IQR 43.5-8.5%], p<0.01, respectively).

MDCT characteristics

The pre-TAVI cardiac MDCT characteristics are presented in **Table 2**. Short- and long-axis annulus diameters were significantly smaller among Japanese patients (19.4±2.0 mm vs. 22.6±2.3 mm, p<0.01; 24.7±1.9 mm vs. 27.6±2.5 mm, p<0.01, respectively). A more eccentric annulus presented as the eccentricity index was observed more frequently in Japanese patients (21.5±6.2 vs. 18.9±5.3, p<0.01). A shorter annulus perimeter and smaller annulus area were observed among Japanese patients (70.3±5.0 mm vs. 80.4±7.0 mm, p<0.01; 375.9 mm² [IQR 333.8-410.7] vs. 472.5 mm² [IQR 415.3-536.6], p<0.01, respectively). **Figure 1** shows the

Table 2. Patient and cardiac CT characteristics, Japanese registry vs. European study group.

	Japanese	European	*p*-value
No. of patients	90	181	
Short-axis annulus diameter, mm	19.4±2.0	22.6±2.3	<0.01
Long-axis annulus diameter, mm	24.7±1.9	27.6±2.5	<0.01
Eccentricity index	21.5±6.2	18.9±5.3	<0.01
Perimeter, mm	70.3±5.0	80.4±7.0	<0.01
Area, mm^2	375.9 (333.8-410.7)	472.5 (415.3-536.6)	<0.01
Area/BSA, mm^2	268.8±36.9	271.8±44.8	0.59
Left coronary height, mm	13.6 (12.0-15.0)	15.1 (13.5-17.2)	<0.01
Right coronary height, mm	15.9 (14.5-17.5)	17.7 (16.0-19.7)	<0.01
Sinus of Valsalva, mm	27.2 (25.6-29.5)	32.0 (29.7-34.0)	<0.01
Sinus of Valsalva height, mm	8.9 (8.0-9.9)	11.5 (10.3-12.6)	<0.01
Shortest diameter of STJ, mm	24.3±2.6	28.2±3.1	<0.01
STJ height, mm	19.3±2.3	22.9±2.9	<0.01
Total aortic valve calcification volume, mm^3	606.4 (378.0-923.3)	740.0 (448.0-1,064.0)	0.07
Ratio calcification/BSA	438.1 (272.4-641.6)	409.7 (262.0-618.5)	0.36

Values are expressed as n (%) or mean±SD or median (interquartile range). BSA: body surface area; STJ: sinotubular junction

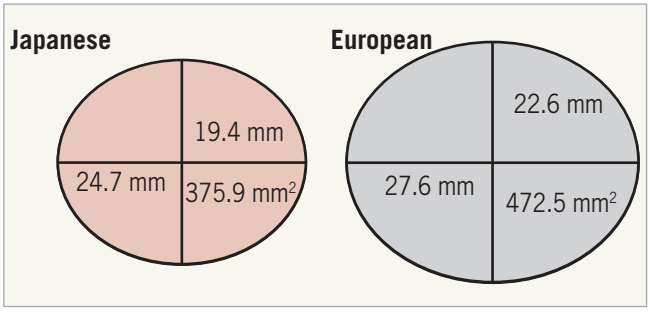

Figure 1. *Comparison of aortic annulus mean diameters between the Japanese and European cohorts. The annulus diameters of Japanese patients were smaller and more eccentric than those of the European patients.*

comparison of aortic annulus mean diameters between patients in the Japanese and the European cohorts. **Figure 2** and **Figure 3** show the comparison of aortic annulus area and perimeter between patients in the Japanese and the European cohorts.

The left coronary height and right coronary height were significantly shorter among Japanese patients (13.6 mm [IQR 12.0-15.0] vs. 15.1 mm [IQR 13.5-17.2], p<0.01; 15.9 mm [IQR 14.5-17.5] vs. 17.7 mm [IQR 16.0-19.7), p<0.01]. **Figure 4** shows the distribution of left coronary heights.

The sinus of Valsalva (SOV), SOV height, sinotubular junction (STJ), and STJ height were smaller in the Japanese patients, suggesting that these patients had a shallow shape of the SOV (27.2 mm [IQR 25.6-29.5] vs. 32.0 mm [IQR 29.7-34.0], p<0.01; 8.9 mm [IQR 8.0-9.9] vs. 11.5 mm [IQR 10.3-12.6], p<0.01; 24.3±2.6 mm vs. 28.2±3.1 mm, p<0.01; 19.3±2.3 mm vs. 22.9±2.9 mm, p<0.01, respectively). **Table 3** shows the risk of coronary occlusion after TAVI, using the threshold data described by Ribeiro et al[9]. According to these threshold data, Japanese patients had a higher risk of coronary occlusion.

No significant differences were observed in total aortic valve calcification volume (606.4 mm^3 [IQR 378.0-923.3] vs. 740.0 mm^3 [IQR 448.0-1,064.0], p=0.07), even when adjusted for BSA (438.1 [IQR 272.4-641.6] vs. 409.7 [IQR 262.0-618.5], p=0.36).

Table 4 shows the gender difference of cardiac CT characteristics, Japanese registry vs. European study group. The short- and long-axis annulus diameter, SOV, and STJ were smaller among Japanese patients compared with European patients, both female and male. Japanese female patients had smaller left coronary height

Table 3. Risk of coronary occlusion after TAVI, using the threshold data from Ribeiro et al.

	Japanese	European	*p*- value
No. of patients	90	181	
Aortic SOV diameter <28.3 mm	60 (66.7%)	17 (13.9%)	<0.01
Ratio SOV/CAAD <1.26	43 (47.8%)	41 (33.6%)	0.04
Left coronary height <10.7 mm	12 (13.3%)	7 (3.9%)	<0.01
Right coronary height <12.7 mm	7 (7.8%)	4 (2.2%)	0.03

Values are expressed as n (%) or mean±SD. CAAD: calculated average annulus diameter; SOV: sinus of Valsalva

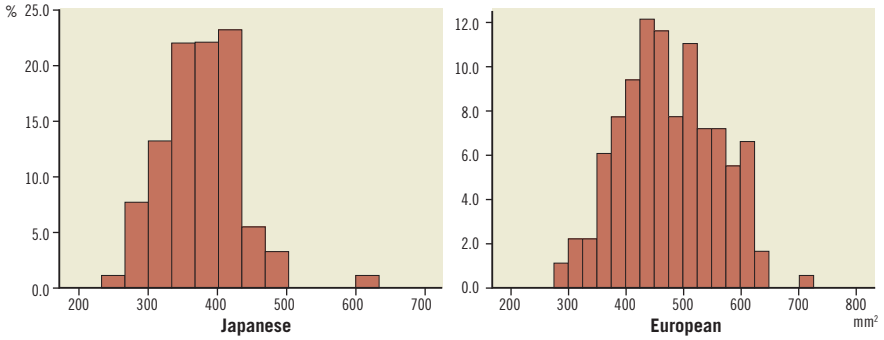

Figure 2. *The distribution of CT measurements of aortic annulus area, Japanese and European cohorts.*

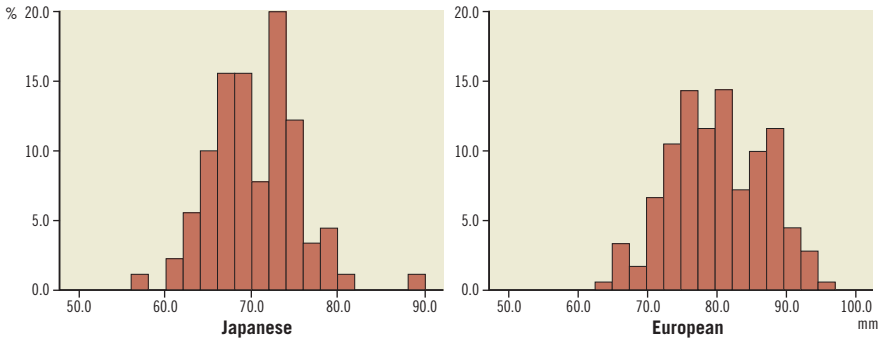

Figure 3. *The distribution of CT measurements of aortic annulus perimeter, Japanese and European cohorts.*

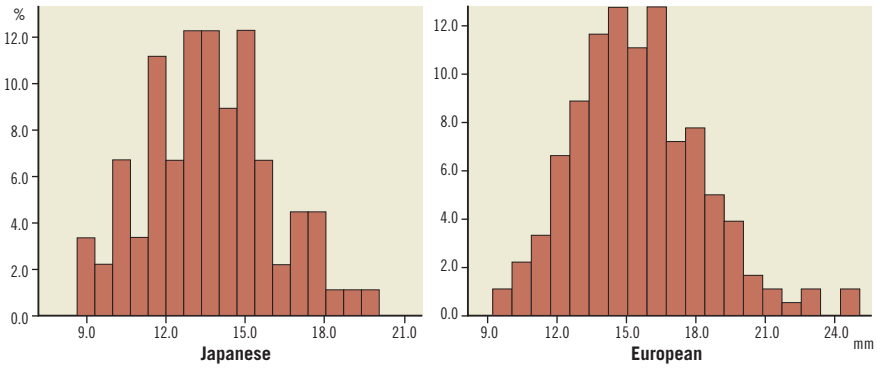

Figure 4. *The distribution of CT measurements of left coronary height, Japanese and European cohorts.*

(13.1±2.1 mm vs. 14.5±2.3 mm, p<0.01) and a more elliptical annulus (eccentricity index 22.3±6.3 vs. 19.1±5.8, p<0.01) compared with European female patients.

CORRELATION BETWEEN THE AORTIC ANNULUS AREA OR THE PERIMETER AND BSA IN BOTH THE JAPANESE AND EUROPEAN COHORTS

Correlations between the aortic annulus area or the perimeter and BSA in the Japanese cohort were moderate (r=0.41, p<0.01, and r=0.45, p<0.01, respectively) **(Figure 5)**. Correlations between the aortic annulus area or the perimeter and BSA in the European cohort were also moderate (r=0.42, p<0.01, and r=0.45, p<0.01, respectively) **(Figure 6)**.

INTEROBSERVER AND INTRAOBSERVER REPRODUCIBILITY

The ICC for the interobserver and intraobserver reproducibility was satisfactory for the measurement of the aortic annulus area (intraobserver ICC 0.98, interobserver ICC 0.95, respectively) and the perimeter (intraobserver ICC 0.96, interobserver ICC 0.94, respectively).

Table 4. Gender difference of cardiac CT characteristics, Japanese registry vs. European study group.

	Female n=147			Male n=124		
	Japanese n=67	European n=80	*p*-value	Japanese n=23	European n=101	*p*-value
BSA, m^2	1.35±0.12	1.65±0.15	<0.01	1.54±0.10	1.85±0.17	<0.01
Short-axis annulus diameter, mm	18.7±1.7	21.0±2.0	<0.01	21.2±1.9	23.3±1.6	<0.01
Long-axis annulus diameter, mm	24.2±1.7	25.9±2.2	<0.01	26.1±1.8	28.9±2.0	<0.01
Eccentricity index	22.3±6.3	19.1±5.8	<0.01	18.9±5.3	19.4±5.2	0.66
Left coronary height, mm	13.1±2.1	14.5±2.3	<0.01	15.1±2.6	16.2±3.0	0.13
Right coronary height, mm	15.7±2.6	16.4±2.2	0.06	18.2±2.8	18.9±2.3	0.18
SOV, mm	26.5±1.8	29.4±2.3	<0.01	30.7±2.1	33.8±2.9	<0.01
STJ, mm	23.7±2.2	26.3±2.1	<0.01	26.2±2.6	29.4±3.0	<0.01
Total aortic valve calcification volume, mm^3	534.0 (268.3-799.7)	545.3 (315.1-775.5)	0.95	780.0 (472.4-1,087.6)	820.4 (495.2-1,145.6)	0.59

Values are expressed as n (%) or mean±SD or median (interquartile range). BSA: body surface area; SOV: sinus of Valsalva; STJ: sinotubular junction

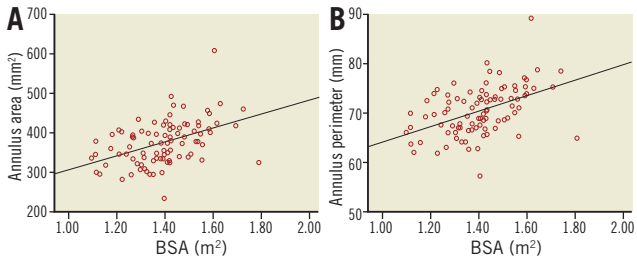

Figure 5. *Correlation between the aortic annulus area or perimeter and BSA in the Japanese cohort. A) Correlation between the annulus area and the BSA was moderate (r=0.41, p<0.01). B) Correlation between the annulus perimeter and the BSA was moderate (r=0.45, p<0.01).*

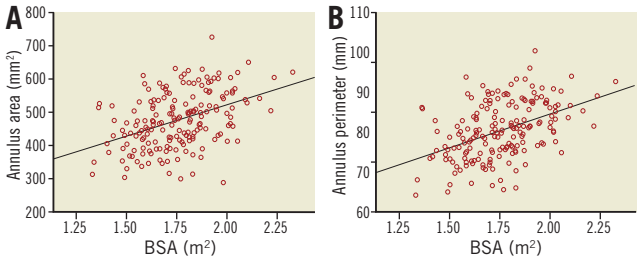

Figure 6. *Correlation between the aortic annulus area or perimeter and BSA in the European cohort. A) Correlation between the annulus area and the BSA was moderate (r=0.42, p<0.01). B) Correlation between the annulus perimeter and the BSA was moderate (r=0.45, p<0.01).*

Discussion

This study is the first direct comparison of aortic annulus dimensions measured by MDCT between Japanese and European patients undergoing TAVI. Nearly all of the measured annulus dimensions were smaller in the Japanese patients than in the European patients. The majority of patients were of female gender in the Japanese cohort, and Japanese female patients had smaller aortic annulus dimensions compared to European female patients. A smaller size of transcatheter valve would be required for Japanese patients.

Difference in physique and race may cause the differences in the diameter of the aortic annulus and in valve sizing. A previous report showed that patients with small body size had smaller annulus and valve size[10]. A comparison of clinical outcomes between European and Japanese cohorts undergoing TAVI demonstrated that Japanese patients had a smaller aortic annulus as shown on echocardiography, and that the most commonly used implant was the Edwards 23 mm valve in the Japanese group and the Edwards 26 mm valve in the European group, suggesting that smaller valves are needed for Asian patients[11].

In the current study, all the annulus dimensions determined using MDCT were smaller among Japanese patients. Patients with a small aortic annulus have a potential risk of prosthesis oversizing and annulus rupture. The introduction of smaller valves such as a 20 mm balloon-expandable transcatheter heart valve may contribute to reducing the risk of annulus rupture in Asian patients with a smaller annulus[12]. Another risk factor for annulus rupture is the amount and distribution of calcification in the aortic annular complex[13,14]. In the current study, no significant differences were observed in terms of aortic valve calcification volume between the European and Japanese cohorts. Although the amount of calcification volume was the same between the two cohorts, patients with a smaller annulus still have a higher risk of annulus rupture.

An elliptical aortic annulus was more frequently seen among Japanese patients. A previous study reported that implantation of the Edwards SAPIEN XT transcatheter valve into elliptical aortic annuli leads to increased paravalvular leakage *in vitro*[15]. Non-circular aortic annuli may cause valve undersizing and pose a risk of annulus rupture unless MDCT is used for measurement[16,17]. Thus, MDCT imaging techniques are more crucial to the evaluation of aortic annulus diameters, especially in patients with an elliptical aortic annulus.

Shorter coronary height from the annulus plane was observed among Japanese patients. Ribeiro et al reported on data from a multicentre registry, which showed that a lower-lying coronary ostium and a shallow SOV were associated with coronary obstruction after TAVI[9]. In the current study, the diameter and height of SOV were shorter in the Japanese group and had a shallow shape, suggesting the existence of racial differences between Japanese and European patients and the potential risk of coronary obstruction after TAVI. In addition, Japanese female patients had smaller left coronary height compared with European female patients. Considering female sex was more frequently observed in the Japanese cohort, special attention to coronary obstruction is needed for Japanese patients during TAVI. Prevention of coronary occlusion using, for example, coronary protection with prior wire placement into the coronary before valve implantation may be a valuable solution[18]. In the registry data, the coronary obstruction rate was more than twice as high among patients who received a balloon-expandable valve than among those who received a self-expanding valve (0.81% vs. 0.34%)[9]. The CoreValve (Medtronic, Minneapolis, MN, USA) system will be suitable for the Japanese patients with a risk of coronary obstruction; however, attention will be needed for the small SOV with a potential risk of coronary obstruction. Anatomical risks of TAVI in Japanese patients are shown in **Figure 7**.

The TAVI procedure has reached relative maturity in European countries, whereas in some Asian countries clinical trials have just concluded and TAVI has started to be used commercially. We believe that our study provides important data in terms of measuring the dimension of the aortic annulus and valve sizing, leading to improved safety and outcomes for Asian patients undergoing TAVI.

Limitations

This non-randomised observational study compared the results between a clinical registry in Japan and a single-centre experience in Europe. Furthermore, because it was a single-centre experience, results from the European cohort do not represent results from all of Europe. The ethnicity of the French cohort was not all Caucasian.

Patient selection bias exists because CT data of only 33% of patients were available in the European cohort. Patient treatment

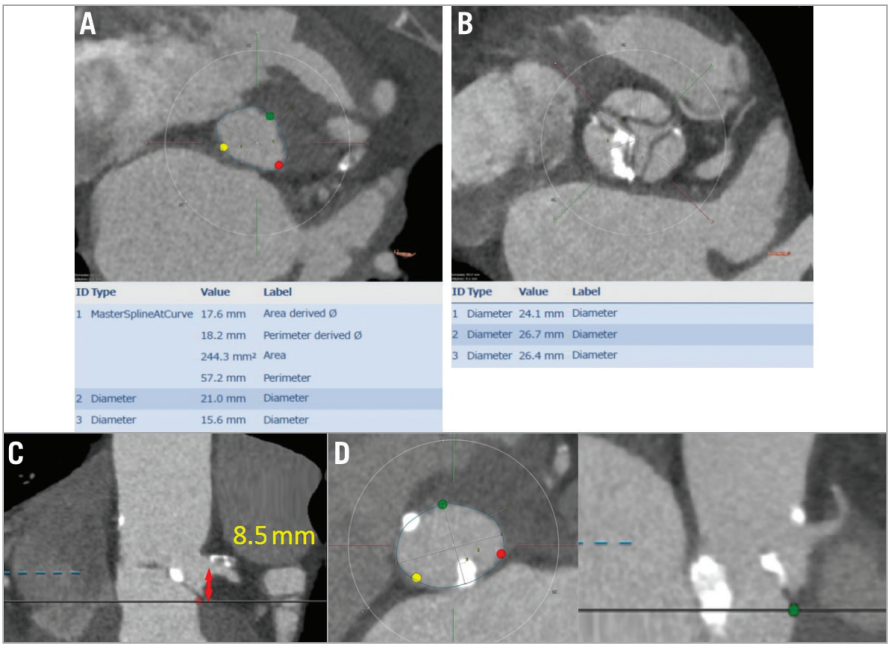

Figure 7. *Anatomical risks of TAVI in Japanese patients. A) Smaller aortic annulus area. B) Smaller diameter of sinus of Valsalva. C) Shorter height of coronary artery. D) Calcified aortic valve.*

bias is inherent in non-randomised observational studies and may have affected the comparison of clinical outcomes between the OCEAN-TAVI cohort and the European single-centre cohort. Procedures on patients in the OCEAN-TAVI cohort are proctored by representatives of the Edwards Company. Thus, patient selection is probably different from that of the selection process for patients in the European cohort. Furthermore, only 23 mm and 26 mm Edwards SAPIEN XT prostheses were available in Japan at the time of this study. Patients with an aortic annulus not suitable for these two available valves were not considered TAVI candidates and were excluded from this study.

Female sex was more frequently observed in the Japanese cohort. In general, Japanese women have a long life expectancy, and therefore female sex was more frequently observed in the Japanese cohort. Japanese male AS patients were likely to have been operated on before consideration for TAVI.

Further studies of a larger group of patients will be required to confirm our results.

Conclusion

Japanese patients had smaller annulus dimensions by MDCT compared with European patients. The risks related to these anatomical characteristics should be taken into consideration for Japanese patients undergoing TAVI.

Impact on daily practice

This study will provide important data for valve selection and sizing for the smaller aortic anatomy of Asian patients undergoing TAVI.

Acknowledgements

We thank Mr Tatsuya Tsunaki for his invaluable assistance.

Conflict of interest statement

Y. Watanabe is a proctor for transfemoral TAVI for the Edwards Company. M. Yamamoto is a proctor for transfemoral TAVI for the Edwards Company. T. Lefèvre is a proctor for transfemoral TAVI for the Edwards Company and is a consultant for Symetis and Direct Flow Medical. K. Hayashida is a proctor for transfemoral TAVI for the Edwards Company. The other authors have no conflicts of interest to declare.

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Combined percutaneous transvenous mitral commissurotomy and left atrial appendage closure as an alternative to anticoagulation for rheumatic atrial fibrillation

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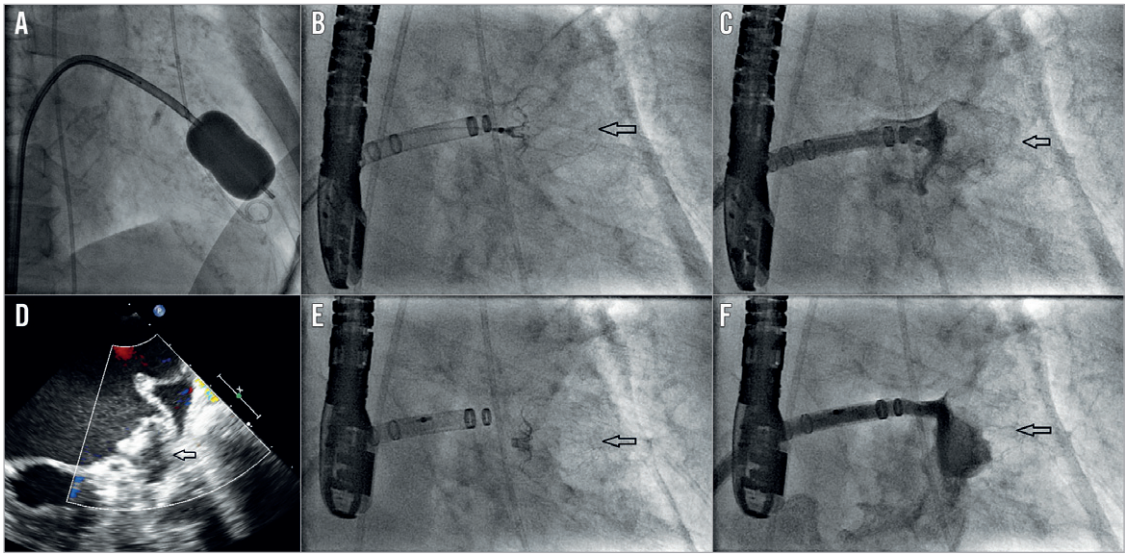

A 75-year-old female who had recently been diagnosed with a haemorrhagic rectal tumour was planned for long-term capecitabine, which has the potential to interact with warfarin, after surgical excision of her tumour. Thus, anticoagulation was deemed unsuitable for her. Combined percutaneous transvenous mitral commissurotomy (PTMC) and left atrial appendage (LAA) closure was carried out to reduce the risk of cardioembolic stroke as well as for cardiac optimisation prior to surgery. PTMC was performed using a 26 mm Inoue-Balloon catheter (Toray Medical Company Ltd., Chiba, Japan) with sequential dilatation up to 24 mm **(Panel 1A, Moving image 1, Moving image 2)**. The post-PTMC mean transmitral gradient improved to 3-4 mmHg with mild mitral regurgitation. An Amplatz Extra Stiff wire (Cook Medical, Bloomington, IN, USA) was kept in the left upper pulmonary vein while the Inoue-Balloon was removed. The LAA ostial diameter was then sized to be between 18 and 22 mm **(Moving image 3)**. The WATCHMAN™ delivery sheath (Boston Scientific, Marlborough, MA, USA) was placed distally in the appendage, following which a 24 mm WATCHMAN device was deployed **(Panel B, Panel C, Moving image 4-Moving image 8)**. The final position of the WATCHMAN device was confirmed by transoesophageal echocardiography (TEE) **(Panel 1D)** and fluoroscopy **(Panel E, Panel F)**. The patient has remained stable with no related adverse events to date.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Supplementary data

Moving image 1. Transseptal puncture.
Moving image 2. Final inflation of stenosed mitral valve with an Inoue-Balloon, size 24 mm.
Moving image 3. Imaging of the left atrial appendage.
Moving image 4. WATCHMAN device being deployed.
Moving image 5. WATCHMAN device redeployed after recapture for optimal placement.
Moving image 6. WATCHMAN device released after optimal placement.
Moving image 7. WATCHMAN device after release.
Moving image 8. Withdrawal of WATCHMAN delivery sheath.

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How should I treat a patient with critical stenosis of a bifurcation of the left main coronary artery with an acute angulation between the left main artery and the left circumflex artery?

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

CASE SUMMARY

BACKGROUND: A 49-year-old male with a history of coronary bypass surgery three months before presented with typical anginal chest pain on exertion. Coronary angiography showed a critical stenosis at the bifurcation of the left main coronary artery and diffuse stenosis in the left internal mammary artery graft.

INVESTIGATION: Physical examination, electrocardiogram, exercise testing, coronary angiography.

DIAGNOSIS: Left main artery stenosis post coronary bypass surgery with internal mammary artery graft failure.

MANAGEMENT: Stenting of the stenosis using a new wiring technique.

KEYWORDS: acute angulation, bifurcation, left main coronary artery

PRESENTATION OF THE CASE

A 49-year-old male with a history of prior coronary bypass graft surgery three months before came back with typical anginal chest pain on exertion. His angina was classified as grade III according to the Canadian Cardiovascular Society grading system. The risk factor for coronary artery disease in this patient was smoking. However, he had stopped smoking after the bypass surgery. An exercise stress test showed a positive result with horizontal ST depression in II, III, aVF, V4, V5, and V6 at low workload. His medications included aspirin 325 mg daily, simvastatin 20 mg daily, and atenolol 50 mg daily. Coronary angiography showed a 95% stenosis at the trifurcation of the left main coronary artery (LMCA) involving the ostium of the left anterior descending artery (LAD), the left circumflex artery (LCX), and the ramus intermedius (RI). The angulation between the left main artery and the left circumflex artery was nearly 90 degrees **(Figure 1, Moving image 1)**. The internal mammary artery was diffusely diseased without antegrade flow into the LAD **(Figure 2, Moving image 2)**. The saphenous grafts to the diagonal branch and the posterior descending artery were patent. Graft to the LCX was not found. He declined re-operation. His healthcare payment did not cover rotational atherectomy.

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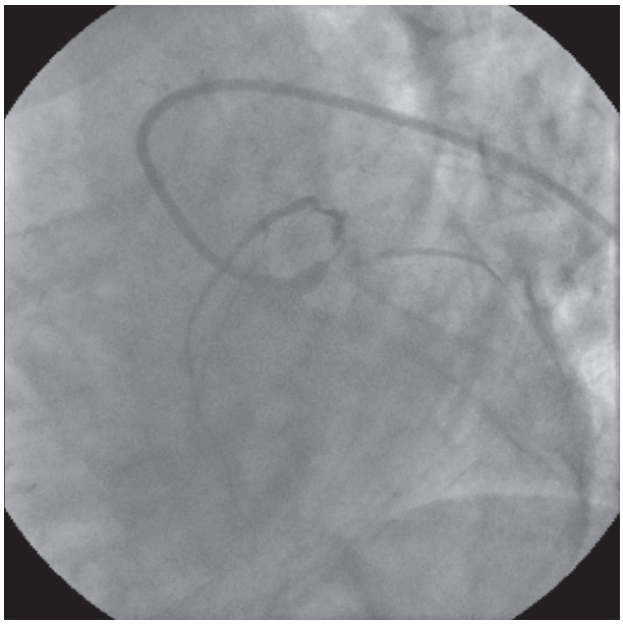

Figure 1. *Coronary angiogram showing a 95% stenosis at the trifurcation of LMCA involving the ostium of the LAD, the LCX, and the RI with angulation between the LMCA and the LCX of nearly 90 degrees.*

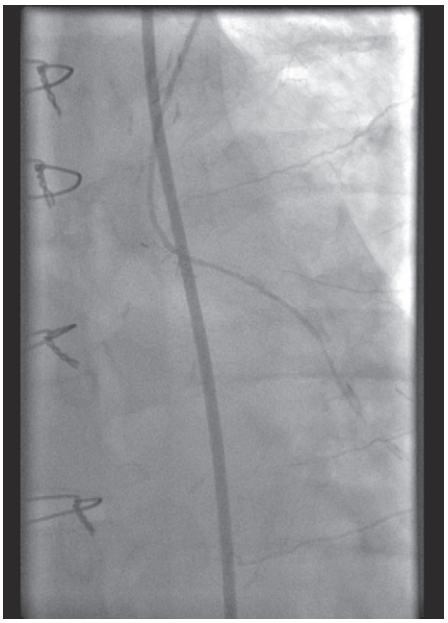

Figure 2. *The diffusely diseased internal mammary artery without antegrade flow into the LAD.*

How would I treat?

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The present case is one of three-vessel disease (3-VD) with a severely obstructive lesion involving a left main coronary artery (LMCA) trifurcation. This latter lesion is particularly complex as the disease involves the distal LMCA and the ostium of the three branches, classifying this trifurcation as "true" or "1,1,1,1", according to the Medina classification. In addition, the angle A ("Approach") between the LMCA and the left circumflex (LCX) is quite unfavourable, being superior to 70°, which is associated with more difficult side branch access. Primarily, this patient was correctly referred to coronary artery bypass grafting (CABG) in view of the diffuse 3-VD and LMCA disease, high anatomical complexity, young age and low surgical risk, as in these conditions surgery has been demonstrated to be more beneficial than percutaneous coronary intervention (PCI)[1]. Despite the technical failure of the surgery, probably due to stealing flow from the mammary artery to a residual collateral ramus, a re-operation is still a treatment option, considering that the estimated CABG operative mortality rate remains reasonably low at <2%, as assessed by the logistic EuroSCORE II. On the other hand, PCI with drug-eluting stents would be a viable, less invasive alternative strategy. Indeed, when the SYNTAX score is intermediate (>22 and <33), as in the present patient, PCI and CABG have similar overall five-year outcomes[2]. In addition, several registries, although small, have shown the feasibility and high procedural success rate of PCI for LMCA trifurcation, with good long-term safety results, despite a relatively high rate of target lesion revascularisation, especially in true trifurcations, suggesting the need for an optimal stenting technique[3,4]. Thus, the collegial assessment by the local Heart Team would be appropriate for decision making in this case, but the patient's refusal of the surgical approach has driven the choice for PCI. In particular, this is a very complex PCI that should be performed in centres with the prompt availability of intensive care and surgical back-up. Moreover, the complexity of the lesion requires precise planning of the materials and PCI technique, and would make it reasonable to use ventricular assistance with the Impella® system (Abiomed, Danvers, MA, USA) or intra-aortic balloon pumping before starting the procedure.

PCI strategy

An 8 Fr left XB (Cordis, Johnson & Johnson, Warren, NJ, USA) is the guiding catheter of choice. Firstly, we would perform the wiring of all three branches, preferably by using a spring coil, floppy, extra support guidewire for the left anterior descending artery (LAD) and polymeric tapered guidewires – with a large radius of tip curvature – for the ramus intermedius (RI) and LCX. After that, we would plan to predilate first only the LAD with a non-compliant 2.0-2.5/20 mm balloon and then the RI and LCX in a kissing fashion with low-profile, short and small balloons (1.5-2.0/15 mm). In case of LCX difficult access, a 7 Fr GuideLiner® (Vascular Solutions Inc., Minneapolis, MN, USA) or the anchor technique would be attempted. A progressive increasing of balloon sizes would be used for predilation in the three branches, based on the appearance of the lesions after each step. Intravascular ultrasound (IVUS) would be performed before stent implantation, to assess vessel diameter and calcium distribution, in order to guide further possible debulking strategies. Regarding the optimal stenting strategy in such a complex case, there is no clear evidence or standardisation, with the best technique being the one that fits the specific anatomy best. While a two-stent technique on the LAD and LCX plus balloon on the RI could be considered, in view of the large plaque burden involving the whole bifurcation, which is a distribution pattern associated with worse outcomes[5], we would opt for a three-stent technique, starting with stenting the LCX and RI by a TAP technique and then a stent on the LMCA-LAD crushing the LCX stenting. We would perform the following post-dilatation sequence: proximal optimisation technique (POT) on the LMCA, distal recrossing of the LCX stent, kissing balloon of the LMCA-LCX and final POT on the LMCA. Post-stenting IVUS or OCT would be performed in order to guide further strategies to optimise stent apposition and expansion, by achieving minimal lumen areas of at least 5 mm^2 in the LCX and RI, 6 mm^2 in the LAD ostium, 7 mm^2 at the polygon of confluence and 8 mm^2 in the LMCA[6].

Conflict of interest statement

The authors have no conflicts of interest to declare.

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How would I treat?

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This is a very interesting and educational case with different important issues to highlight. A young man with multivessel disease and a complex trifurcation lesion at the distal left main (LM), left anterior descending artery (LAD), ramus intermedius (RI) and left circumflex artery (LCX). Bypass surgery was the first option for myocardial revascularisation which he underwent three months before. It is not clear from the two angiographic images presented (obtained after surgery) what the SYNTAX score was and what the left ventricular function was in this patient prior to surgery. Vessel size seems almost small and run-off is not optimal, which had probably contributed to an early occlusion of the LIMA. Also, a depressed left ventricular function might have played an important role.

The second important issue is what is the best option for this patient - re-CABG or PCI? Re-operation is always associated with higher risk, particularly if other grafts are still patent, as in this patient. Consequently, PCI should be considered as the first option, despite the fact that the LM trifurcation lesion in this case is very complex and challenging.

As in any complex lesion, it is very important to plan the procedure carefully before starting. In this case, I would plan a two-stent technique for the LM-LAD–RI bifurcation and only POBA for the LCX to avoid excessive stent overlapping at the carina which might predispose to stent thrombosis and in-stent restenosis. I would choose a 7 Fr guiding catheter. Then I would place three wires in all the trifurcation branches. I would predilate with a kissing balloon from the LM to RI and the LM to LAD with 2.5×15 mm semi-compliant balloons. In the event of any compromise to the LCX, I would also predilate the LCX with a 1.5 mm semi-compliant balloon. Then I would proceed to stenting the RI, simultaneously keeping a 2.5×15 mm balloon in the LM to LAD with a minimal protrusion of the stent from the RI to LM. After deployment of the stent in the RI, I would retrieve the delivery balloon catheter into the LM a bit, and perform a kissing balloon inflation. Then I would completely retrieve the delivery balloon and then at high pressure inflate the balloon still *in situ* from the LM to LAD. Then I would place the second stent covering the whole LM to proximal LAD and jailing both wires in the RI and LCX. I would recross two wires through the LM-LAD stent into the RI and into the LCX. Firstly I would dilate the stent strut towards the LCX and then towards the RI, followed by a second kissing balloon inflation LM-LAD and LM-RI, and finally POT inflation with a short 4.0×8 mm balloon in the LM (this approach can be defined as the DK reverse TAP approach). IVUS guidance, if available, is recommended since it might positively impact on the clinical outcome. In case of any compromise of the LCX ostium, I would perform another dilatation of the LM-LCX with (maximum) 2.0×12 mm balloon followed by a DEB 2.5×18 mm at nominal pressure.

The approach described above offers some advantages over the classic mini-crush or DK crush, since it avoids any overlapping of three layers of struts and makes the procedure easier, particularly in a complex anatomy such as in our case with a full coverage of the carina, despite the SB angulation.

Conflict of interest statement

The author has no conflicts of interest to declare.

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How did I treat?

ACTUAL TREATMENT AND MANAGEMENT OF THE CASE

Percutaneous coronary intervention was selected as the treatment strategy according to the patient's decision. The LAD was wired using the HI-TORQUE Whisper guidewire (Abbott Vascular, Santa Clara, CA, USA). However, attempts to wire in the LCX were unsuccessful. A 2.5×15 mm balloon was then inflated at 2 atm at the bifurcation of the LMCA in an attempt to assist wiring in the LCX, but the wire still could not be passed into the LCX. The same 2.5×15 mm balloon was inflated again in the LAD beyond the lesion and was pulled back against the plaque towards the guiding catheter to change the angulation between the LMCA and the LCX **(Moving image 3)**. The wire could then be passed into the RI branch. The kissing balloon technique was performed in the LAD and RI using a 2.5×15 mm balloon in the LAD and a 2.0×15 mm balloon in the RI, both of which were at nominal pressure. However, the wire still could not be passed into the LCX due to the angulation between the RI and the LCX. The same 2.0×15 mm balloon was inflated again in the RI and was pulled back towards the guiding catheter to reduce the RI-LCX angle **(Moving image 4)**. The wire was then passed into the LCX. The kissing balloon technique was performed using two 2.5×15 mm balloons in the LAD and the LCX, both of which were at 8 atm. The mid-LAD lesion was corrected by placement of a 3×23 mm XIENCE V® drug-eluting stent (DES) (Abbott Vascular). The T-stenting technique was selected for correction of the LMCA lesion using a 2.5×12 mm XIENCE V DES in the proximal LCX and a 3.5×23 mm XIENCE V DES in the LM-LAD junction. Proximal optimisation of the LM-LAD stent was carried out by a 4×8 mm balloon at 12 atm. TIMI 3 flow was achieved in all branches **(Moving image 5)**.

Various techniques for wiring a side branch artery with a nearly acute angle take-off had been considered before the pull-back balloon technique. Kawasaki et al developed the reverse guidewire technique[7], and Suzuki et al combined that technique with a Crusade catheter (Kaneka Medix Corp., Tokyo, Japan)[8]. However, neither of the aforementioned techniques would have helped to pass a wire into the LCX in our case because the severe stenosis in the proximal LAD beyond the LCX ostium would have precluded the bent tip of a wire going into the LCX. Inflating a balloon at the LAD ostium to direct a wire into the LCX might have led to plaque shifting from the ostium of the LAD towards the ostium of the LCX. Colombo and Stankovic suggested other methods, including gradual predilation in the main branch or the use of the Venture™ wire control system (St. Jude Medical, St. Paul, MN, USA)[9]. The former was attempted unsuccessfully earlier as mentioned. To date, the Venture wire control system is not available in Thailand. Rotational atherectomy could have removed the atherosclerotic plaque and helped to pass the wire into the LCX. However, the patient's healthcare payment did not cover that procedure.

I invented the pull-back balloon-assisted wiring technique for a bifurcation lesion with difficult angulation in 2008 and named it the "Plaque-plowing technique" in an oral presentation at EuroPCR 2013. The principle of this technique is to avoid an unfavourable direction of the snowplough phenomenon when an angioplasty balloon is inflated on an atherosclerotic plaque, especially a plaque with an overhanging edge near the bifurcation. Instead of inflating a balloon directly on the plaque, a balloon is inflated beyond the plaque and pulled back to move the plaque out of the side branch ostium. This technique has been performed in five cases with such lesions when the wires were not able to be passed into side branches due to the acute angulation between the side branch and the proximal main vessel. The technique was successful in these five cases without complication in any patient. Nevertheless, it has never been attempted more than once in a single lesion. This case demonstrates that the principle is applicable even in a complex trifurcation lesion **(Figure 3-Figure 7)**. The main advantage of this technique is its simplicity. An additional device such as a Crusade catheter is not required. The manipulation of a wire as in the reverse wire technique is also unnecessary. Theoretical disadvantages of the Plaque-plowing technique include distal embolisation and coronary artery dissection. However, such complications have not yet been demonstrated in any patients.

Conflict of interest statement

The author has no conflicts of interest to declare.

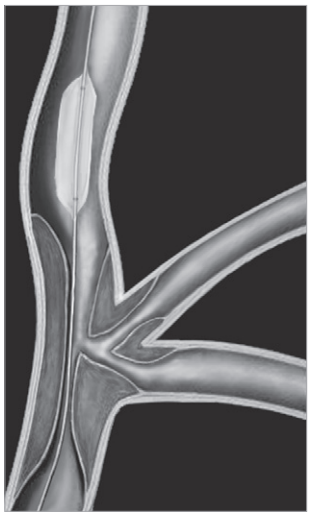

Figure 3. *Balloon inflated beyond LAD plaque.*

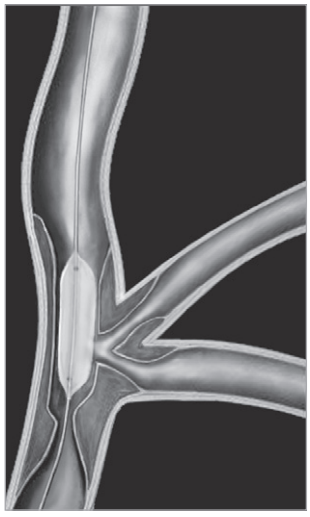

Figure 4. *Balloon pulled back towards a guiding catheter thus widening the angulation between the LMCA and the RI.*

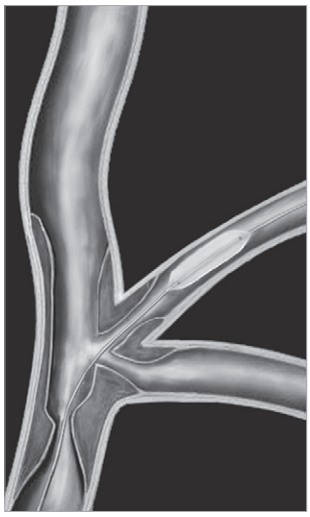

Figure 5. *Balloon inflated in the RI.*

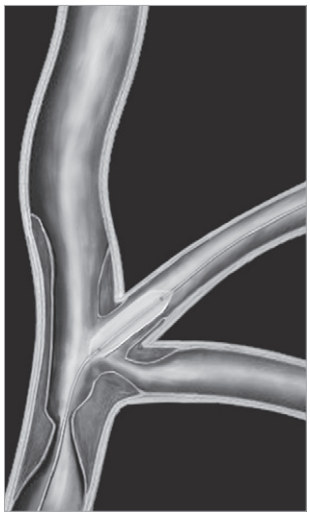

Figure 6. *Balloon pulled back from the RI towards a guiding catheter, resulting in the widening of the angulation between the LMCA and the LCX.*

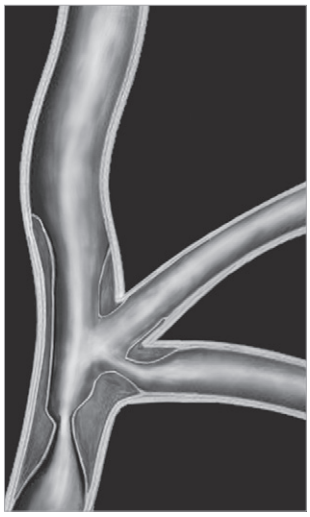

Figure 7. *Schematic drawing of the lesion after two balloon pullbacks had been performed.*

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Supplementary data

Moving image 1. Coronary angiogram showing a 95% stenosis at the trifurcation of LMCA involving the ostium of the LAD, the LCX, and the RI branch with angulation between the LMCA and the LCX of nearly 90 degrees.

Moving image 2. The diffusely diseased internal mammary artery without antegrade flow into the LAD.

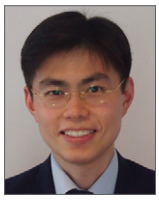
Moving image 3. Balloon inflated again in the LAD beyond the lesion and pulled back against the plaque towards the guiding catheter in an attempt to change the angulation between the LMCA and the LCX.

Moving image 4. Balloon inflated again in the RI and pulled back towards the guiding catheter in an attempt to reduce the RI-LCX angle.

Moving image 5. Final angiogram showing TIMI 3 flow in all branches with no dissection demonstrated.

AsiaIntervention 2016;2:65-72

How should I treat a percutaneous posteromedial mitral periprosthetic paravalvular leak closure in a bioprosthesis with no radiopaque ring?



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1. Mount Elizabeth Hospital, Singapore; 2. Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Invited experts: Nicolas M. Van Mieghem[3], MD, PhD; Eric Eeckhout[4], MD, PhD; Ka-Yip Lo[4], MD; Alain Delabays[4], MD

3. Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; 4. Cardiology Service, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

CASE SUMMARY

BACKGROUND: A 66-year-old male with a previous mitral valve replacement (Mosaic bioprosthesis) presented with worsening cardiac failure due to a severe mitral paravalvular regurgitation.

INVESTIGATION: Transoesophageal echocardiography showed that the defect was located posteromedially with a 3 mm width. Fluoroscopy showed that the Mosaic bioprosthesis had a radiolucent ring with only three markers to indicate the top of the stent posts.

DIAGNOSIS: Severe posteromedial mitral periprosthetic paravalvular leak in a bioprosthesis with no radiopaque ring.

MANAGEMENT: Percutaneous paravalvular leak closure was performed. Formation of an arteriovenous loop was necessary to facilitate antegrade deployment of an AVP III device. However, embolisation into the left ventricle occurred after device release. The device was snared and, subsequently, a larger AVP III device was successfully implanted.

KEYWORDS: bioprosthesis, embolisation, mitral regurgitation, paravalvular leak, percutaneous, prosthetic valve

PRESENTATION OF THE CASE

A 66-year-old male presented with worsening dyspnoea (NYHA Class III-IV), due to cardiac failure for several months. He had had a mitral valve replacement with a 27 mm Mosaic® bioprosthesis (Medtronic, Minneapolis, MN, USA) nine years before. Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) revealed a left ventricular ejection fraction (LVEF) of 45% and severe mitral regurgitation (MR) due to a paravalvular leak (PVL). The defect was located posteromedially (4 o'clock position on the surgical view) and measured 3 mm at its width **(Figure 1A, Figure 1B)**. The effective regurgitant orifice area was calculated to be 0.4 cm² and the regurgitation volume was 64 ml. The bioprosthetic valve leaflets were well visualised to be functioning normally and not thickened, with satisfactory haemodynamics (mean pressure gradient 7 mmHg). Coronary angiography showed no significant coronary artery disease. A left ventriculogram showed an MR jet located posteriorly and medially **(Figure 2A, Figure 2B)**.

A redo open chest surgery to repair the PVL was offered; however, the patient declined surgical intervention. Hence, a percutaneous option was planned. The procedure was performed under general anaesthesia with TEE and fluoroscopic guidance. Transseptal puncture was performed with a Brockenbrough needle and Mullins sheath. As the initial strategy was to access the PVL antegrade from the left atrial (LA) side, the transseptal puncture was made more cranial and anterior to allow room for catheter and wire manipulation. After several attempts, the PVL was

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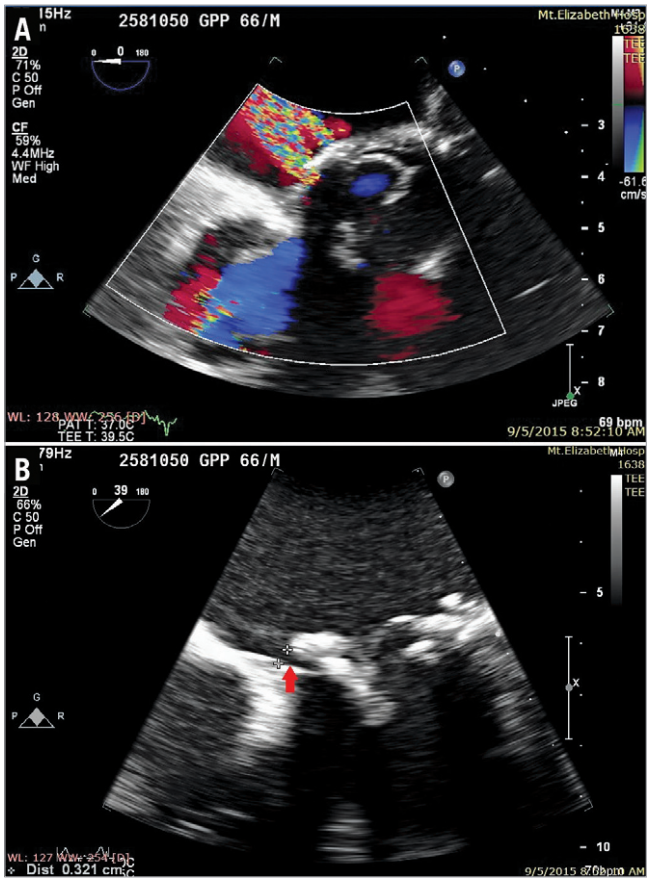

Figure 1. *Pre-procedure TEE. A) TEE image showing severe MR through the PVL. B) TEE image showing the PVL defect (red arrow) measured at 3 mm.*

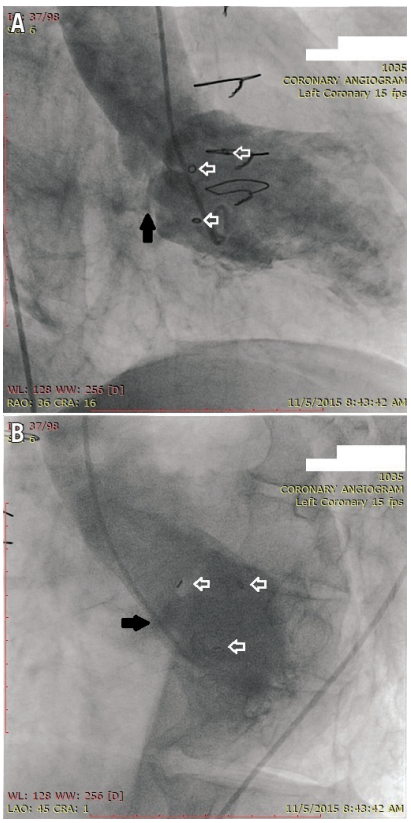

Figure 2. *Pre-procedure LV angiography. A) LV angiography image (RAO cranial view) showing the location of the MR jet (black arrow) and the markers of the stent posts (white arrows). Note the lack of a radiopaque ring. B) LV angiography (LAO view) showing the location of the MR jet (black arrows) and the markers of the stent posts (white arrows). Note the lack of a radiopaque ring.*

crossed with a 4 Fr Cobra catheter (Cordis, Fremont, CA, USA) and a 0.035 inch straight tip Glidewire® (Terumo Crop., Tokyo, Japan), and then a 5 Fr pigtail catheter was placed in the left ventricular (LV) apex **(Figure 3)**. A 260 cm Amplatz Super Stiff™ wire (Boston Scientific, Marlborough, MA, USA) was advanced through the pigtail catheter but the entire system prolapsed back into the LA.

The decision was made to perform retrograde crossing via an access from the femoral artery. The PVL was crossed retrogradely with a 5 Fr AL1 catheter and an angled Glidewire. However, due to the need for the AL1 catheter to be looped back to direct it towards the defect, there was insufficient catheter length to advance it across the PVL. A 15 mm GooseNeck® snare (ev3/Covidien, Plymouth, MN, USA) was then advanced via the femoral vein and the angled Glidewire was snared in the LA and exteriorised, forming a stable arteriovenous (AV) rail **(Figure 4A, Figure 4B)**. A 5 Fr Shuttle® sheath (Cook Medical, Bloomington, IN, USA) was then advanced from the femoral vein across the PVL into the ascending aorta **(Figure 5)**. A 4×8 mm AMPLATZER™ Vascular Plug III (AVP-III) (St. Jude Medical, St. Paul, MN, USA) was positioned across the PVL **(Figure 6)**; due to the lack of a radiopaque sewing ring, only TEE (but not fluoroscopy) was helpful in ascertaining that a disc was on either side of the mitral bioprosthesis. After a stable "tug test", the device was released. Shortly after release, the device was found to have embolised, and was highly mobile in the LV, tumbling back and forth between the mitral valve, the LV apex and left ventricular outflow tract **(Figure 7A, Figure 7B)**.

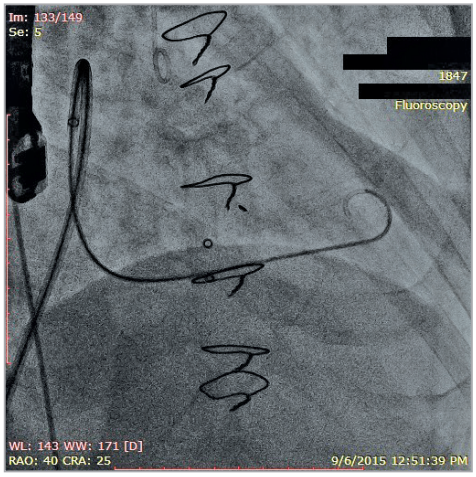

Figure 3. *Fluoroscopy image showing pigtail crossing from LA to the LV apex.*

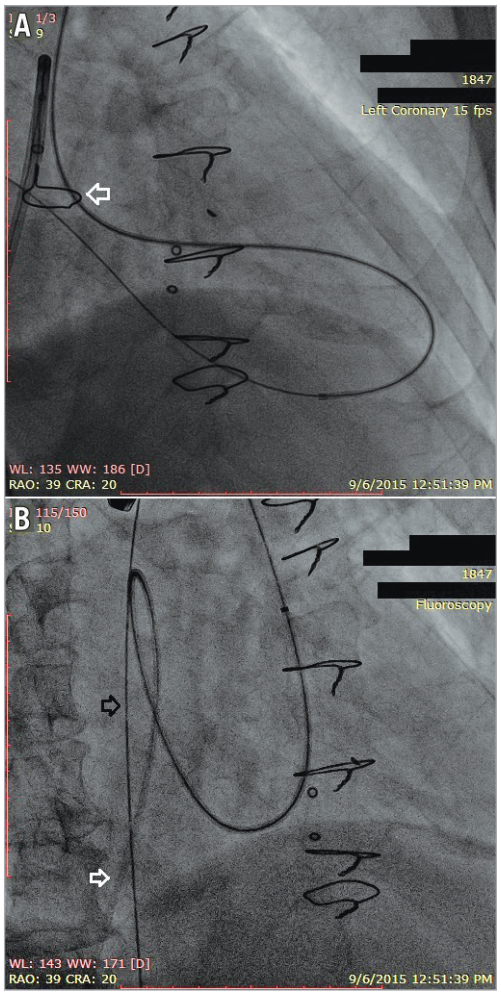

Figure 4. *Intra-procedure fluoroscopic images demonstrating formation of the AV loop. A) Fluoroscopy image showing the AL1 catheter and Glidewire crossing the PVL from the LV side and the GooseNeck snare (arrow) in the LA. B) Fluoroscopy image showing the AV loop (white arrow indicates sheath from the femoral vein and black arrow indicates the Glidewire from the femoral artery).*

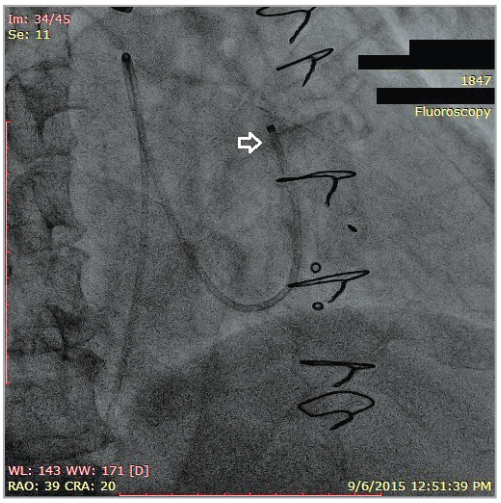

Figure 5. *Fluoroscopy image showing the Shuttle sheath crossing the PVL antegradely into the ascending aorta (arrow).*

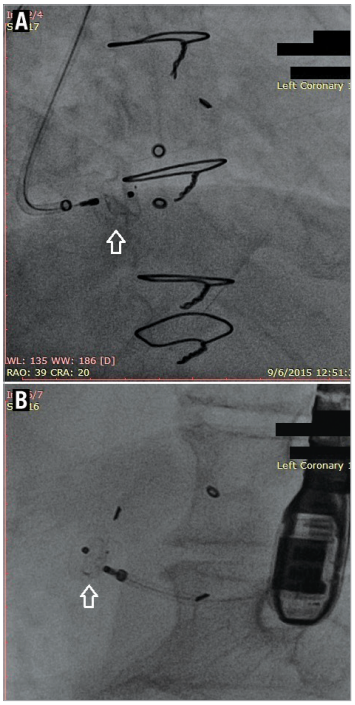

Figure 6. *Intra-procedure fluoroscopic images demonstrating deployment of the AVP-III device. A) Fluoroscopy image (RAO cranial view) showing the AVP-III deployed across the PVL (arrow). B) Fluoroscopy image (LAO view) showing the AVP-III deployed across the PVL (arrow).*

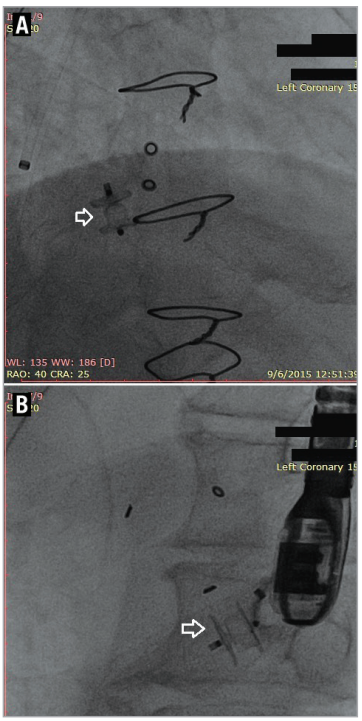

Figure 7. *Intra-procedure fluoroscopic images showing the embolised AVP-III device in the LV cavity. A) Fluoroscopy image (RAO cranial view) showing the embolised AVP-III device (arrow). B) Fluoroscopy image (LAO view) showing the embolised AVP-III device (arrow).*

How would I treat?

Nicolas M. Van Mieghem[3]*, MD, PhD

3. Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

I would like to take one step back and look at the pre-procedural planning. The patient underwent mitral valve replacement with a 27 mm Mosaic bioprosthesis nine years earlier. By echocardiographic evaluation there is a severe paravalvular leak located posteromedially, 3 mm in size with an effective regurgitant orifice area of 0.4 cm^2 and a regurgitation volume of 64 ml.

A crucial step is to figure out how the bioprosthesis would look under fluoroscopy. An important clinical asset in pre-procedural work-up for a failing bioprosthesis is the "Valve in Valve App" by Vinnie Bapat[1]. The app indeed confirms the absence of a radiopaque ring, but also the presence of fluoroscopic markers on the tip of the three stent posts, about 18.5 mm above the ventricular edge of the bioprosthesis.

I would always complete pre-procedural planning of periprosthetic mitral leaks with a contrast multi-slice computed tomography (MSCT) scan of the heart to obtain unique 3D perspectives to facilitate fluoroscopy guidance. The interatrial septum, the mitral valve apparatus and periprosthetic leaks can be identified by MSCT through double-oblique multiplanar and volume-rendered MSCT reconstructions[2]. An optimal C-arm angulation perpendicular or axial to a given anatomical structure can be simulated; in this case the plane connecting the three radiopaque markers on the Mosaic posts would be the reference. The distance of the Mosaic basal plane relative to the radiopaque markers can also be appreciated in the selected angiographic projection. Simulated angiographic views can be projected in the catheterisation room or even (partially) fused onto the fluoroscopy.

Posteromedial leaks close to the interatrial septum can be tough to wire even with steerable catheters from a transseptal left atrial approach. I would favour a transapical access to minimise catheter and wire manipulations, increase coaxiality and augment per-procedural control.

The embolised plug in the current situation needs to be snared. I would first start by crossing the aortic valve with a 6 or 7 Fr Judkins Right 4 guiding catheter. An Amplatz GooseNeck snare can then be advanced through the guiding catheter and released into the left ventricular outflow tract. I would try to snare the plug in the LVOT and, once fixed against the guiding catheter, withdraw the whole assembly from the groin. A "crossover balloon technique" from the opposite groin can help minimise bleeding and create proper circumstances to close the arteriotomy with one or two suture-based closure devices[3]. I would end the procedure there and plan a second attempt for transapical catheter-based leak closure at a later stage. The type and size of the plug would depend on leak characteristics but I would select a larger size AMPLATZER Vascular Plug III (e.g., 10×5 mm) even though the device embolised in this case because both discs were on the ventricular side of the leak during device release.

Conflict of interest statement

The author has no conflicts of interest to declare.

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How would I treat?

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In the present volume of the AsiaIntervention journal, Chiam and colleagues report on a failed attempt at percutaneous closure of a mitral paravalvular leak (PVL). After positioning of a 4×8 mm AVP-III at the level of the leak, device embolisation within the left ventricular cavity occurred. We wish to comment on how this complication could have been prevented and treated.

Prevention

Transoesophageal echocardiography (TOE) (in particular 3D acquisition) is key to locating and quantifying the width and extension of the leak in order to judge the feasibility of percutaneous closure and to define the interventional strategy. In the present case, only 2D images (limited to one dimension) are provided, demonstrating a 3 mm gap between the valve and the annulus measured at an angle of 40°. Only 3D TOE can demonstrate the extension of the leak. The colourjet on **Figure 1A** suggests an extension of at least 10 to 15 mm around the annulus. Precise dimensions can be obtained either on greyscale or in a colour 3D data set using a dedicated software **(Figure 8A, Figure 8B)**. In this particular case, suboptimal image acquisition with undersizing of the leak led to an inappropriate strategy with device embolisation as a consequence.

Interventional strategy

The initial strategy was antegrade leak crossing which failed as advancement of a 260 cm Super Stiff wire resulted in the prolapse of the whole system in the left atrium. To prevent this, a few recommendations can be given. First adequate back-up needs to be assured by a dedicated transseptal sheath. Practically, the steerable Agilis™ 8.5 Fr sheath (St. Jude Medical) provides excellent back-up and enables antegrade exploration of the leak for crossing. From the images provided, it seems that the authors may have used this catheter. Second, a 125 cm long Multipurpose catheter (Cordis, Fremont, CA, USA) may be more appropriate **(Figure 9)** as it can be bent at the apex of the left ventricular outflow tract providing

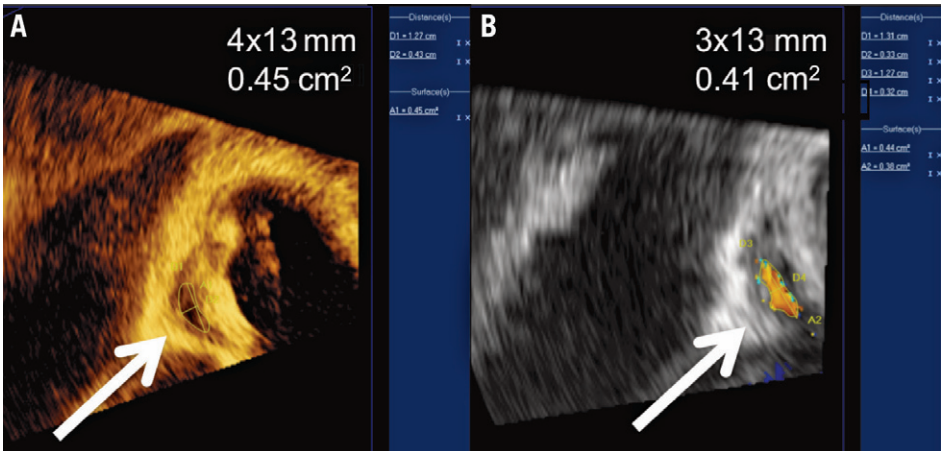

Figure 8. *3D TOE assessment of a paravalvular leak. Assessment using greyscale (A) or colour 3D data set (B) using a dedicated software.*

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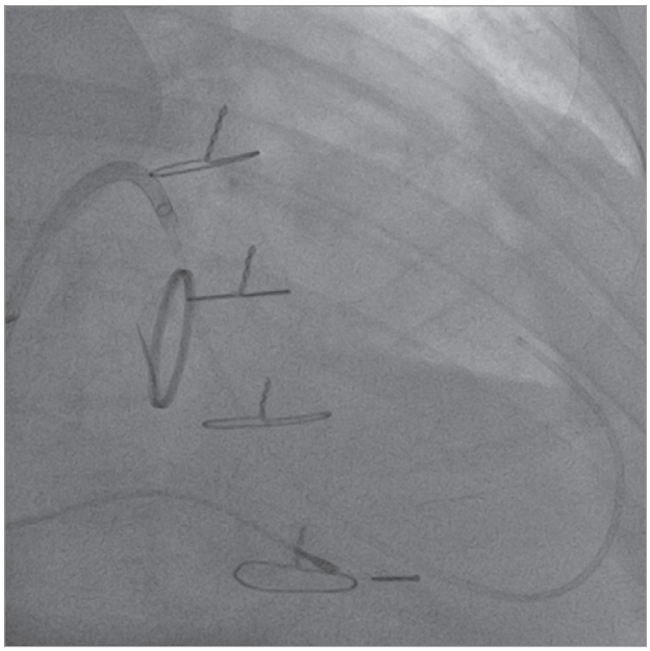

Figure 9. *Bending of a long 6 Fr Multipurpose catheter at the apex of the left ventricle through an Agilis catheter to ensure adequate back-up.*

a longer and more stable working zone to prevent prolapse. Third, new wires specifically for TAVI such as the Confida™ (Medtronic) or Safari™ (Boston Scientific) wires may be preferred to the Amplatz Super Stiff wire as the transition zone between the rigid and soft parts of the wire is more progressive. Even if these recommendations are irrelevant to the final outcome in this case, they are important to simplify a "mostly complex" procedure. Nevertheless, establishing an arteriovenous loop, as an alternative, enabled initial, successful antegrade positioning of a closure device. This approach carries a certain risk, as it exposes the patient to laceration of the native aortic valve during wire and catheter manipulation, partially also because of non-coaxial alignment of the loop across the heart.

Complication management

A 4×8 mm AVP-III device was positioned under echo guidance. Fluoroscopy was not of use because of the presence of a radiolucent ring. Echocardiography (in particular 3D with assessment of any residual leak) is key prior to release of any device. The authors do not provide any images for this part of the procedure but we suspect the presence of a residual leak at this stage. In case of any significant residual leak, the device should be retrieved and a larger or other type of system should be implanted. Once embolised, percutaneous retrieval should be considered, particularly as this implant is relatively small and soft. Through a large 10 Fr arterial sheath, a 6 Fr JR4 guiding catheter may be positioned in the left ventricular outflow tract, and subsequent snaring with an Amplatz GooseNeck snare (15-120 or 20-120 mm) (ev3/Covidien) within the left ventricle should be considered.

Conflict of interest statement

E. Eeckhout and A. Delabays have proctoring contracts with St. Jude Medical. The other author has no conflicts of interest to declare.

How did I treat?

ACTUAL TREATMENT AND MANAGEMENT OF THE CASE

We immediately proceeded to attempt to snare the dislodged AVP-III. The sheath size in the left femoral artery was increased from 6 Fr to 8 Fr. As the device was not in a stable position, but was alternately embolising back and forth from under the mitral valve to the LV apex to the left ventricular outflow tract, it was finally snared after prolonged attempts with a 7 Fr internal mammary shape guide catheter and a 10 mm GooseNeck snare **(Figure 10)**. The device, snare and guide catheter were successfully removed as a unit through the femoral sheath.

The decision was made to proceed with the percutaneous PVL closure. The PVL was again crossed retrogradely in the same fashion, and the Glidewire was snared in the LA and exteriorised to form an AV rail. The 5 Fr Shuttle sheath was advanced from the femoral vein across the defect and into the ascending aorta. The largest diameter available AVP-III (5×10 mm) was selected and deployed across the defect. TEE showed that the two discs were straddling the mitral bioprosthesis, and the MR was reduced **(Figure 11A, Figure 11B)**. After confirming that the device was in a firm and stable position using the "tug test", it was released.

The patient made an uneventful recovery and was discharged from hospital the following day. At one month, he reported that his functional capacity had improved markedly (NYHA II). Echocardiography showed that the AVP-III was in a stable position; LVEF was unchanged at 45% with residual mild MR (effective regurgitant orifice [ERO] 0.2 cm², regurgitant volume 32 ml). Haemoglobin level was stable and there was no evidence of haemolysis.

Discussion

Percutaneous PVL closure is an attractive therapeutic option for patients with periprosthetic paravalvular leaks as it obviates the need for a redo open chest surgery, and is a class IIa recommendation according to current guidelines[4]. An antegrade transseptal or retrograde transarterial approach, or a combination of both could be used for percutaneous mitral PVL closure. A transapical approach allows a more direct access to the PVL and potentially simplifies crossing of the PVL, but this would usually require a mini left thoracotomy in most cases, and adds complexity to the procedure[5,6].

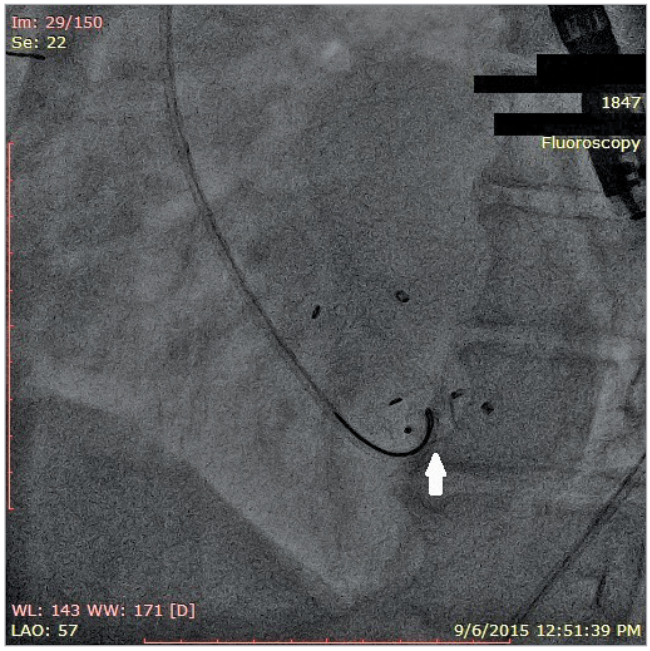

Figure 10. *Fluoroscopy image showing the dislodged AVP-III in the LV and the GooseNeck snare within the internal mammary (IM) guide catheter (arrow).*

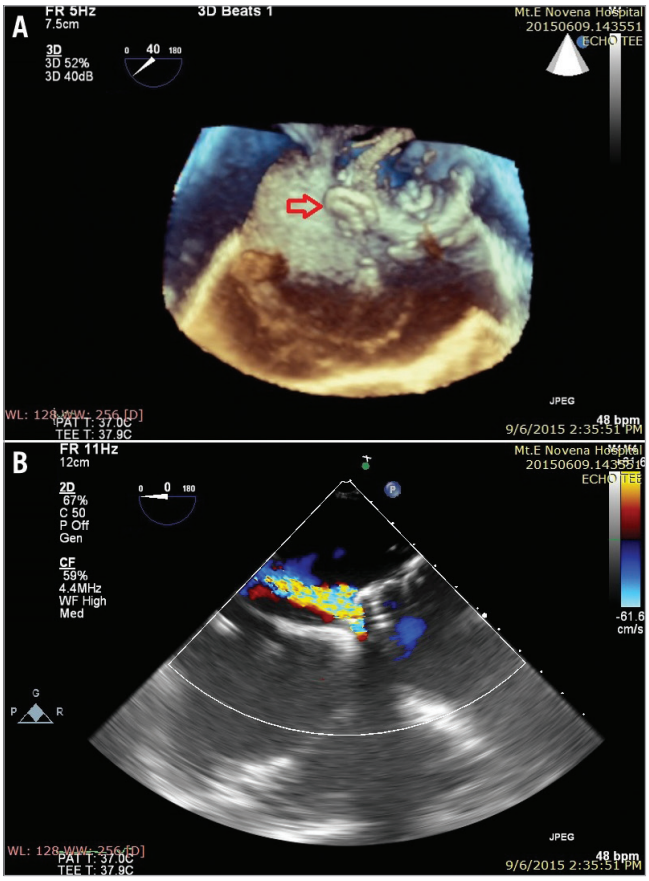

Figure 11. *Intra-procedure 3D TEE and 2D TEE images after final device deployment. A) TEE image showing the AVP-III device disc (arrow) on the LA side (the image is rotated such that the left atrial appendage is on the right of the image). B) TEE image showing a reduced MR jet.*

In our case, the posteromedial location of the PVL defect (4 o'clock on the surgical view from the LA) increased the technical difficulty, making both antegrade and retrograde crossing of the defect very challenging. This was compounded by the lack of a radiopaque sewing ring to act as a marker on fluoroscopy. Although the use of an Agilis steerable catheter could have facilitated antegrade crossing, the main obstacle was the inability to achieve a stable position of the stiff wire to allow subsequent catheter (and delivery system) exchanges. Recognising this, the defect was crossed retrogradely, and wire snaring from the LA side was performed to form a stable and highly supportive AV loop.

Pre-procedure TEE measured the PVL width at 3 mm and this was confirmed on the intra-procedure TEE. Thus, we were initially of the opinion that a 4×8 mm AVP-III device would be sufficient, as the dimensions were of the waist of the device and the larger discs on either side would be larger (8×12 mm). Less oversizing would also theoretically carry a lesser risk of further extending the PVL defect. As the device embolised shortly after release, it was probably undersized, although the possibility that the proximal disc, despite TEE guidance, was not completely in the LA side cannot be excluded. A lack of a radiopaque bioprosthetic ring could have contributed to this complication.

Although early and late device embolisations have been known to occur infrequently, they have mostly occurred with the AMPLATZER Ventricular Septal Defect Occluder, AMPLATZER Duct Occluder or the AVP-II devices (all St. Jude Medical)[7-11], and only rarely with the AVP-III device[6,12]. The AVP-III has been reported to have high success and low complication rates[6,13] due to its oval shape and technical properties, and perhaps could be the device most suited for PVL closures in the majority of cases. Fortunately, in this case, the embolised device was successfully snared despite the technical challenge, as the dislodged device was highly mobile in the LV cavity. Surgical device removal was considered as a back-up option, but that would have entailed conversion to open surgery and a risk of systemic embolisation of the device whilst awaiting transfer.

Our patient experienced significant improvement in functional status despite the residual mild MR. This demonstrates that meaningful clinical benefit can be derived from partial reduction of a PVL, and complete or near complete closure may not be necessary.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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