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Volume 3 - Number 1 - January 2017 - ISSN: 2426-3958

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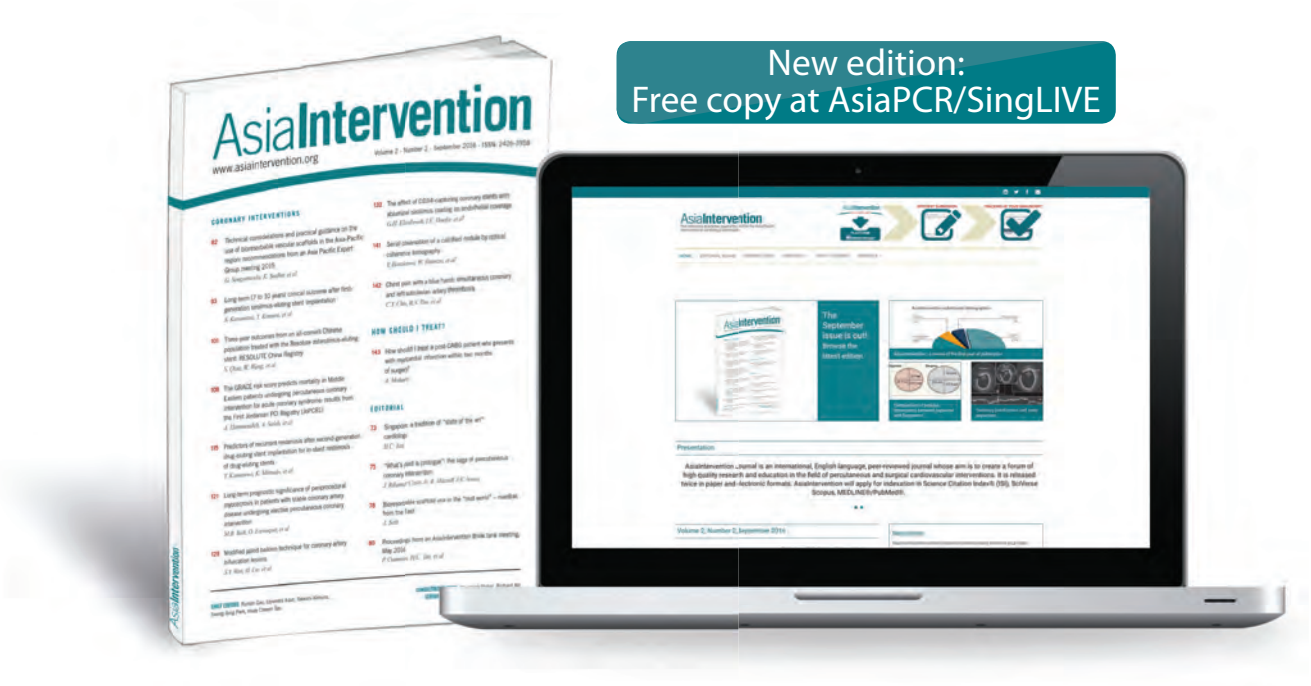

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AsiaIntervention Journal

ASIAINTERVENTION
Publication : 2 numéros par an
Volume 3 - N°1 - janvier 2017

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Editeur :
Frédéric Doncieux

Europa Digital & Publishing est une marque commerciale d'Europa Group

Président: Marc Doncieux.
Principal actionnaire : FINANCIERE MF DONCIEUX;
ISSN : 2426-3958
ISSN Online : 2491-0929
Dépôt légal à parution

Imprimé à Singapour par :
Royale Press Pte Ltd
Blk 1 Ang Mo Kio Industrial Park 2A
#04-05 AMK Tech 1
Singapore 568049

EuroIntervention est édité par la Société Europa Group, SAS au capital de 1 000 000 euros, siège social : 19, allées Jean-Jaurès, 31000 Toulouse, France ; RCS Toulouse 342 066 727, APE 8230 Z.

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A panoply of milestones and achievements

Upendra Kaul, Takeshi Kimura, Seung-Jung Park, Huay Cheem Tan and Runlin Gao

Chief Editors, AsiaIntervention

We begin 2017 having passed several milestones, among which we count this new edition of AsiaIntervention. As you, our readers, are well aware, while this is not the first edition of our fledgling journal, we are still at the early stages of establishing our reputation. Anyone who has ever been involved with a serious, peer-reviewed, scientific publication will know that the growing pains can be considerable and the remedy – at least at first – difficult to apply or find... namely, greater participation from our readership. Our journal is now picking up speed, and developing its own rhythm and personality, but the future depends on your submissions and your critical response. We are convinced both of the quality we offer here and of your active involvement in the coming years.

The dynamic Asian region, which we all represent and which we serve through our educational programmes and the care we offer our patients, is not only a rich and growing source of clinical research, but has gained an international reputation for our experience and clinical excellence. This new edition of AsiaIntervention reflects this, and it is not by chance that its publication coincides with another milestone, AsiaPCR/SingLIVE 2017, a meeting which has established itself as one of the leading educational courses in Asia and worldwide.

Dedicated AsiaIntervention session at AsiaPCR/SingLIVE

AsiaPCR/SingLIVE has been conceived to offer the highest degree of exchange among participants. In this spirit, on Thursday 19 January 2017, we offer a special AsiaIntervention session during the congress that will explore, through open and interactive discussions, some of the topics and concerns we touch on in the journal. Chaired by U. Kaul, T. Santoso and H.C. Tan, this session will focus on clinical research, helping us to understand the clinical development of medical devices as well as the evolution in regulatory pathways within Asia, and will try to provide insights into interpreting data as we move from clinical research to evidence-based medicine. Patrick W. Serruys, Editor in Chief of EuroIntervention and senior consulting editor of AsiaIntervention, will speak on "the art of writing a research paper". U. Kaul, H.C. Tan and S.J. Park will also be speaking. Other topics will include the challenges of innovation as well as recognising current needs and opportunities for conducting clinical trials in Asia.

Well-deserved congratulations

If we need further proof of the rising reputation of Asia – or the recognition we receive from both North America and Europe – then we need look no further than the Editorial Board of AsiaIntervention. Runlin Gao has been repeatedly singled out in Asia and internationally for the quality of his teaching, his clinical practice and his leadership. We, the other Senior Editors of this journal who have the honour of collaborating with him, would like to take this opportunity to congratulate him on the occasion of his latest achievement. Following the prestigious European ETHICA Award, which he received in 2011 at EuroPCR, Professor Gao has now received

DOI: 10.4244/AsiaInterv_V3I1A1

the coveted Transcatheter Cardiovascular Therapeutics (TCT) career achievement award during the recent TCT/Cardiovascular Research Foundation (CRF) conference in Washington, DC, USA. We can only endorse the accolades he has already received as the pioneer of interventional cardiology in China, and a leader throughout Asia and the world in advancing patient care, and note the important role he plays in our speciality in general, and in this journal in particular.

Moving forward

The true attributes of a leader in interventional cardiology – including a certain humility and rigour in research and clinical practice – are something we take very seriously in Asia. This journal offers a range of some of the best critical thinking available today within, but not limited to Asia. We would like to thank all our many contributors including our Consulting Editors, Patrick W. Serruys, Christoph Naber and Richard Ng, for helping us to make this journal relevant for your clinical practice.

To grow strongly, we must grow together. For this journal to represent the best of what we do today and in the future, we need your participation. Submit your articles, become involved in our meetings, visit our websites. Participate, and by participating make the future of our discipline your own. Together we can do so much more and, working together, sharing our work together, we can all offer a better future for our patients, here in Asia and throughout the world.

AsiaIntervention 2017;3:7-9

Chronic total occlusion (CTO) in Japan

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Chronic total occlusion (CTO) was once called an unexplored frontier for interventional cardiologists. The need for a high level of technical expertise, longer procedure time, a higher rate of procedure-related complications, and other available treatment options prevented general cardiologists from revascularising CTO[1,2]. Also, there was a paucity of reliable data supporting the clinical benefit of CTO revascularisation.

However, Japanese expert interventionalists have tackled this challenging subset of coronary lesions. The struggle for the conquest of CTO can be traced from the balloon angioplasty and bare metal stent era as if turning the pages of the history of CTO-PCI. Muramatsu et al reported an early success rate of 76.4% before 2003[3]. Another report by Saito et al showed a success rate of 67% between 1997 and 1999[4]. These unsatisfactory procedural success rates of CTO revascularisation gradually improved with the appearance of novel equipment and revascularisation strategies. The CONFIANZA PRO (ASAHI Intecc, Aichi, Japan), a tapered and stiff-tip guidewire still indispensable in contemporary CTO-PCI, greatly contributed to the higher success rate[3,5]. Another epoch-making idea for the solution of the failed antegrade approach is the retrograde approach. Interestingly, the report by Kahn et al describing the retrograde approach via a bypass graft dates back to 1990[6]. Dilated septal collateral channels were often attempted as safely and easily crossable routes for the retrograde approach[7]. Afterwards, the controlled antegrade and retrograde subintimal tracking (CART) technique was developed as an improved form[8]. Additionally, the Corsair (ASAHI Intecc), a microcatheter mainly used for channel dilation, was introduced in order to make channel dilation safer and more feasible[9]. The CART technique was epoch-making in that intentional subintimal tracking enabled the antegrade or retrograde wire to reach the opposite true lumen. Tsuchikane et al described the reverse CART technique: it was the most frequently employed using the Corsair and a 300 cm guidewire. The method of retrograde wire externalisation was also one of the advantages facilitating the reverse CART technique because of more back-up force and no need for balloon dilation in the retrograde direction[10,11]. These excellent techniques and supporting devices have delineated the overall picture of contemporary CTO-PCI, increasing the procedural success rate of CTO-PCI to as high as about 90%[10,12,13].

Another milestone in our CTO history is the development of the J-CTO score system as a predictor of successful antegrade wiring[14]. One of the points in the J-CTO registry was the minute assessment of periprocedural variables, ranging from contrast

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DOI: 10.4244/AIJV311A2

volume and fluoroscopic time to guidewire manipulation time[13]. The J-CTO score was also unique and convenient in two respects: the prediction rule adopted simple, "presence-or-absence" style variables[14]. The easy scoring was one of the advantages for its widespread and continued use among clinicians. The other point was the introduction of the time required for guidewire crossing. The concept was very practical because many interventionalists had a time limit for the procedure and a prolonged procedure resulted in more complications. This predicting tool's qualities of being simple, convenient and clinically relevant were statistically confirmed and validated in other studies[15,16].

Currently, CTO-PCI is performed by a stepwise approach with the support of intravascular ultrasound (IVUS) as in IVUS guidance in the reverse CART technique or IVUS-guided antegrade wire penetration[11,17]. Now, we have reached a satisfactory level regarding procedural results in the second-generation drug-eluting stent era. However, the current results depend on highly skilled experienced operators and high case volumes. Therefore, the next course that we should pursue is to improve the level of general interventionalists by spreading the knowledge which is essential for successful CTO-PCI. This will certainly lead to the achievement of better mortality rates, which currently remains a topic of debate due to inconsistent results[18,19]. Randomised data, including the minute assessment of myocardial viability and the degree of restoration of ejection fraction, are warranted to elucidate the true clinical relevance of CTO-PCI.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:10-12

Functional PCI in bifurcation lesions

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Introduction

In the contemporary practice of percutaneous coronary interventions (PCI), bifurcation lesions account for approximately 20-30% of all coronary lesion subsets[1]. Bifurcation PCI remains one of the most challenging procedures with respect to procedural complexity and relatively high rates of early and long-term adverse cardiac events, as compared to non-bifurcation PCI. Although there have been marked advancements in stents, devices, techniques, and adjunctive drug therapies, the optimal management of bifurcation lesions is still the subject of considerable debate. Despite great interest in this complex lesion subset and a fast growing body of scientific evidence, over the past decade, the management of bifurcation disease has been focused mainly on technical aspects[2,3]. However, given that adjunctive imaging and functional tools are widely applicable in contemporary practice, an integrated approach combining functional aspects and technical aspects might be helpful to guide treating physicians in their decision making on PCI strategies and procedural optimisation, which are ultimately linked to improvement of the outcomes of patients with such complex lesions. Herein, we highlight the most debated issues and propose our recommendations for a simple and integrated approach while emphasising the functional aspects of bifurcation PCI.

Why bifurcation treatment should be considered as a matter of concept rather than technique

The clinical relevance of a bifurcation lesion is generally based on the anatomic and functional significance of the side branch (SB) and the potential myocardial complications associated with SB occlusion during bifurcation PCI. However, in routine clinical practice, the relevance of the SB has most often been arbitrarily defined on the basis of the subjective judgement of the interventional cardiologist; by coronary angiography, several anatomic factors (i.e., size and length of the main branch [MB] and SB, severity of stenosis, bifurcation angles, calcification, or disease pattern) might be assessed. Beyond such simple angiographic characteristics, more detailed characterisation of atherosclerotic plaque burden involving the bifurcation zone and the functional significance of the lesions can be important for any strategy planning of bifurcation PCI. Put simply, conventional Medina

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DOI: 10.4244/AsiaInterv_V3I1A3

classification for bifurcation lesions can be refined using intravascular ultrasound (IVUS) imaging or fractional flow reserve (FFR) measurement, which lead to a conceptual rather than a technical approach for optimal bifurcation treatment.

Why a functional approach is needed in bifurcation PCI

In the last decade, many clinical studies involving non-randomised and randomised trials have compared the use of a simple versus a complex stenting technique in non-left main (LM) or LM bifurcations. The majority of these studies have shown no advantage in implanting two stents regardless of the lesion location or bifurcation type. Based on this evidence, a simple strategy with provisional SB stenting has now become the preferred strategy in the majority of bifurcation techniques. With such a concept, the provisional SB stenting strategy, if feasible, should be considered the standard approach for bifurcation treatment. When should we treat SB occlusion by a provisional approach? From a practical viewpoint, after crossover stenting of the MB, SB salvage (i.e., provisional balloon or stenting) is usually considered: (1) when there is impaired SB flow (Thrombolysis In Myocardial Infarction flow grade <3); (2) when there is a major SB dissection; or (3) when SB narrowing is regarded as functionally significant leading to significant residual ischaemia. If angiographic narrowing of the SB occurred after MB stenting, how do we assess the functional significance of SB narrowing? Decision making for SB treatment can be guided by functional FFR assessment. A previous study suggested that angiographic and IVUS parameters had poor diagnostic accuracy in predicting the functional significance of SB narrowing, in which the relations between angiographic/IVUS parameters and FFR were different between main vessel (MV) and SB lesions[4]. Despite a high incidence of SB narrowing after provisional bifurcation stenting, ostial SB stenosis after MB stenting in most cases was non-significant by FFR[5,6]. In addition, the presence or absence of final kissing balloon inflation did not substantially improve serial FFR values of the SB immediately after and at follow-up of the procedures[7]. Therefore, if FFR assessment is technically feasible for the SB, such a functional tool might be used to support the choice of a further treatment strategy for SB narrowing after provisional stenting and, as a result, it might reduce SB intervention without increasing subsequent revascularisation along with retaining functional integrity.

In case of a sufficiently large SB with anatomic and functional relevance, a two-stent technique could be initially considered. There are no data showing a significant difference in clinically relevant outcomes according to different two-stent techniques; only a small difference was observed for soft clinical endpoints (i.e., late loss, branch restenosis, or repeat revascularisation)[2,3]. Therefore, any two-stent technique (i.e., T/modified-T/TAP, crush/mini-crush/DKCRUSH, or culotte) can be used and selected according to the size of the MB or SB, bifurcation angle, plaque distribution or location and, importantly, operator experience and expertise.

Why an imaging approach is needed in bifurcation PCI

The LM is a unique bifurcation lesion subset that requires careful clinical and technical consideration: (1) the LM involves more than 70% of the overall myocardium, (2) SB occlusion of an LM bifurcation (left circumflex artery [LCX]) is clinically not acceptable, and (3) the LM, MB, and SB are relatively large vessels compared to other bifurcation lesions. For distal LM bifurcation lesions with intact or diminutive SB, the practical application of FFR for a SB circumflex artery after provisional stenting is similar in approach to non-LM bifurcation treatment. If the LCX is severely diseased at baseline, an initial two-stent approach might be preferred. Intravascular imaging should be mandatory for LM stenting, especially for a distal LM bifurcation lesion. Recently, the results of two large comparative trials (EXCEL and NOBLE) of left main PCI versus bypass surgery have been released[8,9]. Despite disparate conclusions, both studies draw attention to procedural techniques in left main PCI; IVUS utilisation exceeded 70% in both studies. Considering the benefits of IVUS to define disease distribution, inform stent sizing and technique and enhance appropriate stent sizing and expansion, the role of IVUS in reducing left main restenosis and stent thrombosis-related complications may be clinically meaningful. Therefore, at the minimum, IVUS should be performed at the completion of the procedure to assess stent apposition and deployment. For complex stenting of a distal LM bifurcation, the IVUS-measured minimum stent area that best predicts angiographic in-stent restenosis on a segmental basis is 5.0 mm^2 for the LCX ostium, 6.3 mm^2 for the LAD ostium, 7.2 mm^2 for the polygon of confluence (POC), and 8.2 mm^2 for the proximal LMCA above the POC (namely, criteria 5-6-7-8 for distal LM complex stenting)[10]. With these criteria, IVUS optimisation during LMCA stenting procedures may improve clinical outcomes.

Conclusion

In conclusion, for bifurcation PCI treatment, both strategies (provisional stenting or any planned two-stent technique), according to the SB significance and the size of jeopardised myocardium, might be equally feasible in the contemporary DES era. In cases of a provisional strategy for bifurcation lesions, non-significant SB narrowing after MV stenting might rarely show positive FFR (approximately 10-20%), and therefore FFR guidance is helpful in decision making for SB treatment. In true distal LM bifurcation lesions in which a two-stent strategy is planned, IVUS-guided optimisation is crucial and affects early and long-term clinical outcomes. Although there is no common rule for bifurcation treatment, the integrated use of functional and imaging tools (i.e., FFR or IVUS) will make bifurcation treatment a matter of concept rather than technique, which will tailor individualised decision making of the optimal treatment strategy for such complex coronary lesions.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:13-14

Sightseeing: in search of the best vascular view

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Intravascular imaging guidance represents an unrequited romance for most interventional cardiologists. Indeed, the full potential of the "perfect view" of plaque and vessel contours often remains unexpressed in clinical practice.

Optical coherence tomography (OCT) images are very attractive for interventional cardiologists and experts in atherosclerosis. The clinical and research insight of an OCT high-resolution image should not be limited to a simple ideal case, characterised by a mild narrowing located in a proximal coronary segment.

The proper identification and characterisation of atherosclerotic plaque morphology probably represents the most important attribute of FD-OCT images. Indeed, the possibility to assess lesions before any treatment (i.e., predilatation) constitutes an important advantage for the better understanding of the vulnerability of the evaluated plaque (i.e., fibrous cap thickness and macrophage infiltration) and the underlying pathophysiologic mechanism (e.g., plaque erosion or ulceration). This is also true for the evaluation of a restenotic severe lesion or stent thrombosis (e.g., acute underexpansion or late malapposition assessment). In all of these cases, balloon predilatation inevitably leads to plaque disruption with consequent loss of the above-mentioned information. Furthermore, a true understanding of luminal dimensions at lesion and reference sites is key to selecting balloon-stent diameters and lengths[1].

Development of a valid acquisition technique for obtaining OCT images has been a long and difficult battle. Ten years ago, our group proclaimed with enthusiasm the innovative non-occlusive technical solution that enabled the use of time domain OCT without an occlusive balloon[2]. At that time, the infrared light was incorporated in a thin image wire and imaging of a severely stenotic artery was not seen as a problem. A few years later, such an acquisition modality, characterised by simple injection of contrast media through the guiding catheter, served to launch the second-generation frequency domain OCT, characterised by a very high acquisition speed. A drawback of these currently used over-the-wire probes is that they have a larger size, which impairs assessment of severe lesions whenever the catheter totally occludes the lumen. This represents a new problem, which remains difficult to overcome.

Tian and colleagues[3] experimented with a modified FD-OCT acquisition technique to improve imaging of severe lesions, offering a simple solution. Starting from the previous experience of

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Yamaguchi et al[4], who developed a specific technique to obtain good quality imaging in acute patients (i.e., STEMI), Tian et al

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DOI: 10.4244/AsiaInterv_V3I1A4

introduced a temporised distal flushing just before FD-OCT pull-back to increase the imaging quality of severely stenotic coronary lesions. The main advantages of this approach are the simplicity of execution, as compared to the method proposed by Yamaguchi et al, the improved blood clearance distal to the lesion, and the reduced increase of contrast dye needed (only 2.5 ml more than standard acquisition).

As clearly specified by the authors, the observed results in this paper are technically interesting and serve as a proof of concept. The suggested approach seems promising in order to reduce artefacts due to incomplete blood clearance, which limit image resolution and correct interpretation of vascular elements (e.g., residual red blood cells versus intravascular red thrombus). On the other hand, the clinical application of such a technique is still unclear. For instance, the effectiveness and safety of this approach in a larger lesions database, including stable atherosclerosis or acute coronary syndromes, needs to be proved. Furthermore, there are technical aspects which are not yet understood such as the incidence of image distortion due to non-uniform rotation that may affect image quality.

Tian and colleagues should be congratulated. Any technical refinement of OCT acquisition is welcome and their effort to increase intravascular imaging quality with a rather simple technical solution merits proper consideration.

However, it goes without saying that, had we available to us in our armamentarium thinner frequency domain OCT probes, assessment of severe narrowing could be carried out without the need to embrace technical solutions which, on the one hand, are unlikely to enable optimal imaging in all cases and, on the other hand, make procedures a little more complex.

Conflict of interest statement

F. Prati has served as a consultant for St. Jude Medical. The other authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:15-17

The COMBO stent: can it deliver on its dual promise?

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By effectively suppressing neointimal hyperplasia (NIH), drug-eluting stents (DES) have proven highly successful in reducing in-stent restenosis (ISR) compared with bare metal stents. However, after their introduction into clinical practice, concern emerged regarding a possible excess of late adverse events with DES as compared with bare metal stents. In particular, late stent failure due to stent thrombosis (ST) may occur at a higher rate over the medium term, at least with early-generation devices[1].

Insights from autopsy studies and intravascular imaging in patients with late ST implicate two main factors in the pathogenesis of late ST, namely impaired device healing with delayed endothelialisation and accelerated atherogenesis within the stented segment[2-4]. When considering approaches to target the former, it is important to note that stent endothelialisation after vascular injury occurs in one of two ways - through local recruitment of adjacent endothelial cells or by recruitment of blood-derived endothelial progenitor cells (EPC), which adhere to the surface of the device and differentiate into mature endothelial cells[5]. Delayed healing after DES occurs as a result of persistent cell inhibition from potent antiproliferative drugs, with the pro-inflammatory effect of durable polymers on some devices playing a role.

Against this background, the "pro-healing" COMBO™ dual therapy stent (OrbusNeich, Hong Kong, China) was developed. It aims to accelerate device endothelialisation, while maintaining the suppression of NIH achieved by conventional monotherapy DES[6]. To expedite endothelialisation, the stent luminal surface is coated with immobilised anti-CD34+ monoclonal antibodies, which target binding of CD34+ antigen on circulating EPC to promote cell surface adhesion. Meanwhile, sirolimus on the abluminal stent surface is eluted from a biodegradable polymer matrix. Sirolimus is fully eluted within 30 days and the biodegradable polymer within 90 days, with the aim of reducing polymer-induced inflammation.

Preclinical studies with the COMBO stent in porcine coronary arteries have shown promising results, with more rapid endothelialisation compared with early-generation DES and less NIH compared with newer-generation DES[5]. In terms of clinical studies, the randomised REMEDEE first-in-man trial compared the COMBO stent with the TAXUS™ Liberté™ paclitaxel-eluting durable polymer stent (Boston Scientific, Natick, MA, USA) for treatment of *de novo* coronary artery lesions in patients with stable angina, and showed comparable results in terms of the angiographic primary endpoint (late lumen loss)[7]. Clinical events at 12 months were low and comparable in both groups, with no safety concerns regarding late ST.

In this issue of the journal, Lee et al report results from a substudy of the REMEDEE trial, examining differences in vascular healing assessed by optical coherence tomography (OCT) between the COMBO and TAXUS stents[8].

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Vascular healing was determined by strut coverage and apposition, as well as neointimal morphological analysis by OCT at nine-month angiographic follow-up. Thirty-three patients were

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DOI: 10.4244/AsiaInterv_V3I1A5

included, 23 treated with the COMBO stent and 10 with the TAXUS stent. At nine months, both stent platforms were almost completely covered (98.5% for COMBO vs. 97.6% for TAXUS, p=0.40), with comparable neointimal volume and thickness. The main difference between devices was in the morphology of the neointimal tissue, with the COMBO stent displaying significantly more homogeneous tissue than the TAXUS stent (79.2% vs. 40.0%, respectively, p=0.01), and the TAXUS stent showing a trend towards more layered or heterogeneous tissue (0.0% vs. 20.0%, respectively, p=0.08). Because homogeneous tissue is characteristic of mature smooth muscle cell-rich NIH, whereas heterogeneous tissue is characteristic of more immature hypocellular neointima, the authors concluded that the results suggest a favourable healing profile for the COMBO stent[9].

Although the authors should be congratulated for reporting this detailed subgroup analysis of patients with intravascular imaging surveillance, there are some important limitations, which should be considered when interpreting the results. First, there were a number of differences other than the presence or absence of EPC capture technology between the experimental and comparator devices, which may have affected healing. The devices were coated with different antiproliferative agents (sirolimus vs. paclitaxel), eluted from different polymers (one biodegradable vs. one durable), with different drug coating distributions (abluminal vs. circumferential). Second, tissue coverage by OCT is not an indication of completeness of vascular healing. While OCT can quantify neointimal coverage, standard OCT analysis is unable to distinguish between tissue types and cannot, therefore, differentiate degrees of tissue healing. Although not performed in this study, offline greyscale signal intensity (GSI) analysis of OCT images has been shown to be capable of distinguishing immature from mature neointimal tissue in the clinical setting, with one pilot study showing that only one quarter of DES neointimal tissue observed at six-month OCT surveillance represented mature intima[9]. However, it should be acknowledged that association of immature tissue type by GSI analysis with late adverse events has not been proven thus far; therefore, the clinical relevance of these surrogate imaging parameters remains unknown.

Some insight as to whether the potentially accelerated healing with the COMBO stent translates into clinical benefit in high-risk patients can be gained from a second study also published in this issue of the journal[10]. Ananthakrishna et al report the results of a prospective, single-centre study including 117 patients, with a total of 147 lesions treated with the COMBO stent in the setting of primary percutaneous intervention (PCI).

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The primary endpoint of target lesion failure (TLF) at one year – defined as a composite of cardiac death, target vessel myocardial infarction, or clinically driven target lesion revascularisation (TLR) – occurred in 7.7% of patients, with the individual components occurring in 4.3%, 2.6% and 3.4%, respectively. Notably, the rate of definite ST was 2.6% at one year, despite the use of newer, more potent $P2Y_{12}$ receptor antagonists in 85.5% of patients: two of the three cases occurred acutely – one immediately post PCI in a patient with cardiogenic shock and vomiting, another within two hours – with no explanation despite intravascular ultrasound. The third case occurred six months post PCI in the setting of non-compliance with dual antiplatelet therapy (DAPT).

Although the high rates of ST in this study are disappointing, they are difficult to interpret on account of the non-randomised nature of the study and inclusion of very high-risk patients. Randomised studies comparing second-generation DES with bare metal stents in the setting of primary PCI have shown lower rates of ST in both arms, with rates of definite ST of 0.5% and 1.9%, respectively, in the EXAMINATION trial, and 0.9% and 2.1%, respectively, in the COMFORTABLE-AMI trial[11,12]. However, compared with patients enrolled in randomised trials, patients included in this registry were sicker on presentation: 9.4% of patients presented in cardiogenic shock compared with only 1.2% in EXAMINATION and, although the rate of cardiogenic shock was not reported in COMFORTABLE-AMI, only 6.7% of patients presented in Killip class II-IV[12]. In addition, more patients in the registry had TIMI 0 flow on presentation (82.2% compared with only circa 50% in EXAMINATION and circa 68% with 0-1 flow in COMFORTABLE-AMI). Patients in this registry also had higher baseline cardiac risk profiles, with a higher incidence of previous MI (17.1% compared with approximately 5% in EXAMINATION and COMFORTABLE-AMI), previous PCI (12.8% compared with 4% in both EXAMINATION and COMFORTABLE-AMI), and multivessel disease (55.6% compared with 12.5% in EXAMINATION), with planned staged revascularisation in one quarter. Moreover, lesions were longer (mean length 21.7 mm vs. circa 18 mm in COMFORTABLE-AMI). There were also significant differences in procedural characteristics, with high rates of thrombus aspiration in the current registry (88.9% of patients compared with circa 65% in EXAMINATION and circa 63% in COMFORTABLE-AMI), and low use of GP IIb/IIIa inhibitors (14.5% compared with approximately half of patients in both EXAMINATION and COMFORTABLE-AMI). Finally, use of intra-aortic balloon counterpulsation was higher at 6.0% vs. 2.5% in COMFORTABLE-AMI. In the absence of a comparator group in the current study, then, one might conclude that the high rates of adverse events observed may be explained by the inclusion of such high-risk patients.

Looking to the future, more data are certainly required before the place of the COMBO stent in routine clinical practice is defined. In this respect, we await with interest the results of two ongoing randomised clinical trials of the COMBO stent. The investigator-initiated REDUCE trial is investigating the safety of a shorter duration of DAPT (three months) in 1,500 patients with ACS treated with the COMBO stent, compared with conventional therapy (12 months) (NCT02118870). The primary endpoint is a composite of all-cause mortality, myocardial infarction, ST, stroke, and bleeding at one year. The HARMONEE trial, which is designed to fulfil regulatory requirements for stent approval by two major agencies (the United States Food and Drug Administration

and the Japanese Pharmaceuticals and Medical Device Agency), will compare TVF rates at one year in 572 patients treated with the COMBO vs. the XIENCE® everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA) in the setting of stable and unstable angina and NSTEMI (NCT02073565). A secondary analysis will focus on intimal tissue coverage by OCT at one year.

Overall, the COMBO dual therapy, pro-healing sirolimus-eluting stent represents an appealing concept for patients who may benefit from reduced duration dual antiplatelet therapy – such as those at increased risk of bleeding, in need of non-cardiovascular surgery, or at risk of non-compliance – owing to its endothelial-capturing coating technology in combination with antiproliferative drug release to inhibit restenosis. However, there is a long road ahead and there are many scientific hurdles to be overcome before we may be satisfied that the COMBO stent can deliver on its dual promise.

Conflict of interest statement

R. Colleran reports support from the Irish Board for Training in Cardiovascular Medicine sponsored by MSD. M. Joner reports consultancy fees from OrbusNeich International, Biotronik and AUM Cardiovascular, Inc., and lecture fees from Biotronik, OrbusNeich, Boston Scientific, and AstraZeneca.

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AsiaIntervention 2017;3:18-19

Interventional Cardiovascular Society of Malaysia (ICSM)

Prof. Dr Wan Azman Wan Ahmad FNHAM, FAPSIC, FSCAI, FACC, FESC

ICSM was formed under the umbrella of the National Heart Association of Malaysia (NHAM) in 2003. NHAM was officially registered in 1978. Our Vision is to reduce the burden of cardiovascular disease in Malaysia. Our Mission is to promote quality cardiovascular care through education and research and to influence healthcare policies. This journey has been marked by significant developments and challenges amidst a fluidly changing social-economic landscape to become an Association that its members are proud of. NHAM now has 761 active members (including associate members) and ICSM has 156 active members. NHAM is an affiliate society of the European Society of Cardiology, the American College of Cardiology, the ASEAN Federation of Cardiology and is a member society of the World Heart Federation.

Following the formation of ICSM, although it was initially mooted as an organising body in conjunction with Malaysia's first international interventional live course, MYLIVE in 2004, its activities have evolved and progressed over the years to encompass larger educational, training and advocacy roles. Since 2004, the mainstay of its work has focused on the organisation of MYLIVE, an annual international cardiovascular "live" interventional conference, usually conducted in July. The MYLIVE meetings offer a unique opportunity for the cardiovascular fraternity and people in related fields to meet, discuss and network with colleagues from the region and abroad in order to share the best practices and know-how for the betterment of cardiovascular care in the region.

This meeting is often organised with participation from closely affiliated international societies, e.g., The Society for Cardiovascular Angiography and Interventions (SCAI), EuroPCR, Asia-Pacific Society of Interventional Cardiology (APSIC), and Asian Interventional Cardiovascular Therapeutics (AICT). In 2016, we started a new chapter, Asia Endovascular and Cardiac Complications (ECC), a collaboration with the ECC Conference which is held in CHUV Hospital Lausanne and organised by Prof. Eric Eeckhout. Besides live transmission from the National Heart Institute or University Malaya Medical Centre, we have overseas live transmissions from Washington DC, India, The Netherlands, Singapore, Indonesia, Thailand, China, Saudi Arabia and Bangladesh. The number of attendees to the MYLIVE meeting has increased from 200 in 2004 to about 1,000 in 2016.

ICSM has been invited to conduct educational sessions at many annual international cardiovascular meetings, e.g., AsiaPCR Singapore, China Interventional Therapeutics (CIT), Transcatheter Cardiovascular Therapeutics Asia Pacific (TCTAP) and EuroPCR. Under the banner of the ICSM, a few cardiology centres, e.g., the National Heart Institute, University Malaya Medical Centre, have also shared their expertise in the transmissions of live interventional procedures to various conferences around the world.

With important contributions from the National Heart Institute, ICSM also runs a popular biennial cardiac valve intervention meeting, the KL Valve Summit. Angio Club meetings were organised from time to time for members to share experiences, technical tips and knowledge of complex, interesting or rare interventional cases. Individual centres around the country have conducted mini-conferences/courses/workshops in collaboration with ICSM to teach and share complex interventional procedures.

The society is also involved in the development of clinical practice guidelines, e.g., for coronary interventional procedures in Malaysia (2009), and Appropriate Use Criteria (AUC) for Investigation and Revascularization in CAD (2015). These serve as a reference to Malaysian interventional cardiologists for practice standards that meet international guidelines. The National Cardiovascular Database Percutaneous Coronary Intervention (NCVD-PCI) was established in 2007 to improve patient care through quality data. To date, we have data on more than 50,000 PCI patients and four reports published.

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Office-bearers for term 2015-2017:

Chairman: Dr Wan Azman Wan Ahmad

Committee Members:
Dr Choo Gim Hooi
Dr Ng Wai Kiat
Dr Al Fazir Omar
Dr Ramesh Singh Arjan Singh
Dr Azmee Mohd Ghazi
Dr Sazzli Shahlan Kasim

Past Chairman:
Dr Rosli Mohd Ali

Advisor:
Dr Robaayah Zambahari

DOI: 10.4244/AsiaInterv_V3I1A6

Elections for the office-bearers are held in April and members are elected for a two-year term. At present, we have 269 cardiologists registered in our National Specialist Register (NSR). Based on the NCVD-ACS Registry 2011-2013 Report, in 2014, there are 85 catheterisation laboratories in the country, 2.8 per million population.

What does APSIC membership mean for the national society?

APSIC has been a very important organisation, providing vision and guidance for the present and future development of this subspeciality in this part of the world. The practice of interventional cardiology in the Asia-Pacific Region has much in common and may differ from the West; therefore, our ability to share and learn from each other is particularly beneficial. ICSM has been collaborating very closely with APSIC in MYLIVE meetings. Many of the faculty members are APSIC members and we have many joint symposiums together. Four of the ICSM members are Board members (2014-2016) of APSIC and many of the ICSM members have been invited as faculty in many of the APSIC meetings.

APSIC is an important educational platform to mentor fellows and young cardiologists. It is through the sharing of information, exchange programmes, proctorships and workshops for specialised procedures such as atherectomy, optical coherence tomography, chronic total occlusion and others, that young cardiologists can fully develop their skills and learn from experts. The National Heart Institute and University Malaya Medical Centre have accepted fellows from the ASEAN countries for advanced interventional training. At the same time, we also encourage our fellows and young cardiologists to learn and grow using the APSIC platform. Currently, we have 44 ICSM members who are also APSIC members.

Current issues related to the national society

We are still short of registered cardiologists, particularly in public hospitals. We have about nine cardiologists per million population. There is uneven distribution of cardiologists and cardiac catheterisation laboratories in Malaysia – more on the West Coast especially in Klang Valley, Pulau Pinang and Melaka as compared to the East Coast and Sabah. NHAM has been given the task of setting up a uniform training programme and setting criteria for fellows to be registered in the National Specialist Register for cardiology.

From our NCVD-ACS Registry 2011-2013, in-hospital mortality for ST-elevation myocardial infarction (STEMI) was 10.6%, and less than 10% of our STEMI patients received primary PCI as their reperfusion strategy. Hospitals with cardiac catheterisation facilities registered lower in-hospital and 30-day mortality, and patients who underwent urgent cardiac catheterisation and urgent PCI had better outcome than those who did not. The society has taken up the initiative by setting up the My STEMI network, a collaboration between PCI-capable and non-PCI-capable hospitals. An issue that needs to be addressed is the reimbursement for devices, particularly for underprivileged patients.

As the number of interventional cardiologists in Malaysia grows, ICSM will continue to consolidate and expand its roles for the education of practitioners and promotion of a high standard of cardiovascular care both locally and internationally.

MYLIVE 2017 is to be held from 27 to 29 July 2017 at the Hilton Hotel, Kuala Lumpur. The theme for MYLIVE 2017 is “Doing It Right”. We look forward to your presence at this exciting MYLIVE 2017.

AsiaIntervention 2017;3:20

Asia-Pacific Hotlines at TCT 2016: Randomized Evaluation of Routine Follow-up Coronary Angiography After Percutaneous Coronary Intervention Trial (ReACT)

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

In several previous studies, routine follow-up coronary angiography (FUCAG) after percutaneous coronary intervention (PCI) has been reported to have increased the rate of coronary revascularisation, but not to have improved clinical outcomes. Based on these study results, the current clinical guidelines in the United States of America have already disregarded routine FUCAG, even after PCI for left main coronary artery disease. On the other hand, prior studies carried out in the drug-eluting stent (DES) era were performed in the context of pivotal randomised trials. There have been no randomised clinical trials evaluating the clinical impact of routine FUCAG post PCI in the real-world clinical practice including in patients with, for example, complex coronary artery disease and acute myocardial infarction, at high risk for cardiovascular events.

What is unique about this study in your country?

In Japan, routine FUCAG after PCI is still commonly performed in real-world clinical practice. This trial is the first dedicated randomised trial comparing an angiographic follow-up (AF) strategy with a clinical follow-up only (CF) strategy after PCI in daily clinical practice.

Did you experience any unexpected challenges?

The ReACT trial is a prospective, multicentre, open-label randomised trial comparing a routine AF strategy with a CF strategy in daily clinical practice in Japan[1]. Between May 2010 and July 2014, 700 patients who had successful PCI without planned staged PCI in 22 participating centres were randomly assigned to the routine AF group, in which patients were to receive FUCAG at eight to 12 months after PCI, or to the CF group. The definition of the primary endpoint was a composite of death, myocardial infarction, stroke, emergency hospitalisation for acute coronary syndrome, or hospitalisation for congestive heart failure during a minimum 1.5 years of follow-up. During a median 4.6 (interquartile range: 3.1-5.2) years of follow-up, the cumulative five-year incidence of the primary endpoint was 22.4% in the AF group and 24.7% in the CF group (hazard ratio [HR]: 0.94, 95% confidence interval [CI]: 0.67-1.31, p=0.71). Also, there were no significant differences between the AF and CF groups in terms of any other clinical endpoints. Although any coronary revascularisation within the first year after the index PCI was more frequently performed in the AF group than in the CF group (12.8% versus 3.8%, log-rank p<0.001), the difference in any coronary revascularisation between the two groups attenuated over time with a similar cumulative five-year incidence (19.6% versus 18.1%, log-rank p=0.92).

How does the conclusion apply to your daily practice?

Given the costs involved and the invasive nature of coronary angiography, it is likely that FUCAG would be reserved only for patients with recurrent symptoms or evidence of ischaemia. However, the scheduled angiographic follow-up would still be acceptable in the first-in-man coronary device trials, or as the mechanistic substudy in the pivotal coronary device trials, because there was no excess of adverse clinical events with the routine AF strategy except for the increased rate of early repeat coronary revascularisation.

Funding

This study was supported by an educational grant from the Research Institute for Production Development (Kyoto, Japan).

Conflict of interest statement

The author has no conflicts of interest to declare.

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DOI: 10.4244/AsiaInterv_V3I1A7

AsiaIntervention 2017;3:21-27

The COMBO dual therapy stent in patients presenting with acute ST-elevation myocardial infarction: a one-year follow-up study

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KEYWORDS

- clinical outcomes
- COMBO dual therapy stent
- endothelial progenitor cell
- primary percutaneous coronary intervention
- ST-elevation myocardial infarction

Abstract

Aims: The aim of this study was to evaluate the safety and efficacy of the COMBO dual therapy stent in patients with acute ST-elevation myocardial infarction (STEMI). We report the one-year clinical outcomes.

Methods and results: Patients with acute STEMI who underwent primary percutaneous coronary intervention (PCI) between November 2013 and March 2015 and received the COMBO dual therapy stent were enrolled in this prospective single-centre registry. The primary outcome was target lesion failure (TLF), defined as a combination of cardiac mortality, target vessel myocardial infarction (TVMI), or clinically driven target lesion revascularisation (TLR). A total of 117 patients received 147 COMBO dual therapy stents during the study period, and 9.4% of the patients presented with cardiogenic shock. Thrombolysis In Myocardial Infarction (TIMI) 3 flow post procedure was achieved in 98.5% of lesions. At one year, the TLF rate was 7.7%. The rates of cardiac mortality, TVMI, and TLR were 4.3%, 2.6%, and 3.4%, respectively. The incidence of definite/probable stent thrombosis was 4.3% at 12 months, with four of the five cases occurring within 30 days. The all-cause mortality was 5.1% at one year.

Conclusions: COMBO stent implantation during primary PCI for acute STEMI showed acceptable rates of TLF at one year, although the rates of early ST were not negligible. Further studies are warranted to evaluate the safety in a larger high-risk population.

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SUBMITTED ON 29/09/2016 - REVISION RECEIVED ON 1st 24/10/2016 / 2nd 09/11/2016 - ACCEPTED ON 14/11/2016

DOI: 10.4244/AsiaInterv_V3I1A8

Abbreviations

DES	drug-eluting stent(s)
EPC	endothelial progenitor cell(s)
MI	myocardial infarction
PCI	percutaneous coronary intervention
ST	stent thrombosis
STEMI	ST-elevation myocardial infarction
TLF	target lesion failure
TLR	target lesion revascularisation
TVMI	target vessel myocardial infarction

Introduction

Drug-eluting stents (DES) have demonstrated a significant reduction in the rate of repeat revascularisation in comparison to bare metal stents. However, late stent failure is still an issue with the current generation of DES[1,2]. A major concern is the inhibitory effect of the antiproliferative drug on endothelial cell regeneration. This has resulted in delayed and incomplete endothelialisation of the stented segment. The regeneration of endothelial cells results from the local recruitment of adjacent cells or from an adhesion of bone marrow-derived endothelial progenitor cells (EPC)[3,4]. Previous studies with EPC capture technology have shown enhanced stent endothelialisation[5,6].

EPC capture on sirolimus-eluting stents augments endothelialisation. The presence of mature endothelium was higher in the EPC captured sirolimus-eluting stents (80%), in contrast to sirolimus elution alone (40%) at 14 days[7]. Similar high rates of endothelialisation were demonstrated on optical coherence tomography with the use of anti-CD34 sirolimus-eluting stents[8]. The inhibitory effect of sirolimus on smooth muscle cell proliferation will be sustained while accelerating the endothelial healing process. An early restoration of functional endothelium may be beneficial, especially in the setting of ST-elevation myocardial infarction (STEMI). The COMBO™ dual therapy stent (OrbusNeich Medical, Ft. Lauderdale, FL, USA) combines EPC capture technology with an antiproliferative, biodegradable sirolimus drug elution. This stent has shown similar rates of angiographic in-stent restenosis in comparison to the paclitaxel-eluting stent, and an overall low rate of clinical events in uncomplicated patients with stable angina[9]. In addition, the stent has demonstrated a unique late neointimal regression, with minimal restenosis and no late stent thrombosis (ST)[10]. Evidence of the safety and efficacy of the COMBO stent in patients presenting with STEMI is lacking. In the thrombogenic milieu of STEMI, hastening the process of vascular repair may lead to improved clinical outcomes. The aim of this study was to evaluate the clinical outcomes of patients with acute STEMI receiving the COMBO stent during primary percutaneous coronary intervention (PCI).

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Methods

STUDY DESIGN AND POPULATION

This was a prospective, single-centre, single-arm observational registry study from a tertiary care cardiac centre. The study was approved by the National Ethics Committee and Hospital Research Board. Consecutive patients who underwent primary PCI with the COMBO dual therapy stent between November 2013 and March 2015 were enrolled in this study. Patients were eligible if they were ≥18 years old with electrocardiographic evidence of acute STEMI. The study excluded patients with a contraindication to dual antiplatelet therapy, limited life expectancy (less than one year), and patients unwilling to give written informed consent.

STUDY DEVICE

The COMBO dual therapy stent is a balloon-expandable stent consisting of a 316L stainless steel alloy, with a strut thickness of 100 µm. It has an abluminal coating of a biocompatible, biodegradable polymer containing sirolimus (5 µg/mm) and a luminal covering of murine, monoclonal, anti-human CD34 antibody. The antibody specifically targets circulating EPC to accelerate endothelial coverage. The polymer degrades completely in 90 days. Fifty percent of the sirolimus is released in seven days, 75% in 10 days, and the rest is eluted within 30 days[8].

PROCEDURE

All patients in the study received dual antiplatelet therapy, which included a loading dose of 300 mg of aspirin and one of the following $P2Y_{12}$ receptor antagonists: 600 mg of clopidogrel (300 mg for those patients already receiving chronic clopidogrel therapy), 180 mg of ticagrelor, or 60 mg of prasugrel. Primary PCI was carried out in accordance with the current standard of practice. All patients received heparin anticoagulation, guided by an activated clotting time monitoring. The use of a glycoprotein IIb/IIIa receptor inhibitor and a thrombus aspiration device was at the discretion of the primary operator. The patients were subsequently maintained on 100 mg of aspirin indefinitely and on a $P2Y_{12}$ receptor antagonist for at least 12 months.

DATA COLLECTION AND STUDY ENDPOINTS

Baseline demographic and clinical characteristics were collected. The angiographic variables, procedural characteristics, and outcomes were analysed. Device success was defined as a successful COMBO dual therapy stent placement with Thrombolysis In Myocardial Infarction (TIMI) flow grade 2/3 post stenting and less than 10% residual stenosis. The one-month, six-month, and 12-month follow-ups were carried out by clinic visits or telephonic enquiry. These follow-ups were achieved in all of the patients in this study.

The primary outcome of interest was target lesion failure (TLF), defined as a combination of cardiac mortality, target vessel myocardial infarction (TVMI), or clinically driven target lesion revascularisation (TLR). Exploratory secondary outcomes of interest included in-hospital mortality, all-cause mortality, major adverse cardiac events (defined as the composite of all-cause mortality, MI, or ischaemia-driven target vessel revascularisation), the components of TLF, target vessel revascularisation and ST. Deaths that could not be attributed to another cause were regarded as cardiac deaths. MI was defined according to the third

universal definition of MI[11]. ST was classified according to the Academic Research Consortium criteria[12].

STATISTICAL ANALYSIS

Continuous data are expressed as means and standard deviations; discrete variables are given as absolute values and percentages. Data were analysed using the statistical software package SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 147 COMBO dual therapy stents were implanted in 117 patients during the study period. The baseline demographic and clinical characteristics are shown in **Table 1.** The mean age was 56±11 years and 90.6% of the patients were male. The most common risk factor for MI was current tobacco use (59.8%); 18.8% of the patients were diabetic. Cardiogenic shock was present in 9.4% of the patients. The left ventricular ejection fraction on the two-dimensional echocardiogram was 49±11%.

The lesion and procedural characteristics of the study population are defined in **Table 2**. The right coronary artery was the culprit vessel in 52.8% of the lesions, followed by the left anterior descending artery (41.9%). Initial TIMI flow 0/1 occurred in 87% of the lesions. Thrombus aspiration was performed in 88.9% of the patients. At the end of the procedure, 98.5% of the lesions achieved TIMI 3 flow. Device success was seen in all the patients.

Table 3 shows the clinical outcomes up to one year. TLF was recorded in 7.7% of the patients at one year. Cardiac mortality occurred in 4.3% of the patients. TVMI was observed in 2.6% and TLR was performed in 3.4% of the patients. The in-hospital mortality rate was 1.7%. The all-cause mortality rate was 5.1% at one year. Among the 117 patients included in the study, 91.5% were compliant with the dual antiplatelet therapy at the end of one year. Definite ST was seen in three patients (2.6%) and probable ST was seen in two (1.7%). The details of cases of ST are illustrated in **Table 4**.

Table 1. Baseline demographic and clinical characteristics.

Variable	Patients (n=117)
Age (years)	56±11
Male	106 (90.6%)
Hypertension	42 (35.9%)
Diabetes mellitus	22 (18.8%)
Dyslipidaemia	39 (33.3%)
Current tobacco use	70 (59.8%)
Family history of CAD	5 (4.3%)
Prior AMI	20 (17.1%)
Prior PCI	15 (12.8%)
Prior CABG	1 (0.9%)
Cardiogenic shock	11 (9.4%)
LVEF	49±11

Values are mean±SD or n (%). AMI: acute myocardial infarction; CABG: coronary artery bypass graft; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention

Table 2. Lesion and procedural characteristics.

Variable		Patients (n=117) Lesions (n=129)
$P2Y_{12}$ receptor antagonist	Clopidogrel	17 (14.5%)
	Prasugrel/ticagrelor	100 (85.5%)
Access	Femoral	62 (53%)
	Radial	55 (47%)
Culprit lesion location	LMCA	1 (0.8%)
	LAD	54 (41.9%)
	LCX	5 (3.9%)
	RCA	68 (52.8%)
	SVG	1 (0.8%)
Initial TIMI flow	0	106 (82.2%)
	1	6 (4.7%)
	2	9 (7.0%)
	3	8 (6.2%)
Lesion length (mm)		21.7±8.4
Number of stents per lesion		1.1±0.3
Average stent length (mm)		21.1±5.8
Average stent diameter (mm)		3.0±0.4
Final TIMI 3 flow		127 (98.5%)
Final TIMI 2/3 flow		129 (100%)
Adjunctive therapy in PCI	Glycoprotein IIb/IIIa receptor inhibitors	17 (14.5%)
	Aspiration thrombectomy	104 (88.9%)
IABP use		7 (6.0%)
Device success		129 (100%)
Multivessel CAD on presentation		65 (55.6%)
Multivessel PCI		2 (1.7%)
Staged PCI		26 (22.2%)
Staged CABG		3 (2.6%)

Values are mean±SD or n (%). CAD: coronary artery disease; IABP: intra-aortic balloon pump; LAD: left anterior descending artery; LCX: left circumflex artery; LMCA: left main coronary artery; PCI: percutaneous coronary intervention; RCA: right coronary artery; SVG: saphenous vein graft; TIMI: Thrombolysis In Myocardial Infarction

Table 3. Clinical outcomes at 30 days, 6 months, and 12 months.

	1 month (n=117)	6 months (n=117)	12 months (n=117)
Death	4 (3.4%)	4 (3.4%)	6 (5.1%)
Cardiac death	4 (3.4%)	4 (3.4%)	5 (4.3%)
MI	2 (1.7%)	3 (2.6%)	4 (3.4%)
TVMI	2 (1.7%)	3 (2.6%)	3 (2.6%)
Definite ST	2 (1.7%)	3 (2.6%)	3 (2.6%)
Definite/probable ST	4 (3.4%)	5 (4.3%)	5 (4.3%)
TLR	2 (1.7%)	4 (3.4%)	4 (3.4%)
TVR	2 (1.7%)	4 (3.4%)	4 (3.4%)
TLF	6 (5.1%)	8 (6.8%)	9 (7.7%)
MACE	6 (5.1%)	8 (6.8%)	11 (9.4%)

Values are n (%). MACE: major adverse cardiac events; MI: myocardial infarction; TLF: target lesion failure; TLR: target lesion revascularisation; TVMI: target vessel myocardial infarction; TVR: target vessel revascularisation; ST: stent thrombosis

Table 4. Narrative of cases with stent thrombosis.

	Baseline characteristics	Treated lesion	Timing of ST	Predisposing factors for ST	Angiographic findings	Treatment
1	58 years, male. LVEF: 55%	Proximal RCA. 3.5×33 mm	Acute. Immediate post PCI.	Non-absorption of antiplatelets due to profuse vomiting, hypotension.	Thrombus at the stented segment.	Thrombus aspiration, plain balloon angioplasty, glycoprotein IIb/IIIa inhibitor, volume replacement.
2	70 years, male. LVEF: 35%	Proximal LAD. 3.0×18 mm (IABP for haemodynamic support)	Acute. 2 hours post PCI	Heart failure, incomplete inhibition of platelet activation, probable clopidogrel resistance*.	Intravascular ultrasound: well expanded stent, no edge dissection or malapposition. MLA: 5.2 mm^2.	Thrombus aspiration, glycoprotein IIb/IIIa inhibitor, change to ticagrelor.
3	48 years, male. LVEF: 50%	Distal RCA. 3×33 mm	Late. 6 months post PCI	Drug non-compliance, DM.	Focal ISR with superimposed thrombus.	Drug-eluting balloon angioplasty
4	58 years, male. LVEF: 25%	Proximal LAD. 2.5×23 mm	Subacute. 15 days post PCI	DM, small vessel disease, low ejection fraction.	NA	NA
5	62 years, male. LVEF: 35%	Proximal LAD. 3.5×33 mm	Subacute. 7 days post PCI	Low ejection fraction.	NA	NA

Cases 4 and 5 had unexplained sudden deaths within the first month (probable ST). * Assays to confirm clopidogrel resistance were not performed. DM: diabetes mellitus; IABP: intra-aortic balloon pump; ISR: in-stent restenosis; LAD: left anterior descending artery; LVEF: left ventricular ejection fraction; MLA: minimum luminal cross-sectional area; NA: not applicable; PCI: percutaneous coronary intervention; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction

Discussion

This is the first reported study on the use of the COMBO dual therapy stent in patients with acute STEMI undergoing primary PCI. The implementation of this novel technology has shown acceptable clinical outcomes. The device success rate was high, and the primary endpoint of TLF occurred in 7.7% of the patients at one year. Definite ST occurred in three patients, two acute cases and one late case. The need for TLR in our cohort was low at 3.7% at one year.

Primary PCI is the reperfusion strategy of choice in patients with acute STEMI, and the use of DES in this setting has consistently been shown to reduce the incidence of target vessel revascularisation[13]. Although vascular smooth muscle cell proliferation and neointimal hyperplasia are effectively inhibited by the antiproliferative drug, the vessel healing at the culprit site is often incomplete and delayed[14]. The most important aspect of vascular repair is surface endothelialisation, and its delay is associated with an increased risk of ST. Bone marrow-derived circulating EPC have regenerative capacities and play an important role in the repair of endothelium after injury. EPC are mobilised in large numbers from the bone marrow during STEMI, occurring within the first few hours of the event, and they peak at day seven[15]. During primary PCI, implanting stents with luminal anti-human CD34 antibody coating may optimally harness the increased levels of circulating EPC and accelerate endothelial healing. These are designed to attract circulating EPC onto the stent surface and, with time, these EPC will differentiate into a functional endothelial lining over the stent. This concept has been shown to be promising with the Genous™ stent (OrbusNeich Medical)[6]. The Genous stent has demonstrated acceptable clinical outcomes in various studies[16-18]. In spite of the beneficial pro-healing effects of EPC capture, there was a trend of higher target vessel failure with the Genous stent in comparison to first-generation DES[19]. The in-stent late loss in patients who received the Genous stent was 0.87±0.67 mm, similar to the bare metal stent[20]. This prompted the development of a COMBO dual therapy stent, which combines the properties of enhanced vascular repair and antiproliferative drug elution with sirolimus[7,8].

The REMEDEE trial and the REMEDEE registry have shown favourable outcomes with the use of the COMBO dual therapy stent[9,21]. However, our study is the first to assess the preliminary safety and efficacy of the COMBO dual therapy stent in a specific patient cohort with acute STEMI. The TLF rate of 5.1% at one month, 6.8% at six months, and 7.7% at one year is encouraging, given that this is a high-risk population. TLF was mainly driven by cardiac mortality. In the REMEDEE registry, a total of 1,000 patients were enrolled, and more than two thirds (69.6%) underwent elective PCI. The primary endpoint of TLF occurred in 5.7% of the patients at one year[21]. When compared to the outcomes from other studies using the current generation of DES in the setting of STEMI, the one-year TLF and TLR rates of the COMBO dual therapy stent in our study were similar to those of the everolimus-eluting stents[22]. Major adverse cardiac events were higher in our study when compared to those from the biolimus-eluting stent reported by Tomai et al[23]. This could be explained by the much higher incidence of cardiogenic shock, an important predictor of adverse outcome, in our cohort (9.4%) in comparison to the 3.8% reported by Tomai et al.

The incidence of definite/probable ST in our study was 3.4% at one month and 4.3% at one year, which is higher than anticipated. In the COMBO dual therapy stent, early restoration of functional endothelium and the presence of a biodegradable polymer are expected to result in an overall low rate of ST. However, the risk is not eliminated, as the pathophysiology of ST is complex and multifactorial. The common potential mechanisms for early ST are patient-related (acute coronary syndrome presentation, high

platelet reactivity, diabetes mellitus, low ejection fraction), lesion-based (thrombus containing, small vessel, long lesions), or stent-related factors (edge dissections limiting inflow or outflow, stent underexpansion). The most important risk factor for late and very late ST is a premature discontinuation of antiplatelet therapy[24]. The majority of the cases of ST in our study were clustered within 30 days (four of the five cases), in the setting of STEMI. Patients with acute coronary syndrome are at an increased risk of early ST in view of the marked inflammation and enhanced platelet reactivity. Similar findings were observed in the REMEDEE registry, where 303 patients underwent urgent PCI for acute coronary syndrome, and five of the six cases of early ST occurred in the setting of acute coronary syndrome[21]. In the EXAMINATION trial, the incidence of definite/probable ST was 0.9% in the everolimus-eluting stent group and 2.5% in the bare metal stent group. The majority of the study population (97%) were in Killip class I and II in the EXAMINATION trial[25]. In contrast, the incidence of cardiogenic shock, an important predictor of adverse outcome and contributing factor to ST, was high in our cohort (9.4%). Hence, the reported increased incidence of ST in our registry should be interpreted with great caution considering the high-risk patient cohort and the small sample size. This should be evaluated further in a larger cohort.

Individuals with acute STEMI represent a cardiac emergency, and blood flow in the culprit vessel needs to be restored at the earliest opportunity. During primary PCI, it is often difficult to assess completely a patient's suitability for the standard recommended duration of dual antiplatelet therapy[26]. Therefore, the accelerated endothelial regeneration and pro-healing benefits of the COMBO stent may be a safer option, if the need for an early interruption of dual antiplatelet therapy is warranted during the follow-up (urgent non-cardiac surgery, active bleeding, or drug non-compliance). The risks of ST may then be potentially low. The current guidelines do not recommend short dual antiplatelet therapy duration with the use of a COMBO dual therapy stent. The outcome of the REDUCE (NCT02118870) study is eagerly anticipated and will clarify the safety of a shorter, three-month duration of a dual antiplatelet regimen with the use of the COMBO stent.

The combination of EPC capture and antiproliferative drug elution is a rational and an attractive concept. The efficacy and safety of the COMBO dual therapy stent is currently being evaluated in the HARMONEE study (NCT02073565), under the framework of the joint Japan-US Harmonization-By-Doing initiative, for approval of commercial use in both the USA and Japan. The patients to be enrolled include those with stable angina, unstable angina and stabilised non-STEMI. They are randomised to receive the COMBO dual therapy stent versus the current-generation everolimus-eluting stent.

Study limitations

This was an observational registry study with inherent limitations and without a control group. The study enrolled a relatively small number of patients. However, it represents the outcome of consecutive patients in an actual clinical setting. Although it is a single-centre study and the findings may not be generally applicable to all healthcare facilities, the management in our centre is in accordance with the current standard of practice. The study assessed only the clinical outcome; the novel concept of EPC capture was not evaluated. In addition, routine follow-up coronary angiography to evaluate strut coverage and late lumen loss was not performed.

Conclusions

Clinical outcomes with the use of a COMBO dual therapy stent in patients who undergo primary PCI for acute STEMI are acceptable, although the rates of early ST were not negligible. These preliminary real-world observational data suggest the feasibility of future randomised trials to test the expanded indications for this novel stent in high-risk patients.

Impact on daily practice

EPC capture technology is unique as it facilitates rapid endothelialisation. The COMBO dual therapy stent has shown a low rate of clinical events in uncomplicated patients with stable ischaemic heart diseases. In this prospective single-centre registry, the use of the COMBO dual therapy stent in acute STEMI showed acceptable rates of TLF at one year. The higher incidence of early ST mandates further assessment in a larger study cohort. Further, our findings provide a platform for future evaluation of the COMBO dual therapy stent in a randomised controlled trial against the current-generation DES in an all-comers STEMI population.

Acknowledgements

The authors thank the National University Health System's Medical Publications Support Unit, Singapore, for assistance in the preparation of this manuscript.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:28-34

Differences in optical coherence tomography findings between an endothelial progenitor cell-capture sirolimus-eluting stent and a paclitaxel-eluting stent: insights from the OCT substudy of the REMEDEE first-in-man trial

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KEYWORDS

- endothelial progenitor cell
- neoatherosclerosis
- neointima
- optical coherence tomography
- sirolimus
- vascular healing

Abstract

Aims: First-generation DES are associated with delayed endothelial coverage and poor stent healing, increasing the risk of late stent thrombosis, late catch-up and neoatherosclerosis. This observational REMEDEE substudy aimed to examine differences in vascular healing by OCT between the EPC-capture sirolimus-eluting COMBO stent and a paclitaxel-eluting stent (TAXUS).

Methods and results: A subset of 33 patients (COMBO=23, TAXUS=10) with *de novo* coronary artery lesions in the REMEDEE study had OCT examination at the nine-month angiographic follow-up. Between-stent differences of OCT strut coverage, apposition, and neointimal morphology were compared by a core laboratory. Four thousand eight hundred and seventy-five COMBO and 2,697 TAXUS stent struts were analysed. More COMBO (98.5%) than TAXUS (97.6%) struts were well apposed and covered (p=0.3998); when overlying the ostium of a side branch, more TAXUS (0.7%) than COMBO (0.2%) struts were uncovered (p=0.0135). The COMBO stent was associated with a more homogeneous neointimal pattern (79.2% vs. 40.0% for TAXUS, p=0.04) and less layering (0.0% vs. 20.0% with TAXUS, p=0.08).

Conclusions: OCT showed nearly complete (98.5%) coverage of the COMBO stent by nine months and significantly more homogeneous neointimal tissue than with the TAXUS. These observations suggest better healing with the COMBO stent in comparison with the TAXUS stent at nine months.

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SUBMITTED ON 21/07/2015 - REVISION RECEIVED ON 1st 06/07/2016 / 2nd 23/11/2016 - ACCEPTED ON 28/11/2016

DOI: 10.4244/AsiaInterv_V3I1A9

Abbreviations

BMS bare metal stent(s)
DES drug-eluting stent(s)
DAPT dual antiplatelet therapy
EPC endothelial progenitor cell(s)
IQR interquartile range
OCT optical coherence tomography
REMEDEE Randomised study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt

Introduction

By reducing the rates of restenosis and target vessel revascularisation, drug-eluting stents (DES) have improved the outcome of patients with coronary artery disease[1-3]. However, because DES are associated with delayed endothelial healing[4,5], the development of neoatherosclerosis and the associated risk of (very) late stent thrombosis remains an important safety concern[6,7].

Endothelial progenitor cells (EPC) are circulating bone marrow-derived cells that will be immobilised by vessel injury and differentiate into mature endothelial cells promoting re-endothelialisation and healing[8-10]. In animal models, as well as in human *ex vivo* arteriovenous shunts, stents coated with anti-CD34 antibodies capturing circulating EPC have been shown to accelerate re-endothelialisation and reduce thrombogenicity[11-14].

The aim of the present substudy was to compare the midterm (nine months) vascular healing of a "dual-therapy" EPC-capture stent with abluminal sirolimus-eluting coating (COMBO™ stent; OrbusNeich Medical, Fort Lauderdale, FL, USA) with the TAXUS® Liberté™ paclitaxel-eluting stent (Boston Scientific, Marlborough, MA, USA) in a subset of patients enrolled in the REMEDEE (Randomized study to Evaluate the safety and effectiveness of an abluMinal sirolimus coatED bio-Engineered StEnt) multicentre, randomised, controlled trial using frequency-domain optical coherence tomography (OCT).

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Methods

STUDY DESIGN

The COMBO stent combines sirolimus elution from an abluminal biodegradable polymer matrix together with a covalently bound anti-CD34 antibody layer in a "dual-therapy" approach targeting anti-neointimal proliferation as a DES while maintaining the EPC-capturing benefit promoting vessel healing with accelerated stent endothelialisation. REMEDEE is a first-in-man randomised controlled trial[15], with a non-inferiority design to demonstrate the efficacy and safety of the COMBO stent in the treatment of single *de novo* lesions in native coronary arteries (NCT00967902). One hundred and eighty-three patients were randomly assigned (2:1) to receive treatment with the COMBO or TAXUS. The COMBO stent met the study primary endpoint and was found to be non-inferior to TAXUS in nine-month angiographic in-stent late lumen loss of 0.39±0.45 mm, versus 0.44±0.56 mm with TAXUS, $p_{(non\text{-}inferiority)}$=0.0012 [15]. Additionally, IVUS was performed in a subgroup of 66 patients at six sites (45 COMBO and 21 TAXUS). The IVUS follow-up at nine months consisted of 35 patients from the COMBO group and 17 from the TAXUS group. A VH-IVUS comparison of the COMBO with the TAXUS found a significantly less necrotic core area at the maximum site of neointimal hyperplasia of 0.25 mm^2 versus 0.46 mm^2 (p=0.04) and a less confluent necrotic core of 10% versus 80% (p=0.02).

OCT PATIENT COHORT

During the nine-month angiographic follow-up, two of the enrolling REMEDEE centres undertook OCT imaging in a subset of 23 COMBO and 10 TAXUS patients as an integral part of their daily clinical practice. This was not pre-specified in the REMEDEE study protocol. OCT examination was not yet available during the baseline stent implantation procedure. The differences in strut coverage (i.e., healing response) and neointima characteristics between the two stents were examined with OCT imaging. The objective of this comparative substudy was observational and it was not powered for clinical endpoints.

OCT IMAGING PROCEDURE

OCT images were obtained using the frequency-domain C7XR™ OCT system and the Dragonfly™ OCT catheter (both St. Jude Medical, St. Paul, MN, USA) at a pullback speed of 20 mm/sec (5 frames per mm) and a pullback distance of 54 mm, with two sequential pullbacks being used for longer distances.

OCT QUANTITATIVE AND QUALITATIVE ANALYSES

OCT image analyses were performed by observers blinded to the stent type from an independent OCT core laboratory (Cardiovascular Research Foundation, New York, NY, USA) using offline software (OCT System Software B.0.1; LightLab Imaging [now St. Jude Medical]). Analyses included strut coverage and apposition, and all neointimal metrics. Quantitative analysis was performed at 1 mm intervals (1/5 frames) along the length of the stent[16,17]. In case of the presence of blood artefacts, the closest artefact-free frame was used.

Each strut was classified into one of the following categories: (i) well apposed covered, (ii) well apposed uncovered, (iii) malapposed covered, (iv) malapposed uncovered, (v) orifice branch site covered and (vi) orifice branch site uncovered **(Figure 1)**. If the strut was covered with neointima, the neointimal thickness was measured from the endoluminal surface of the tissue to the centre of the strut blooming artefact. An uncovered strut was defined as having no visible tissue on the luminal surface of the strut. To assess malapposition, the distance from the centre of the stent blooming artefact to the nearby endoluminal surface of the intima was measured while the assessor was blinded to the stent type. Malapposition was decided afterwards and defined as being present if the measured distance was greater than the sum of the thickness of the stent strut metal and that of the polymer: 104 µm (100+4 µm) for the COMBO and 113 µm (97+16 µm) for the TAXUS. Stent and luminal cross-sectional areas (CSA)

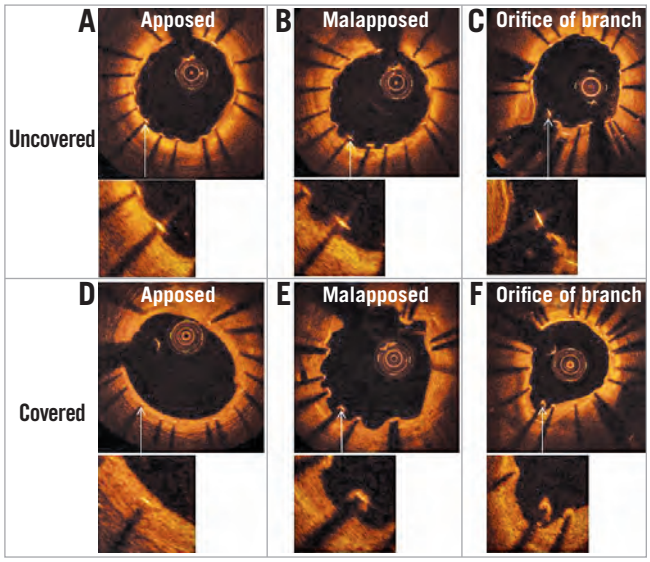

Figure 1. *Classification of stent strut coverage. A) Well apposed struts without tissue coverage. B) Malapposed struts without tissue coverage. C) Uncovered struts overlying the ostium of a side branch. D) Well apposed struts with tissue coverage. E) Malapposed struts with tissue coverage. F) Covered struts overlying the ostium of a side branch.*

were measured, and the percentage neointimal CSA was calculated (stent area-lumen area)/(stent area×100).

For neointimal morphological qualitative analysis, every individual frame was examined. The cross-sectional OCT morphological appearance of the neointimal tissue was labelled as: (i) homogeneous, (ii) heterogeneous, or (iii) layered, as reported by Gonzalo[18]. Features suggestive of neoatherosclerosis (lipidic plaque and/or calcification within the neointima), together with the presence of microvessels, macrophages, thin-cap fibroatheroma, intraluminal material with mass protruding into the lumen ≥250 μm), and neointimal rupture, were also evaluated[19,20].

STATISTICAL ANALYSIS

Continuous variables are expressed as median and interquartile range (IQR). Generalised estimating equation (GEE) relative risk statistics were used to assess differences in the median strut coverage. Categorical variables are expressed as percentages. Comparisons between stents were performed with the Pearson's chi-square test for categorical variables and Student's t-test or analysis of variance for continuous variables. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS software, Version 16.0.1 (SPSS Inc., Chicago, IL, USA).

Results

Thirty-three patients (COMBO 23 and TAXUS 10) underwent OCT evaluation at nine-month angiographic follow-up. Baseline demographics, clinical and lesion characteristics were similar[15]. Four thousand eight hundred and seventy-five COMBO struts and 2,697 TAXUS struts were analysed. Planar and volumetric analysis of the stents is presented in **Table 1** and **Table 2**.

Table 1. OCT planar analysis.

	COMBO (n=23) Median [IQR]	TAXUS (n=10) Median [IQR]	*p*-value
Minimum lumen area site			
Lumen CSA (mm²)	4.24 [3.30, 6.56]	4.93 [2.84, 5.78]	0.4567
Stent CSA (mm²)	6.11 [4.60, 9.04]	6.47 [6.05, 7.12]	0.9064
Neointima CSA (%)	27.1 [15.4, 38.3]	22.0 [14.3, 48.3]	0.9376
Minimum stent area site			
Stent CSA (mm²)	6.03 [4.23, 8.46]	5.96 [5.72, 6.46]	0.9844
Proximal most normal-looking site			
Lumen CSA (mm²)	7.06 [3.72, 8.92]	8.45 [5.72, 8.95]	0.4278
Distal most normal-looking site			
Lumen CSA (mm²)	6.08 [4.49, 9.79]	6.27 [5.13, 6.87]	0.8408
CSA: cross-sectional area			

Table 2. OCT volumetric analysis.

Stent segment	COMBO (n=23) Median [IQR]	TAXUS (n=10) Median [IQR]	*p*-value
Stent length (mm)	18.4 [17.3, 23.4]	24.3 [20.4, 26.2]	0.0312
Neointimal volume (%)	15.3 [12.0, 22.4]	16.1 [7.4, 27.4]	0.9376
Normalised* lumen CSA (mm²)	5.91 [3.85, 8.35]	6.03 [4.49, 7.16]	0.9688
Normalised stent CSA (mm²)	7.14 [4.83, 9.60]	7.15 [6.19, 7.73]	0.8447
Normalised neointima CSA (mm²)	1.25 [0.91, 1.52]	1.18 [0.58, 1.70]	0.8142
*total volume/length. CSA: cross-sectional area			

At the strut level **(Table 3)**, more COMBO struts (98.5%) were well apposed and fully covered as compared with TAXUS (97.6%) (p=0.3998). Over the ostia of side branches, more TAXUS struts lacked tissue coverage (0.7%) compared with the COMBO (0.2%),

Table 3. OCT strut coverage and malapposition (strut level, by generalised estimating equations [GEE]).

	COMBO (n=4,875) % (n) or Median [IQR]	TAXUS (n=2,697) % (n) or Median [IQR]	*p*-value
Well apposed covered	98.5 (4,801)	97.6 (2,633)	0.3998
Well apposed uncovered	1.2 (60)	1.6 (44)	0.5311
Malapposed covered	0.2 (8)	0.6 (15)	0.1646
Malapposed uncovered	0.1 (4)	0.2 (5)	0.4035
Orifice branch site covered	0.5 (24)	0.8 (22)	0.2518
Orifice branch site uncovered	0.2 (8)	0.7 (19)	0.0135
Total covered struts	98.6 (4,809)	98.2 (2,648)	0.4855
Total uncovered struts	1.3 (64)	1.8 (49)	0.4469
Neointimal thickness (mm)	0.16 [0.13, 0.19]	0.16 [0.11, 0.20]	0.8953

resulting in a significant GEE relative risk (p=0.0135). Analysed at the stent level, 99.1% and 98.4% of the COMBO and TAXUS stents were considered well apposed and covered (p=0.2705).

Based on qualitative analysis (**Table 4**, **Figure 2**, **Figure 3**), the COMBO stents had a more uniform and homogeneous neointimal response (79.2%), while the TAXUS was more variable and heterogeneous (p=0.04) (**Figure 2**-**Figure 4**). No case of thin-cap fibroatheroma, neointimal rupture or calcification was observed with either stent. All other qualitative parameters were similar between stents.

Table 4. OCT qualitative analysis.

	COMBO (n=24*) % (n)	TAXUS (n=10) % (n)	*p*-value
Neointimal tissue appearance			
Homogeneous	79.2 (19)	40.0 (4)	0.04
Heterogeneous	20.8 (5)	40.0 (4)	0.40
Layered	0.0 (0)	20.0 (2)	0.08
Peri-strut low-intensity area	33.3 (8)	70.0 (7)	0.07
Microvessel	8.3 (2)	30.0 (3)	0.14
Macrophage-like appearance	4.2 (1)	10.0 (1)	0.51
TCFA-like neointima	0.0 (0)	0.0 (0)	N/A
Neointimal rupture	0.0 (0)	0.0 (0)	N/A
Neointimal calcification	0.0 (0)	0.0 (0)	N/A
Total lesions with single abnormal intraluminal tissue	4.2 (1)	10.0 (1)	0.51

*sample with partial image was included in the qualitative data, but excluded from the quantitative data. N/A: not available; TCFA: thin-cap fibroatheroma

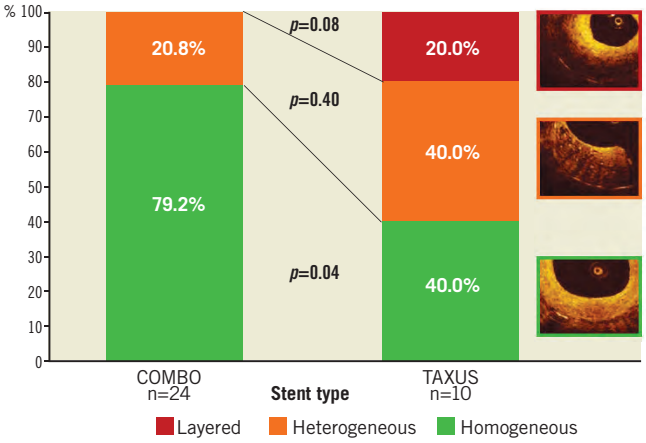

Figure 2. *Neointimal tissue characterisation (OCT). COMBO (n=24); TAXUS (n=10).*

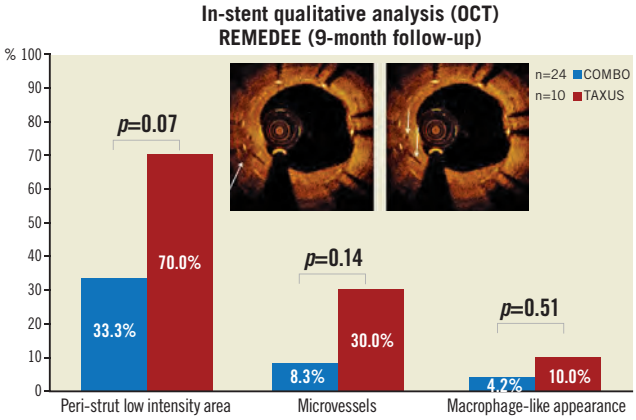

Figure 3. *Qualitative tissue characterisation (OCT, in-stent).*

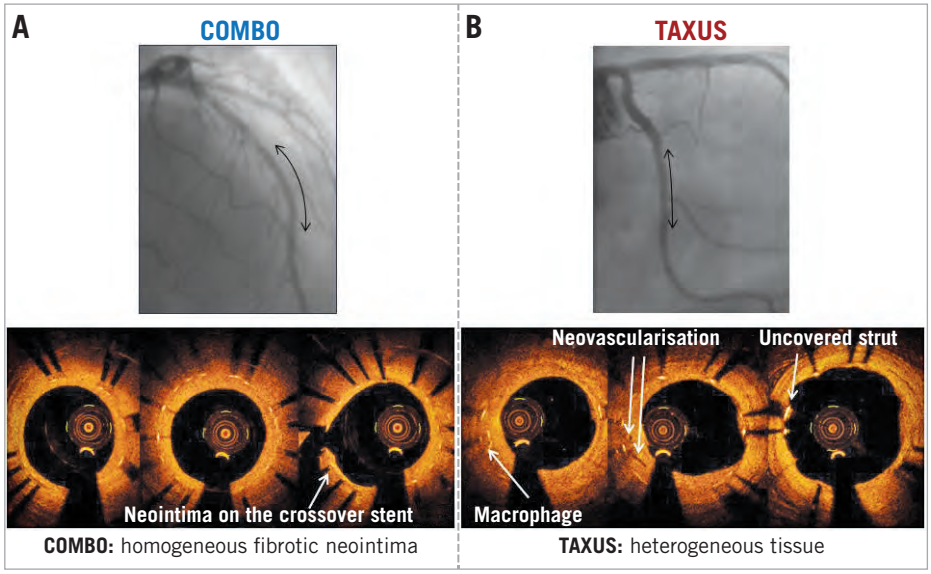

Figure 4. *Case examples of neointimal tissue. A) COMBO: homogeneous fibrotic intima. B) TAXUS: heterogeneous tissue.*

Discussion

The present study is a small-scale observational study comparing the vascular healing response associated with the COMBO and TAXUS stents using OCT. At nine-month follow-up, the major findings are: 1) neointimal volume and thickness were similar between the two stents, but 2) the neointima over the COMBO stents was more uniform and homogeneous whereas it was more variable and heterogeneous with TAXUS, 3) fewer COMBO struts at the orifice branch sites were uncovered. These observations could represent the pro-healing capability of the COMBO stent, as reflected by the better strut coverage indicative of better endothelial healing, while retaining its antiproliferative properties (neointimal suppression) as a DES.

By quantitative analysis, 98.5% of the COMBO struts were well apposed and covered compared with 97.6% of the TAXUS struts (p=0.3998). Even across the ostium of a side branch, which is often associated with impaired healing and the development of late stent thrombosis[21], more COMBO struts were covered than TAXUS. These clinical observations are consistent with animal studies which have demonstrated enhanced re-endothelialisation when EPC are present at the site of vessel wall injury[11-14], and that the combination of anti-CD34 antibodies with sirolimus results in a faster and greater degree of endothelialisation than sirolimus alone[14]. These differences can be related to various factors in the stent design, including: (i) sirolimus vs. paclitaxel, (ii) abluminal vs. conformal drug delivery, and (iii) fully biodegradable vs. permanent drug delivery polymer matrix[4,5].

The OCT morphological findings that the neointimal tissue quality inside the COMBO stents had a more homogeneous pattern while that for the TAXUS was layered or heterogeneous suggest a favourable alteration in the development of neointimal hyperplasia; however, it remains unclear whether these differences originate from the recruitment of circulatory EPC, the nature of the polymer matrix and/or the antiproliferative drug. In the case of the COMBO stent, all of the sirolimus is eluted and the polymer is completely resorbed at the nine-month time point, whereas the permanent polymer of the TAXUS stent may lead to chronic inflammatory effects[4,22].

It has been reported that early neointima formation may represent a homogeneous tissue[23,24], which may indicate normal neointima[20], while heterogeneous patterns may be associated with worse subsequent outcome[25]. Neoatherosclerosis is frequently observed in bare metal stents (BMS) and DES, and is a final common pathway leading to late stent failure[26,27]. There are, however, significant differences in the timing of development and incidence of lesions between different stent types. Indeed, after reviewing the histology findings of autopsy cases, Nakazawa and colleagues found that the accelerated neoatherosclerotic changes could occur just four months after DES implantation, while the same changes occurred beyond two years in BMS and remained a rare finding up to four years[28]. They also found that the incidence of neoatherosclerosis was significantly greater with DES and, if present, the DES would remain patent for a shorter period of time (median of 420 days with DES vs. 2,160 with BMS)[29].

OCT qualitative analysis revealed the presence of significantly more morphologically homogeneous tissue with the COMBO in comparison with the TAXUS. These observed OCT healing patterns with the COMBO are consistent with the VH-IVUS findings at nine-month follow-up of the REMEDEE study[15], revealing a dense composition and morphology of the neointimal tissue, with significantly less confluent necrotic core in the COMBO stent. This could reflect the pro-healing benefits of the immobilised anti-CD34 antibody and the reduced magnitude of inflammation with the rapid disappearance of biodegradable polymer within 90 days. These observational results suggest that the COMBO stent shows improved stent healing compared with the TAXUS stent.

Limitations

This OCT substudy in the REMEDEE trial has the following limitations. First, our results are derived from an observational study at a single time point at nine months in a small number of patients with stable angina and relatively simple coronary lesions. Second, despite the high resolution of OCT, abnormal in-stent tissue including late fibrin accumulation, excessive inflammation or abundant extracellular matrix, may be difficult to discriminate, casting difficulties on interpreting true healthy neointima. Third, further studies with long-term follow-ups are required to evaluate the relationships between early stent re-endothelialisation, vascular healing, and clinical performance.

Conclusions

Treatment of *de novo* coronary artery lesions with the dual-therapy EPC-capturing sirolimus-eluting COMBO stent was safe and effective. OCT confirmed the complete coverage of the COMBO stent and the dense homogeneous nature of the in-stent neointimal tissue at nine months, which is consistent with the previously reported observation with VH-IVUS.

Impact on daily practice

DES are often associated with delayed endothelial coverage and poor stent healing with an increased risk of late stent thrombosis and the development of neoatherosclerosis. The aim of the present substudy was to compare the midterm (nine months) vascular healing profile of a unique "dual-therapy" EPC-capturing stent with abluminal sirolimus-eluting coating (COMBO stent) to that observed with a first-generation monotherapy paclitaxel-eluting stent (TAXUS) using OCT. Both devices were equally effective in controlling neointimal proliferation, yet the healing profile as assessed by OCT demonstrated a marked difference in tissue homogeneity and uniformity in favour of the COMBO stent, which may translate into better long-term clinical outcomes.

Acknowledgements

The authors wish to thank Danielle Libersan, PhD, for her assistance in preparing this manuscript.

Funding

OrbusNeich Medical, Inc., Ft. Lauderdale, FL, USA provided the funding to conduct the REMEDEE trial.

Conflict of interest statement

M. Haude has received support from Abbott, Biotronik, OrbusNeich, Medtronic, and Volcano. A. Maehara has received speaker's fees from St. Jude Medical, research grant support from Boston Scientific, and is a consultant to Boston Scientific and ACIST. R. Mehran is a consultant to and/or receives honoraria from AstraZeneca, Abbott Vascular, Boston Scientific, Covidien, CSL Behring, Janssen (J & J), Merck, Maya Medical, Regado Biosciences and Sanofi, and also receives research/grant support from AstraZeneca, BMS/Sanofi Aventis, DSI/Eli Lilly and The Medicines Company. The other authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:35-40

A modified frequency domain optical coherence tomography procedure for imaging severely stenotic coronary artery lesions

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KEYWORDS

- coronary artery disease
- frequency domain optical coherence tomography
- imaging

Abstract

Aims: This proof-of-concept study aimed to investigate the clinical feasibility of a modified frequency domain optical coherence tomography (FD-OCT) procedure for imaging severely stenotic coronary artery lesions.

Methods and results: In total, 46 patients in whom clear images were unobtainable using conventional FD-OCT examination were consecutively enrolled in this study. Then, they were randomly divided into two groups: group A (FD-OCT examination using the new modified procedure, n=23), and group B (FD-OCT examination using a previously described procedure, the Yamaguchi method, n=23). The procedure success was 100% in group A and 86.96% in group B. Clear images of the proximal segment were obtained by both procedures for all patients. The percentage of clear images for the distal segment was 95.65% in group A and 85% in group B. Clear images of the maximal stenosis segment were 100% in group A and 95% in group B. However, these outcomes were not significantly different between the two groups. The amount of contrast agent used in group A was lower than that used in group B.

Conclusions: The new modified procedure can obtain clear images of severely stenotic coronary artery lesions. The difference in contrast volume is of statistical significance but may be of minimal clinical significance.

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SUBMITTED ON 06/01/2016 - REVISION RECEIVED ON 13/11/2016 - ACCEPTED ON 25/11/2016

DOI: 10.4244/AsiaInterv_V3I1A10

Introduction

Frequency domain optical coherence tomography (FD-OCT) is increasingly used to assess coronary artery lesions in clinical practice. Compared with time domain optical coherence tomography (TD-OCT), FD-OCT has a higher pullback speed without necessitating balloon occlusion of the artery[1,2]. However, the profile diameter of the FD-OCT catheter (approximately 2.7 Fr, 0.9 mm diameter) is larger than that of TD-OCT, which can occlude severely stenotic coronary artery lesions and cause insufficient distal contrast flushing and blood clearance, ultimately leading to poor OCT imaging and examination failure. Therefore, the use of FD-OCT is not recommended for severely stenotic coronary artery lesions with a minimum vessel diameter below 0.9 mm. Yamaguchi et al[3] recently recommended a new FD-OCT imaging procedure that could better characterise severely stenotic coronary artery lesions. Their imaging protocol allowed the acquisition of approximately 5 cm of the coronary segment in 3.5 s, with a contrast medium volume of 14 ml (using a cardiovascular injection pump to deliver the contrast medium through the guide catheter at a rate of 4 ml/s for a total of 14 ml or 3.5 s). The new FD-OCT imaging procedure was an improvement over conventional procedures, and images were obtained for most patients in whom conventional procedures had failed. Using their proposed procedure, the Dragonfly™ imaging catheter (St. Jude Medical, St. Paul, MN, USA) is first passed through the lesion and then retracted to a position proximal to the target lesion. The catheter is then passed through the target lesion again before initiating the pullback. Passing the catheter through severely stenotic coronary artery lesions twice is inconvenient and may damage the Dragonfly catheter. To image severely stenotic coronary artery lesions better, we modified the procedure of Yamaguchi et al. Two important adjustments were made: 1) the Dragonfly catheter was passed through the lesions just once, and pullback was triggered automatically when distal blood was cleared sufficiently, and 2) 5 ml mixed liquid (saline and contrast 1:1) was injected manually to flush the blood before injecting contrast medium into the target coronary artery (flow rate 3 ml/s, volume 9 ml). This proof-of-concept study aimed to analyse the new FD-OCT imaging procedure in patients with severely stenotic coronary artery lesions.

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Methods

STUDY POPULATION AND PROTOCOL

In total, 46 patients with acute coronary syndrome (ACS) who had undergone unsuccessful FD-OCT imaging were enrolled consecutively between December 2013 and December 2014. Examination failure occurred due to severely stenotic coronary artery lesions which resulted in insufficient distal contrast flushing and blood clearance. Patients were randomly divided into two groups, group A (n=23) and group B (n=23), as shown in **Figure 1**. Patients in group A underwent FD-OCT examination using the new modified procedure, and patients in group B underwent FD-OCT examination using the Yamaguchi et al procedure[3]. All patients provided written informed consent prior to coronary angiography and FD-OCT examination. The study protocol was approved by the local research ethics committee.

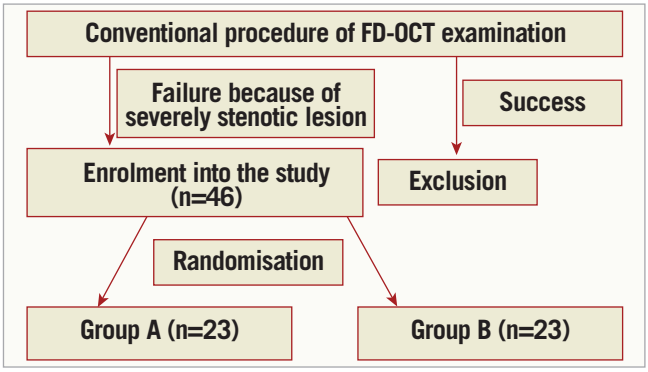

Figure 1. *Flow chart. Flow chart of the study protocol, showing the enrolment procedure. FD-OCT: frequency domain optical coherence tomography; Group A: FD-OCT examination using our modified procedure; Group B: FD-OCT examination using the procedure of Yamaguchi et al[3].*

CORONARY ANGIOGRAPHY AND ANALYSIS

Coronary angiography was performed using a 6 Fr guiding catheter through the femoral or radial artery, and images were acquired after 200 µg of nitroglycerine had been administered into the coronary artery. All results were analysed at an independent core laboratory. The quantitative coronary angiography (QCA) software package QCA-CMS (Medis medical imaging systems, Leiden, The Netherlands) was used for imaging analysis **(Figure 2)**. The minimal lumen diameter, proximal and distal reference lumen diameters, diameter stenosis percentages, the total lesion length, and the length of maximal stenosis were measured.

OCT IMAGE ACQUISTION

The C7-XR™ FD-OCT™ system (St. Jude Medical) using an automatic pullback speed of 20 mm/s was used in this study. A 2.7 Fr Dragonfly catheter (St. Jude Medical) was used to acquire the images. The procedure was attempted using a 6 Fr guiding catheter through the radial artery, and the guiding catheter was placed coaxial to the left or right coronary artery, before passing a 0.014-inch guidewire through the target lesion to deliver the Dragonfly catheter.

In group A, the modified FD-OCT imaging procedure was performed as follows: 1) a cardiovascular pump with a guide catheter was connected, 2) 5 ml of mixed liquid (1:1 saline and contrast) was placed into the injector (volume 5 ml) connected to the flush port of the Dragonfly catheter, air was ejected out of the Dragonfly catheter, then the catheter was connected to the pullback device, 3) the Dragonfly catheter was passed through the target lesion, 4) the pullback trigger of the FD-OCT system was set to automatic and the system mode switched to live view, 5) the 5 ml of liquid was injected manually (flow rate ~1 ml/s), before injecting

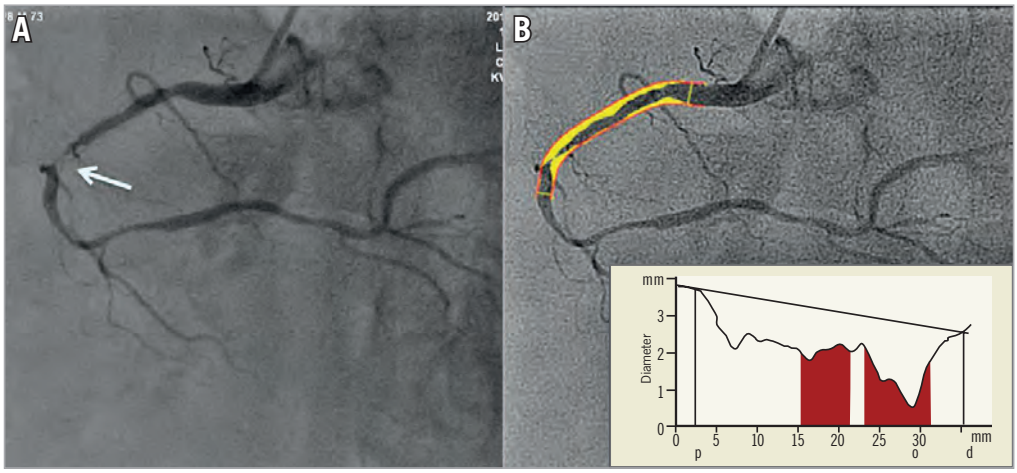

Figure 2. *Quantitative coronary angiography (QCA) analysis. A) Severely stenotic lesions in the right coronary artery (white arrow). B) QCA-CMS software from Medis for imaging analysis of the severely stenotic lesions in the right coronary artery.*

the contrast medium into the coronary artery (flow rate 3 ml/s, volume 9 ml), 6) the catheter was automatically pulled back when the distal blood was cleared sufficiently, 7) when pullback was complete, contrast flush was discontinued, and the Dragonfly catheter was retracted into the guide catheter.

In group B, the procedure proposed by Yamaguchi et al was performed as follows: 1) a cardiovascular injection pump was connected to the guide catheter, 2) an injector (volume 2 ml contrast) was connected with the flush port of the Dragonfly catheter, air was ejected out of the Dragonfly catheter, then the catheter was connected to the pullback device, 3) the lesion size and the ability of the catheter to pass through were confirmed before retracting the catheter to a proximal position, 4) the pullback trigger of the FD-OCT system was set to manual, the system mode switched to live view, and pullback enabled, 5) the contrast medium was injected into the target coronary artery (left coronary artery: flow rate 4 ml/s, volume 14 ml; right coronary artery: flow rate 3 ml/s, volume 12 ml), 6) the Dragonfly catheter was passed through the target lesion and, as soon as positioning was complete, pullback was initiated, 7) when pullback was complete, contrast flush was discontinued, and the Dragonfly catheter was retracted into the guide catheter.

ENDPOINT AND PARAMETERS

The primary endpoint was the proportion of patients in the two groups for whom clear images had been obtained. Clear images were defined as having a clear vessel lumen profile and target lesion segment **(Figure 3)**. The images were assessed by two independent investigators, and the length of the target lesion was divided into three segments (maximum stenosis, distal and proximal); OCT imaging at the three segments was then analysed. The safety endpoint was complications associated with the FD-OCT examination, such as acute vessel occlusion, angina pectoris, dissection, significant arrhythmias and vasospasm. The amount of contrast medium was also recorded.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±standard deviation and categorical variables as absolute numbers and percentages. Differences between groups were assessed using Pearson's χ^2 test or the Student's t-test. A p-value <0.05 was considered statistically significant. Statistical evaluation was performed using dedicated software (SPSS 11.5 for Windows; SPSS Inc., Chicago, IL, USA).

Results

BASELINE CHARACTERISTICS

FD-OCT examination was performed in 46 patients who exhibited ACS between December 2013 and December 2014. The demographic baseline, serological indicators, current treatments, and angiographic characteristics were not significantly different between the groups **(Table 1)**.

OCT EXAMINATION AND RESULTS

The results of the OCT examinations are shown in **Table 2**. The OCT examination procedure was successful on the first attempt, and clear images were acquired in group A **(Figure 3)**; however, clear images could not be acquired in three patients of group B due to insufficient distal contrast flushing and blood clearance. Therefore, the procedure success rate was higher in group A compared with group B, but the results were not significantly different (100 vs. 86.96%, p=0.233). There were no complications associated with FD-OCT examination in group A. However, one patient in group B experienced angina pectoris which stopped after the examination ended. The OCT images were assessed from the maximal stenosis, distal, and proximal segments. Clear images of the proximal segment were obtained for all patients. The percent of clear images obtained from the distal segment (95.65 vs. 85%, p=0.465) and maximal stenosis segment (100 vs. 95%, p=0.465) in group A was higher than that in group B; however, the differences

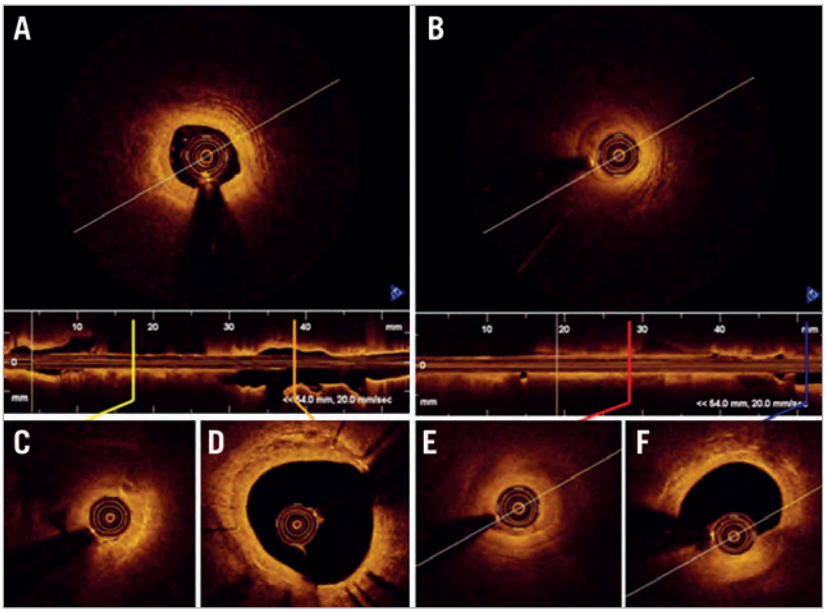

Figure 3. *Optical coherence tomography imaging achieved using the new procedure and the Yamaguchi et al procedure. OCT image of the new procedure: clear image segments show the distal side of the lesion (A), the stenotic lesion (C), and the proximal side of the lesion (D). OCT image of the Yamaguchi et al procedure: image segments show the distal side of the lesion (B), the stenotic lesion (E), and the proximal side of the lesion (F).*

Table 1. Baseline clinical and angiographic characteristics.

	Group A (n=23)	Group B (n=23)	*p*-value
Age (years)	54.8±11.4	58.6±10.9	0.258
Proportion of males, n (%)	16 (69.6)	15 (65.2)	0.753
Hypertension history, n (%)	12 (52.2)	14 (60.9)	0.552
Hypercholesterolaemia, n (%)	8 (34.8)	10 (43.5)	0.546
Current smoker, n (%)	13 (56.5)	11 (47.8)	0.555
Diabetes mellitus, n (%)	9 (39.1)	7 (30.4)	0.536
Systolic blood pressure, mmHg	117.2±20.6	123.1±17.1	0.304
Diastolic blood pressure, mmHg	72.1±15.4	73.7±13.9	0.724
Blood glucose, mmol/L	6.3±1.9	6.1±1.9	0.608
CHO, mmol/L	4.5±0.8	4.3±0.9	0.626
LDL-C, mmol/L	2.8±0.7	2.4±0.9	0.125
Medical treatment			
Aspirin, n (%)	23 (100)	23 (100)	–
Statin, n (%)	23 (100)	23 (100)	–
ACEI/ARB, n (%)	9 (39.1)	10 (43.5)	0.765
ß-blocker, n (%)	9 (39.1)	9 (39.1)	–
Coronary angiography			
Minimum vessel diameter, mm	0.66±0.15	0.68±0.13	0.736
Maximal diameter stenosis (%)	81.06±3.87	79.69±4.44	0.27
Total length of lesion, mm	29.70±6.38	31.96±7.02	0.259
Length of maximal stenosis, mm	7.62±1.35	7.71±1.45	0.784
Proximal reference diameter, mm	3.51±0.28	3.34±0.35	0.156
Distal reference diameter, mm	3.11±0.25	2.98±0.28	0.104

ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; CHO: total cholesterol; LDL-C: low-density lipoprotein cholesterol; Medical treatment: the in-hospital treatment

Table 2. Results of the FD-OCT examinations.

	Group A (n=23)	Group B (n=23)	*p*-value
Procedure success, n (%)	23 (100)	20 (86.96)	0.233
Clear images			
Proximal segment, n (%)	23 (100)	20 (100)	–
Maximal stenosis segment, n (%)	23 (100)	19 (95)	0.465
Distal segment, n (%)	22 (95.65)	17 (85)	0.323
Contrast medium, ml	7.87±1.01	9.74±1.57	<0.001
Complications, n (%)	0 (0)	1 (5)	0.465

were not significant. The amount of contrast agent used in group A was significantly less than that in group B (7.87±1.01 vs. 9.74±1.57 ml, p<0.001).

Discussion

OCT is useful for elucidating the morphologic characteristics of coronary plaques, with high sensitivity and specificity[4-8]. First-generation OCT, TD-OCT, requires a balloon to block the coronary lumen to acquire clear images. This disadvantage limits its clinical application. The second-generation OCT, FD-OCT, can achieve a rapid pullback speed of up to 25 mm/s with no need for balloon occlusion[1,2]. This advantage has expanded its clinical application. However, the catheter used in FD-OCT is larger than that in TD-OCT and may block the coronary lumen and cause blurring of the distal segment in severely stenotic coronary artery lesions. Severely stenotic coronary artery lesions are frequently

overestimated by coronary angiography due to the severe narrowing of the lumen and may result in longer than necessary stent implantation. Therefore, FD-OCT is sometimes necessary to determine the appropriate stent length[9]. Conventional procedures fail to acquire clear images because the catheter occludes the coronary artery when traversing a severe stenosis. This prevents the contrast medium from flushing out the blood for clear imaging. Yamaguchi et al[3] reported that their method could effectively and safely obtain clear images in severely stenotic coronary artery lesions for which conventional procedures failed. However, their proposed procedure requires the catheter to be passed through the lesion at least twice, which is inconvenient and may damage the catheter. For this reason, the FD-OCT procedure was modified for the imaging of severely stenotic coronary artery lesions. Two important modifications were: 1) the Dragonfly catheter was passed through the severely stenotic coronary artery lesion just once, and pullback was triggered automatically when distal blood was cleared sufficiently, and 2) 5 ml mixed liquid (saline and contrast 1:1) was first injected manually to flush out the blood before injecting contrast medium into the coronary artery (flow rate 3 ml/s, volume 9 ml). In this study, we compared our newly modified procedure with that of Yamaguchi. The results of this proof-of-concept study showed that the modified procedure provided clear images without failure, whereas the method by Yamaguchi et al resulted in unclear images due to insufficient distal contrast flushing and blood clearance. The procedure success rate was 86.96% using the Yamaguchi method and 100% using the modified method. The procedure success rate was numerically, although not significantly, lower when using the Yamaguchi method compared with the modified method. Both procedures can acquire clear images from proximal segments; however, imaging the maximal stenosis and distal segments is more challenging due to contrast flushing and blood clearance. The percentage of clear images obtained from the distal (95.65 vs. 85%, p=0.465) and maximal stenosis segments (100 vs. 95%, p=0.465) was higher when using the modified procedure compared with the Yamaguchi procedure. The modified procedure was successful on the first attempt and without complications; however, one patient (5%) experienced angina pectoris when undergoing the Yamaguchi et al procedure. In the study by Yamaguchi et al, clear images were obtained from the 20 patients enrolled. In the three remaining patients, OCT signal attenuation due to blood flow was observed due to inadequate blood clearance distal to the lesion. The main reason for the success of the modified procedure was the use of a mixed liquid (saline and contrast, 1:1) to flush away blood in the maximal and distal segments before the injection of contrast medium. Although the results showed no statistically significant differences, the modified procedure is more convenient than both Yamaguchi's and conventional procedures and may reduce the risk of damaging the Dragonfly catheter. Successful imaging of the lesion ultimately leads to better guidance for stent implantation.

Another advantage of the modified procedure is the reduced use of contrast medium. Conventional procedures require repeated contrast injections, which can enlarge the coronary dissection and result in contrast-induced nephropathy[10,11]. The mean amount of contrast medium used for OCT in Yamaguchi et al's study was 35 ml, with a maximum of 56 ml. These contrast medium volumes were not sufficient for patients with longer lesions or those who required repeat interventional treatment. For the modified method, 5 ml mixed liquid (saline and contrast, ratio 1:1) was injected (flow rate 1 ml/s) before the contrast medium was injected into the target coronary artery (flow rate 3 ml/s, volume 9 ml). The advanced flushing of blood distal to the lesion allowed precise timing for the contrast medium, and the automatic pullback trigger also assured further contrast medium reduction. In this study, the modified method resulted in reduced contrast medium use compared with the method of Yamaguchi et al (7.87±1.01 vs. 9.74±1.57 ml, p<0.001). The difference of approximately 2 ml contrast volume is of statistical significance but has minimal clinical significance. We still hope that patients with severely stenotic coronary artery lesions that are much longer and often require repeat imaging, and patients who may have multivessel coronary stenosis, both of which lead to increased use of contrast medium, could benefit from this. In these cases, the modified FD-OCT procedure may be even more valuable.

Limitations

There are several limitations for this proof-of-concept study. First, the absence of any statistical differences may be due to the small sample size, so further studies are needed to verify the results. Second, the newly modified procedure is unsuitable for complicated lesions. Third, no follow-up data from these patients were obtained, so additional effects were not discovered.

Conclusions

The newly modified procedure can effectively obtain clear images from severely stenotic coronary artery lesions, is more convenient and requires the use of a lower amount of contrast medium.

Impact on daily practice

Severely stenotic coronary artery lesions are frequently overestimated by coronary angiography due to the severe narrowing of the lumen. This may result in a longer than needed stent implantation. Therefore, FD-OCT is sometimes necessary to determine the appropriate stent length. Conventional FD-OCT procedures fail to acquire clear images because the catheter occludes the coronary artery when traversing a severe stenosis. This prevents the contrast medium from flushing out the blood. The modified procedure developed in this study is clinically feasible, is more convenient, and uses a slightly smaller amount of contrast medium compared with the procedure by Yamaguchi et al[3].

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:41-48

Optical coherence tomography analysis of neointimal tissue in drug-eluting stents with biodegradable and durable polymer coatings: the ALSTER-OCT registry

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KEYWORDS

- biodegradable polymer
- drug-eluting-stents
- optical coherence tomography

Abstract

Aims: Optical coherence tomography (OCT) for follow-up after drug-eluting stent implantation permits detection of strut coverage, apposition and neointimal tissue. We aimed to compare OCT follow-up data and clinical outcome of two new-generation drug-eluting stents, Orsiro sirolimus-eluting stents (O-SES) and zotarolimus-eluting stents (ZES).

Methods and results: Eighty patients underwent OCT following implantation of O-SES (n=34) or ZES (n=46). Imaging was performed after three (n=39), six (n=28) or nine months (n=13). OCT data were acquired (coverage, apposition, neointimal thickness) and neointimal maturation was assessed by novel greyscale signal intensity analysis. Image analysis revealed increased strut coverage, tissue maturation and neointima formation over the three time points. There were no significant differences between O-SES and ZES in terms of coverage and apposition at any time. We also found no differences for neointimal thickness, maturation and rate of major adverse cardiac events (a composite of cardiac death, myocardial infarction and ischaemia-driven target lesion revascularisation within 12 months, O-SES 9.4% vs. ZES 6.8%, p=0.69).

Conclusions: No statistical differences were observed between O-SES and ZES concerning stent healing as well as one-year clinical outcome. Although preliminary, our findings may support the hypothesis that OCT-based analyses in small patient cohorts sensitively detect stent healing and could possibly be regarded as surrogates for DES healing and closely correlated to clinical outcome.

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SUBMITTED ON 15/08/2016 - REVISION RECEIVED ON 1st 09/11/2016 / 2nd 15/11/2016 / 3rd 30/11/2016 - ACCEPTED ON 05/12/2016

DOI: 10.4244/AsiaInterv_V3I1A11

Introduction

Since the introduction of second-generation drug-eluting stents (DES), event rates for target lesion failure (TLF) and late stent thrombosis (LST) have been remarkably low. Yet, these events are potentially fatal complications of percutaneous coronary interventions (PCI) and contribute to the long-term outcome[1]. Recent findings suggest that inflammatory reactions caused by durable polymers play an important role in neoatherosclerosis, delayed DES healing, LST and stent restenosis[2]. New technologies combine thinner struts, biocompatible polymers and different drug release kinetics to tackle these remaining problems. New-generation DES showed similar effectiveness compared to second-generation DES after one year[3,4]; however, improved safety may become apparent in larger sample sizes or expanded follow-up. Validated parameters for stent healing may allow judgement on the safety and efficacy of a particular stent in small patient cohorts prior to large studies with clinical outcome parameters. While post-mortem and *in vivo* studies have presented a significant relation of LST and uncovered and malapposed struts, optical coherence tomography (OCT) allows highly detailed *in vivo* imaging and has become a useful tool to evaluate stent coverage and apposition[5-7]. Therefore, quantitative parameters such as coverage and malapposition assessed by OCT have been proposed as surrogate parameters for stent biocompatibility and possibly clinical outcome in DES[8,9]. The ALSTER-OCT (AskLepios ST. GEoRg's Hospital-Optical Coherence Tomography) registry used quantitative OCT analyses to compare healing characteristics to clinical outcome of patients receiving new-generation Orsiro Hybrid sirolimus-eluting stents with biodegradable polymer (O-SES) (Biotronik AG, Bülach, Switzerland) to zotarolimus-eluting-stents with durable polymer (ZES) (Resolute Integrity® and Endeavor® Resolute; Medtronic, Santa Rosa, CA, USA).

Methods

DESIGN AND PATIENT ENROLMENT

The ALSTER-OCT registry **(Figure 1)** was a prospective, all-comers, single-centre registry to investigate DES healing at three (90±30 days), six (180±30 days) and nine-month (270±30 days) follow-up. Between June 2010 and January 2014, clinically indicated surveillance angiography was performed with OCT in 110 patients (121 lesions). The type of DES and the time point of angiography were determined by the initial operator or the referring physician. Patients with complex lesions (ostial stenosis, stenosis of the left main trunk, lesions ≥10 mm length in vessels ≤3.5 mm diameter) treated with ZES (n=46) or O-SES (n=34) were eligible. Written informed consent was obtained from all patients.

STUDY DEVICES

Detailed device characteristics have been previously reported[10,11]. Concerning ZES, two different types were analysed. The Endeavor Resolute ZES comprises a cobalt-chromium alloy (same CoCr alloy as used in the Driver® BMS; Medtronic) coated by the polymer combined with zotarolimus. The Resolute Integrity ZES is the latest version of the ZES. It uses the same drug and polymer mounted on an altered cobalt-chromium alloy platform (Integrity™; Medtronic). Both bare metal stent backbones (Driver/Integrity) have a strut thickness of 91 µm; therefore, we did not differentiate between these platforms.

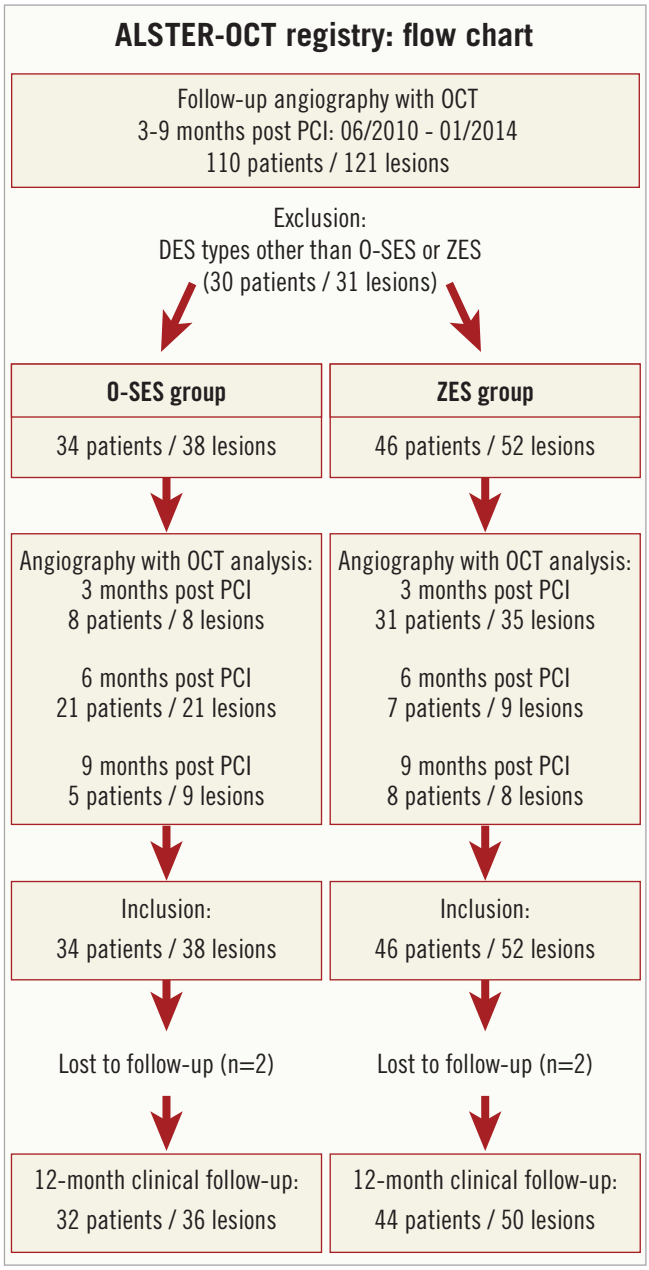

Figure 1. *ALSTER-OCT registry - flow chart. Flow chart of patients included in this prospective registry.*

OCT IMAGING AND ANALYSIS

As recently described by our group, frequency-domain OCT was performed according to the latest consensus documents and obtained with the ILUMIEN™ system (St. Jude Medical, St. Paul, MN, USA) combined with the C7 Dragonfly™ imaging catheter (St. Jude)[5,12]. Acquired data were analysed using LightLab software (OCT system software B.0.1; LightLab Imaging [now St. Jude])[5]. All images were initially screened for quality assessments and

excluded from analysis if any portion of the image was out of the screen or the image had poor quality due to artefacts[13]. In case of ostial lesions, the proximal part of the stent was excluded from the analysis. Struts located at the ostium of coronary artery side branches were designated as non-apposed side branch struts and were excluded from the analysis[7,12]. A strut was considered suitable for analysis only if it had a well-defined, bright "blooming" and a characteristic shadow perpendicular to the light source[12]. Image assessments were performed in every third cross-section. According to previously described methods, stents were analysed strut by strut and classified into four categories. Struts covered by tissue and not interfering with the lumen contour were defined as "covered embedded". Struts covered by tissue protruding into the vessel lumen were defined as "covered protruding". If no evidence of tissue was visualised above the struts and the struts were abutting the vessel wall they were defined as "uncovered apposed". Struts not covered by tissue and separated abluminally from the luminal contour of the vessel wall were defined as "uncovered malapposed"[12]. If neointimal tissue was observed, its average thickness was measured[12]. Two independent expert observers (blinded to the clinical and procedural characteristics) performed the analysis and intra- and inter-observer reproducibility was calculated[8].

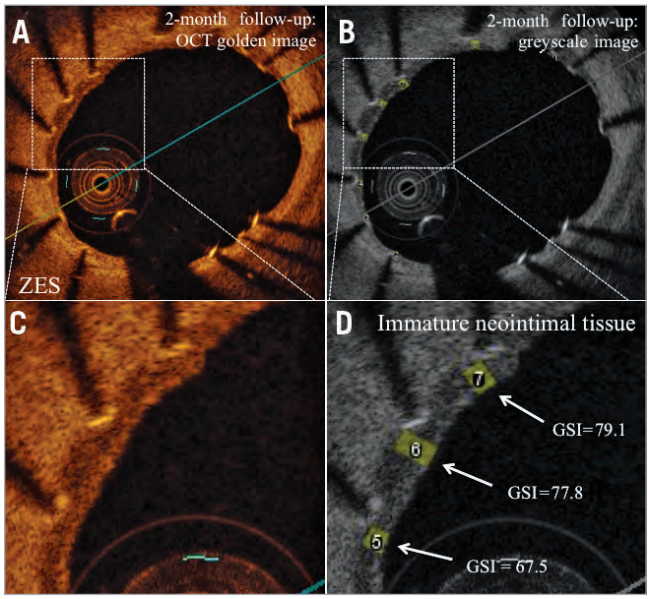

Figure 2. *OCT-based GSI analysis - immature neointimal tissue. A) Representative OCT golden image at two-month follow-up and corresponding GSI image (B) as well as magnification (C & D). GSI values presenting evidence for immature neointimal tissue.*

GREYSCALE SIGNAL INTENSITY MEASUREMENTS

To discriminate between mature and immature neointimal tissue, OCT-based greyscale signal intensity (GSI) analysis was assessed previously[9]. Exemplary figures are presented in **Figure 2** and **Figure 3**. In brief, analysis of cross-sections was assessed at every fifth cross-section. In each section 10 to 12 regions of interest (ROI) luminal to each covered strut were chosen (every 30°±10° of 360° cross-section) and each width was predefined to 0.1 mm. To normalise the brightness level (GSI=256), the guidewire was set as a reference in each analysed frame, while the darkest level (GSI=0) of the vessel lumen was set as the minimum value. A 256-level GSI was measured for every pixel within the given ROI. The previously validated histology-based GSI cut-off value (GSI=109.7) was used for the differentiation between mature and immature neointimal tissue[9].

CLINICAL FOLLOW-UP

The patients were followed up with telephone interviews at 12 months after PCI. TLF was defined as a composite of cardiac death, target vessel myocardial infarction (MI), ischaemia-driven target lesion revascularisation within 12 months[3]. Target vessel revascularisation (TVR) was defined as non-target lesion revascularisation of the target vessel[14]. The composite of cardiac death, MI and ischaemia-driven target lesion revascularisation within 12 months was considered as a major adverse cardiac event (MACE)[15].

STATISTICAL ANALYSIS

Continuous data were summarised as means and standard deviations or as medians and 25th and 75th percentiles, as appropriate. Categorical data are presented as N (%). We examined strut coverage, cross-section and GSI data between the two stent groups. As recently reported by our group, to account for the clustered nature of OCT data, multilevel regression analyses on lesion level, cross-section level and strut level were realised[13,16]. For intra-group analysis within each group, an analysis of variance was performed.

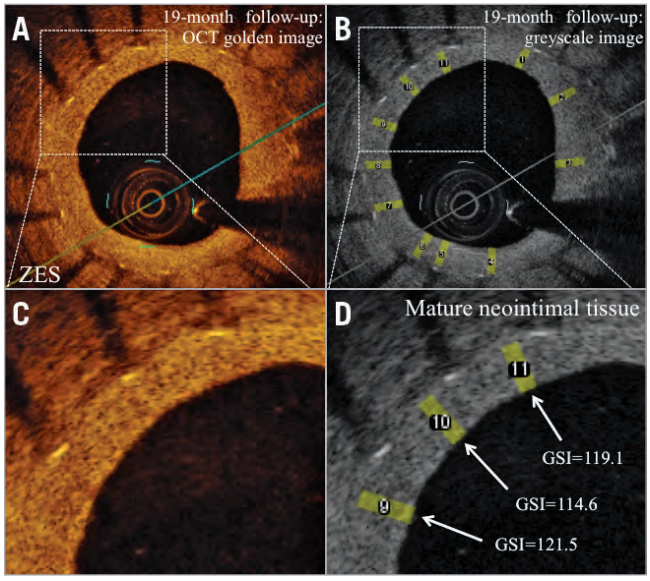

Figure 3. *OCT-based GSI analysis - mature neointimal tissue. A) Representative OCT golden image at 19-month follow-up and corresponding GSI image (B) as well as magnification (C & D). GSI values presenting evidence for mature neointimal tissue. White arrows show GSI values of respective region of interest. Yellow marked area indicates region of interest. GSI: greyscale signal intensity*

A p-value <0.05 was considered to be statistically significant and all analyses were two-tailed. Intra-observer and inter-observer reproducibility was assessed using the intraclass correlation coefficient. Statistical analysis was performed using GraphPad Prism, version 6 (GraphPad Software, Inc., San Diego, CA, USA).

Results

PATIENT BASELINE CHARACTERISTICS

Table 1 summarises patient baseline characteristics and procedural details. The two groups showed no statistical differences concerning baseline characteristics. Concerning ZES, 33 patients with Endeavor Resolute (71.7%) and 13 patients with Resolute Integrity (28.3%) were analysed.

QUANTITATIVE OCT IMAGE ANALYSIS

Results of OCT analysis are shown in **Table 2**. As expected with stent healing, the percentage of uncovered struts decreased over time while GSI parameters of tissue maturation increased. Interestingly, mean neointima thickness did not change in the O-SES group (0.5 mm), while it significantly increased between six and nine months in the ZES group (0.5-1.3 mm). No differences were found concerning coverage and apposition. One subclinical intra-stent thrombus formation of a ZES at three-month follow-up was detected while the patient was under DAPT. In this specific patient the rate of uncovered malapposed struts was remarkably high (10.7%).

Intra-group analyses between different time points showed no differences for coverage and apposition. The qualitative assessments were reproducible and comparable to findings of other groups. The measurements of five randomly chosen patients (n=2,124 struts) were repeated and the intra-observer and inter-observer reproducibility was calculated as 0.87 and 0.89, respectively[17].

OCT-BASED GSI ANALYSES

Findings of GSI analyses are presented in **Figure 4** and **Table 2**. We found no differences for the intra-group comparison of GSI values and percentage of mature neointimal tissue concerning the O-SES and no differences within the inter-group analysis compared to the ZES. Nevertheless, ZES had increased neointima maturation over time (p=0.0001), while O-SES showed stable measurements at all three time points (p=0.532), again possibly reflecting the different release kinetics of polymer and drug.

CLINICAL FOLLOW-UP

Clinical follow-up is shown in **Table 3**. Concerning O-SES, no TVR and MI were reported but one patient died due to major cerebral bleeding while she was on DAPT seven months after PCI. One further patient died due to respiratory insufficiency related to pneumonia after ten months. Four patients of the ZES group were readmitted requiring TVR (9.1%). Although not reaching statistical significance, this observation is in line with the observed increase of neointimal formation between six and nine months when ZES already equals a bare metal stent, while O-SES (TVR=0%) still releases drug and the polymer is slowly degraded. One patient experienced a transient ischaemic attack, most likely due to a cardiac embolic event caused by unknown atrial fibrillation without intake of oral anticoagulation. He recovered totally after 24 hours. The 12-month rates of cardiac death, MACE (O-SES 9.4% vs. ZES 6.8%, p=0.69) and TLF (O-SES 9.4% vs. ZES 6.8%, p=0.69) were not significantly different. Additionally, no differences were found for the duration of DAPT.

Table 1. Patient baseline characteristics and procedural data.

Characteristics	O-SES (n=34 patients)	ZES (n=46 patients)	*p*-value
Clinical features			
Age (years)	66.5±1.3	65.3±1.5	0.89
Male sex	25 (73.5)	36 (78.3)	0.79
Obesity	22 (64.7)	28 (50)	0.82
Hypertension	31 (91.2)	39 (84.8)	0.51
Hyperlipidaemia	19 (55.9)	30 (65.2)	0.49
Diabetes mellitus type 2	11 (32.4)	12 (26.1)	0.62
Smoking	14 (41.2)	23 (50.0)	0.50
Prior PCI	15 (44.1)	23 (50.0)	0.66
Prior MI	14 (41.2)	14 (30.4)	0.35
Prior CABG	3 (8.8)	5 (10.9)	>0.99
Multivessel disease	23 (73.5)	33 (71.7)	>0.99
Left ventricular ejection fraction	50.3±1.8	51.5±1.0	0.51
Antiplatelet therapy at baseline			
Acetylsalicylic acid	33 (97.1)	46 (100)	0.43
$P2Y_{12}$ inhibitors	34 (100)	46 (100)	>0.99
Clinical presentation at baseline			
Stable angina pectoris	5 (14.7)	6 (13.0)	>0.99
Unstable angina pectoris	19 (55.9)	31 (67.4)	0.35
NSTE-ACS	8 (23.5)	6 (13.0)	0.25
STEMI	2 (5.9)	3 (6.5)	>0.99
Treatment			
Number of treated lesions	38	52	
Left anterior descending artery	14 (36.8)	18 (34.6)	0.83
Left circumflex artery	6 (15.8)	7 (13.5)	0.77
Right coronary artery	18 (47.4)	27 (51.9)	0.83
Chronic total occlusions	5 (13.2)	9 (17.3)	0.77
Ostial lesions	1 (2.6)	3 (5.7)	0.64
Bifurcations	8 (21.1)	11 (21.2)	>0.99
Drug-eluting stents/lesion	1.4±0.1	1.2±0.1	0.13
Total stent length (mm)	24.7±2.7	25.0±1.8	0.33
Mean stent diameter (mm)	2.9±0.06	2.9±0.06	0.92
Stent overlap	15 (39.5)	13 (25.5)	0.18

Values are mean±SEM or n (%) as appropriate.

Discussion

This registry aimed to compare OCT data regarding coverage, apposition, neointimal formation and maturation as well as clinical outcome of two specific DES designs.

Table 2. OCT findings.

	O-SES				ZES				*p*-value O-SES vs. ZES		
	3 months	6 months	9 months	*p*-value	3 months	6 months	9 months	*p*-value	3 months	6 months	9 months
Time to follow-up (days)	104.6±15.8	182.1±14.4	267.3±13.8	–	92.9±15.3	174.3±16.0	278.9±21.3	–	0.68	0.15	0.13
Lesion level											
Analysed patients	8	21	5	–	31	7	8	–	–	–	–
Analysed lesions	8	21	9	–	35	9	8	–	–	–	–
Lesions with ≥10% uncovered struts	2 (25.0)	8 (38.1)	1 (11.1)	0.33	19 (54.3)	4 (44.4)	3 (37.5)	0.66	0.40	>0.99	0.29
Lesions with ≥30% uncovered struts	1 (12.5)	1 (4.8)	0 (0.0)	0.53	12 (34.3)	2 (22.2)	1 (12.5)	0.44	0.40	0.21	0.47
Lesions with ≥5% malapposed struts	1 (12.5)	7 (33.3)	1 (11.1)	0.32	12 (34.3)	3 (16.7)	1 (12.5)	0.49	0.40	>0.99	>0.99
Cross-section level											
Analysed cross-sections	367	663	343	–	1,064	263	240	–	–	–	–
Analysed cross-sections per patient	45.9±11.2	31.6±3.4	38.1±5.8	0.23	30.4±2.2	29.2±4.8	30.0±6.9	0.98	0.41	0.90	0.15
Struts analysed per cross-section	6.9±0.6	6.7±0.2	6.9±0.4	0.74	10.1±0.4	9.9±0.7	8.9±0.8	0.44	0.0003	<0.0001	<0.0001
Cross-sections with ≥10% uncovered struts, %	15.5 [12.2, 33.1]	10.5 [1.2, 37.4]	3.8 [0, 11.5]	0.16	41.5 [8.5, 83.3]	17.1 [6.8, 64.4]	13.9 [2.6, 46.4]	0.37	0.51	0.30	0.13
Cross-sections with ≥30% uncovered struts, %	5.1 [1.0, 9.9]	8.7 [0, 20.1]	0 [0, 1.3]	0.25	10.7 [0, 43]	9.1 [0, 27.1]	3.3 [0, 12.5]	0.43	0.71	0.85	0.08
Cross-sections with ≥5% malapposed struts, %	4.8 [0, 14.6]	5.1 [0, 21.8]	0 [0, 1.4]	0.17	9.4 [0, 31]	4.5 [1.2, 37.6]	0.8 [0, 7]	0.28	0.43	0.81	0.19
Vessel diameter, mm	2.7±0.2	2.8±0.1	2.6±0.1	0.69	2.9±0.1	2.6±0.1	2.8±0.3	0.33	0.23	0.09	0.72
Vessel area, mm^2	5.9±0.9	6.4±0.6	5.3±0.5	0.56	6.8±0.4	5.4±0.5	6.9±1.3	0.30	0.23	0.30	0.41
Stent diameter, mm	2.7±0.1	2.9±0.1	2.7±0.1	0.61	2.9±0.7	2.7±0.1	3.0±0.2	0.18	0.08	0.32	0.36
Stent area, mm^2	5.9±0.4	6.8±0.6	5.9±0.5	0.49	7.0±0.3	5.7±0.4	8.0±1.2	0.10	0.16	0.32	0.23
Neointimal area, mm^2	0.5±0.1	0.5±0.1	0.6±0.1	0.46	0.5±0.1	0.4±0.1	1.3±0.3	<0.001	0.37	0.18	0.19
Area of malapposition, mm^2	0 [0, 2.6]	0 [0, 0.3]	0 [0, 0]	0.13	0 [0, 2]	0 [0, 0.1]	0.03 [0, 0.9]	0.67	0.97	0.69	0.09
Strut level											
Analysed struts	2,671	4,307	2,458	–	10,817	2,774	2,109	–	–	–	–
Struts analysed/patient	307 [102, 583]	187 [142, 242]	258 [162, 358]	0.10	276 [176, 399]	225 [143, 458]	224 [114, 449]	0.80	0.99	0.27	0.79
Covered embedded struts, %	56.8±9.5	63.8±5.0	68.9±8.1	0.59	58.3±4.6	61.1±8.1	75.7±7.2	0.24	0.99	0.67	0.53
Covered protruding struts, %	27.2 [15.7, 38.4]	29.3 [13.7, 38.6]	18.9 [14.5, 43.4]	0.90	17.1 [7.2, 27.1]	19.6 [6.2, 42.7]	18.0 [6, 23.8]	0.50	0.08	0.80	0.41
Uncovered apposed struts, %	4.5 [3.7, 7.7]	1.4 [0.4, 8.5]	0.6 [0.1, 2.9]	0.15	9.9 [1.4, 28.8]	5.0 [1.9, 17]	2.0 [0.7, 9.9]	0.20	0.63	0.07	0.19
Uncovered malapposed struts, %	2.7 [0, 3.7]	1.9 [0.2, 6.5]	0.0 [0, 3]	0.37	1.4 [0, 9.9]	0.6 [0.1, 7.8]	0.8 [0, 2.2]	0.30	0.98	0.63	0.75
Neointimal thickness of covered struts, µm	92.7 [68, 101]	100.0 [85, 115]	91.0 [81, 106]	0.82	90.0 [70, 110]	80.0 [60, 120]	145.0 [103, 233]	0.002	0.98	0.26	0.07
GSI analysis											
Analysed ROIs, n	803	2,366	1,153	–	3,402	1,326	1,594	–	–	–	–
ROI lengths, µm	64.3 [49, 75]	67.7 [57, 89]	65.0 [54, 70]	0.39	67.5 [49, 87]	51.9 [43, 73]	109.4 [79, 145]	0.0001	0.71	0.06	0.01
GSI value	96.2±2.3	98.9±1.6	99.0±1.8	0.47	91.9±1.2	96.1±2.8	104.0±2.2	0.0001	0.16	0.52	0.07
Mature neointimal tissue, %	51.4±6.4	59.3±3.8	58.0±4.1	0.532	42.5±2.9	50.1±6.1	68.9±4.8	0.0001	0.284	0.189	0.069

Values are mean±SEM or n (%) as appropriate. GSI: greyscale signal intensity; ROI: region of interest

The main findings are:

1. No differences were found in intra- and inter-group comparisons for coverage and apposition.
2. The inter-group comparison showed no differences for neointimal thickness and maturation.
3. The O-SES showed no differences over time, while the ZES presented an increased neointimal thickness and tissue maturation between three, six and nine months.
4. Strut coverage was already nearly complete after three months in both DES.

CLINICAL IMPLICATIONS

The O-SES has shown promising results in TLF and LST at nine-month follow-up (BIOFLOW-I)[10]. The BIOFLOW-II trial compared the nine-month late lumen loss of O-SES with everolimus-eluting-stents (EES). The first results showed a comparable late lumen loss, non-inferiority and comparable clinical safety and efficacy[18]. The combination of sirolimus and poly-L-lactic acid used in O-SES seems to reduce neointimal hyperplasia effectively without decreasing neointimal coverage. The present registry found no differences for neointimal thickness,

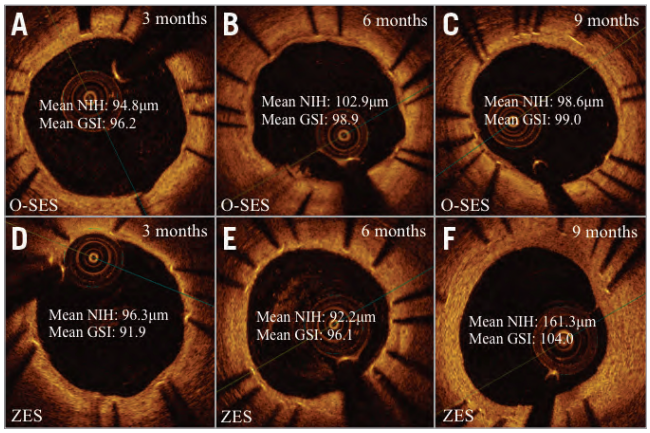

Figure 4. *OCT images at three, six and nine-month follow-up. Representative OCT images at three, six and nine-month follow-up after implantation of O-SES (A, B, & C) and ZES (D, E, & F). The figure presents the comparable healing pattern of the two DES. In the case of nine-month follow-up of ZES, an increased neointimal thickness and maturation was observed. GSI: greyscale signal intensity; NIH: neointimal hyperplasia*

maturation or coverage. ZES showed a significantly increased neointimal formation after nine months when analysed over time; yet, this increase did not reach clinical significance in an intergroup analysis to O-SES. These results possibly reflect the different drug release kinetics. While zotarolimus is released over about three months, the drug release and polymer degradation of O-SES occur within 12 to 24 months. We therefore suggest that OCT should be able to measure even small differences between different DES. If any differences exist, our OCT data suggest that they occur later than nine to 12 months.

Guidelines for DAPT duration after PCI depend on the underlying disease. If DAPT is prescribed only for DES healing in non-ACS patients, current instructions for use allow interrupting DAPT after even one month (ZES) and six months (O-SES). DAPT reduces the risk of stent thrombosis, but long-term use increases the rate of bleeding events. Balancing these risks remains a challenge; therefore, reliable detection of DES coverage with mature tissue may allow stopping DAPT early in individual patients. We found both DES to be almost completely covered after three months, with no differences in coverage, apposition and clinical outcome, suggesting a reduction of DAPT to three months for O-SES in non-ACS patients to be possibly safe.

OCT-BASED GSI ANALYSIS FOR THE ASSESSMENT OF NEOINTIMAL MATURATION

Although OCT analysis has improved our capability to distinguish covered from uncovered struts, not all covered struts are covered by mature neointimal tissue[9]. Coverage by immature tissue was previously shown as an important risk factor for LST[13]. An OCT-based GSI analysis was previously introduced to assess tissue characterisation and discriminate mature and immature tissue[9]. This may have important implications for clinical practice.

Table 3. Clinical follow-up.

Characteristics	O-SES (n=34 patients)	ZES (n=46 patients)	*p*-value
12-month follow-up			
Lost to follow-up	2 (5.9)	2 (4.3)	>0.99
Completed 12-month follow-up	32 (94.1)	44 (95.7)	>0.99
MACE	3 (9.4)	3 (6.8)	0.69
All-cause death	2 (6.3)	0 (0)	0.17
Cardiac death	0 (0)	0 (0)	>0.99
Unstable angina pectoris	6 (18.8)	7 (15.9)	0.77
NSTE-ACS	0 (0)	0 (0)	>0.99
STEMI	0 (0)	0 (0)	>0.99
Target vessel revascularisation	0 (0)	4 (9.1)	0.13
Target lesion failure	3 (9.4)	3 (6.8)	0.69
Target lesion revascularisation	3 (9.4)	3 (6.8)	0.69
In-stent restenosis	3 (9.4)	3 (6.8)	0.69
Late stent thrombosis	0 (0)	0 (0)	>0.99
Major bleeding events	1 (3.1)	0 (0)	0.42
Minor bleeding events	1 (3.1)	0 (0)	0.42
Cerebrovascular events	1 (3.1)	1 (2.3)	>0.99
Antiplatelet therapy			
Patients following MI	9	8	
Dual at 3 months	9 (100)	8 (100)	>0.99
Dual at 6 months	8 (88.9)	8 (100)	>0.99
Dual at 12 months	8 (88.9)	7 (87.5)	>0.99
Patients following non-MI	23	36	
Dual at 3 months	21 (91.3)	35 (97.2)	0.63
Dual at 6 months	19 (82.6)	30 (83.3)	>0.99
Dual at 12 months	13 (56.5)	23 (63.9)	0.60

The data are presented as number of events (n) and percentage of total number (%). No differences were found concerning the observed parameters.

To determine the quality of neointimal tissue, GSI analyses were performed in the present registry. While no differences were found between the two DES, ZES demonstrated significant maturation over time, which was not observed in O-SES. The six- and nine-month data showed no additional maturation compared to three-month data. This may be explained by the higher effectiveness of sirolimus concerning suppression of smooth muscle cell proliferation compared to zotarolimus[19]. Furthermore, these results again reflect the different drug release kinetics. Interestingly, O-SES did not exhibit more malapposition despite less neointimal tissue. This may support the concept of biocompatible polymers.

OCT - A SURROGATE FOR CLINICAL OUTCOME?

Although event rates after PCI with new-generation DES are remarkably low, no plateau is reached over time[1]. Therefore, there is an unmet need to improve current PCI strategies. Due to the low event rates, clinical studies with large numbers are necessary to compare

clinical endpoints of upcoming DES generations. Surrogate markers could be able to predict clinical outcome even in smaller populations[7]. Detailed OCT analysis may allow judgement on safety and efficacy in a much smaller cohort and give surrogates until data from large clinical trials are available. In addition, OCT may be hypothesis-generating, as recently executed with biolimus-eluting stents (BES)[4]. After encouraging OCT data this DES has now been tested in a randomised trial for one month of DAPT (LEADERS FREE)[20]. Furthermore, an OCT substudy of the LEADERS trial presented evidence for 0.6% of uncovered struts after nine months[21]. Although we present only a limited number of patients, our findings regarding clinical outcome are similar to the findings of multicentre trials. The BIOFLOW-III registry aimed to test O-SES in clinical practice and found a low 12-month TLF rate of 5.1%[14]. Additionally, the RESOLUTE All-Comers trial compared the 12-month TLF rates of ZES (8.2%) and EES (8.3%)[22]. Recently published data from the BIOSCIENCE trial found no significant differences in TLF for O-SES (6.5%) and EES (6.6%)[3]. The clinical outcome of O-SES and ZES have not been evaluated head-to-head to date. Since our results show comparable findings of OCT data and clinical outcome, our findings may suggest a similar clinical performance.

Limitations

A limitation of this registry was the absence of a baseline OCT analysis. A primary stent-vessel mismatch, as a reason for late malapposition, may therefore be an issue, and the results of the intra-group comparison have to be interpreted with caution. The MACE rate is in the range of current studies and supports the PCI techniques used as being the best available standard. Additionally, the time point of OCT analysis was determined by chance at the index procedure. Therefore, the groups differed in size, which limits our findings. A further limitation is OCT accuracy. Due to its resolution, a precise analysis of neointimal cellular tissue cannot be distinguished and a misclassification of struts could be possible. Cut-off values regarding tissue maturation are arbitrary and should be further validated. Nevertheless, the characterisation of neointimal maturation by OCT-based GSI analyses may be an important step towards the assessment of vascular healing. The fact that no randomisation was performed also limits our results. Although there was no LST or recurrent MI, the small number of patients involved in this registry limits the validity of our findings. Furthermore, we cannot exclude type II error in the detection of adverse events and further complications.

Conclusions

Neointimal coverage was nearly complete at three-month follow-up in both DES. Between three and nine months, stent healing had progressed with no significant differences concerning strut coverage and apposition between the DES. Furthermore, no difference in clinical outcome was found in this OCT analysis, as in large clinical trials comparing these two DES to the current standard, namely the EES. We propose OCT-based follow-up of DES as a potential surrogate parameter to predict a patient's clinical outcome.

Impact on daily practice

No differences were found concerning OCT-based assessments as well as clinical follow-up between the two DES. Our findings may support the hypothesis that OCT-based analyses in small patient cohorts sensitively detect stent healing and could possibly be regarded as surrogates for DES healing and clinical outcome.

Conflict of interest statement

C-H. Heeger has received travel grants from St. Jude and Biotronik. R. A. Byrne reports receiving lecture fees from B. Braun Melsungen AG, Biotronik and Boston Scientific and research grants to the institution from Boston Scientific and Heartflow. M. Joner reports the following financial decision-making role: Biotronik, Medtronic and Terumo Corporation. K-H. Kuck has received research contracts/grants from Medtronic, St. Jude and Boston Scientific as well as consulting fees from St. Jude and Edwards Lifesciences. M. Bergmann has received travel grants, research grants and speaker honoraria from Medtronic, Biotronik and St. Jude. The other authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:49-57

Imaging outcomes of bioresorbable scaffold overlap: an optical coherence tomography analysis from the ABSORB EXTEND trial

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KEYWORDS

- bioresorbable scaffold
- optical coherence tomography
- overlap

Abstract

Aims: The purpose of this study was to assess the vascular response and vessel healing of overlapped Absorb scaffolds (Abbott Vascular, Santa Clara, CA, USA) compared to non-overlapped devices in human coronary arteries as assessed by optical coherence tomography (OCT) in the same treated segment.

Methods and results: The ABSORB EXTEND (NCT01023789) trial is a prospective, single-arm, open-label clinical study which enrolled 800 patients. The planned overlap OCT subgroup in the ABSORB EXTEND trial was analysed and two-year OCT follow-up was performed in seven patients. In cross-section level analysis at baseline, lumen and abluminal scaffold areas were larger in overlap segments than in non-overlap segments, whereas the endoluminal scaffold area was similar. At two-year follow-up, lumen area and endoluminal scaffold areas were similar in both segments despite the neointimal area being larger in the overlap segments. The neointimal coverage was essentially fully complete in both non-overlap (99.4±0.8%) and overlap segments (99.8±0.4%) at two-year follow-up.

Conclusions: The imaging results of this small OCT subgroup analysis in the ABSORB EXTEND trial demonstrated substantial vessel healing and vascular response in the overlap segments of Absorb at two-year follow-up comparable to the non-overlap segments.

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SUBMITTED ON 11/10/2016 - REVISION RECEIVED ON 09/11/2016 - ACCEPTED ON 23/11/2016

DOI: 10.4244/AsiaInterv_V3I1A12

Introduction

Overlapping of Absorb scaffolds (Absorb BVS; Abbott Vascular, Santa Clara, CA, USA) is generally associated with a number of issues. 1) Technically, thick struts (157 µm) could hinder implantation of the second Absorb device, which could result in difficult scaffold delivery or disruption of struts. 2) Overlap might be associated with an increased risk of periprocedural myocardial infarction. In the ABSORB II trial (n=501), treatment with overlapping devices was the only independent determinant of periprocedural myocardial infarction (odds ratio: 5.07, 95% CI: 1.78-14.41, p=0.002)[1]. 3) Animal studies have suggested delayed coverage of overlapping struts. In a juvenile porcine model, the overlapped Absorb scaffolds showed more delay in tissue coverage than non-overlapped scaffolds[2].

The segments with overlapped scaffolds (overlap segments) are possibly associated with delayed healing and greater neointimal growth compared to the segments with no overlapped scaffolds (non-overlap segments), which could result in smaller luminal dimension at follow-up[2]. However, the vessel healing and vascular response at segments with overlapped Absorb BVS in human coronary arteries have, thus far, not been precisely evaluated by optical coherence tomography (OCT).

The purpose of the current study was to assess by OCT the vascular response and vessel healing in the Absorb scaffold overlap segments compared to the non-overlap segments in human coronary arteries.

Methods

STUDY DESIGN

The ABSORB EXTEND trial is a prospective, single-arm, open-label clinical study that has enrolled 812 patients at up to 100 global sites (NCT01023789). Details on the study and the study device (Absorb BVS; Abbott Vascular) have been described previously[3] **(Table 1)**. Initially, a subset of up to 50 patients who received planned overlapping Absorb BVS at selected sites with OCT capability was planned to be included in the OCT subgroup. In this OCT subgroup, OCT imaging after the BVS implantation and at two-year follow-up was mandated in all patients. Despite the initial plan to include 50 patients with planned overlapping, the actual OCT subgroup included only 14 patients. The main reasons were: i) the small number of sites due to limited availability of OCT at the time of the study initiation in 2009; ii) the premature termination of the study; iii) the low patient consent rate due to invasive imaging follow-up. The need for planned overlapping of BVS was determined by the investigator at the time of the index procedure. The research ethics committee of each participating institution approved the protocol and all enrolled patients provided written informed consent before inclusion.

OCT METHODOLOGY

The image acquisition was performed with the C7-XR™ imaging console and the Dragonfly™ intravascular imaging catheter (both St. Jude Medical, St. Paul, MN, USA). Analysis of the OCT images was performed with the QCU-CMS software (Medis medical imaging systems, Leiden, The Netherlands), using the methodology for BVS analysis described in a previous publication[4]. All analyses were performed at 1 mm longitudinal intervals within the non-overlap segment, and at 0.2 mm intervals within the overlap segment. In addition, the analysis for scaffold coverage was performed at 0.2 mm intervals in the whole scaffold segment.

Details of the OCT analysis are illustrated in **Figure 1**. Definitions of OCT parameters were described in a previous publication[4]. Specifically, in overlap segments at baseline, the struts of the first (outer) and second (inner) scaffolds could appear stacked or overhanging. The struts of the inner scaffold could look malapposed in a cross-section, but that does not necessarily indicate absence of contact with other structures, since such struts are touching the other scaffold **(Figure 1)**[5]. As a surrogate for vessel stretch, the abluminal side of the outer scaffold area ratio was calculated as the ratio of mean abluminal scaffold area of the outer scaffold in the overlap segment to the mean abluminal area of the single scaffold implanted in the adjacent non-overlap segments (5 mm of both sides). The endoluminal scaffold area ratio was also computed in the same way. At two years, the scaffold has already lost its mechanical integrity and could present late discontinuities, as expected from the bioresorption process[6]. Therefore, it is not always possible to differentiate the two layers of struts in an overlap segment. In the current study, the analysis delineated the inner and outer contour of the struts without distinction of the two scaffolds. Wherever two struts were overhanging or stacked, the

Table 1. Diameter of target vessel(s), length of target lesion(s) and Absorb BVS size used.

Target vessel diameter	Length of target lesion(s)	BVS size to be used
Distal Dmax and proximal Dmax		
≥2.0 mm and ≤3.0 mm	≤14 mm	Single 2.5×18 mm
	>14 mm and ≤22 mm	Single 2.5×28 mm
	>22 mm and ≤28 mm	Two overlapping 2.5×18 mm
≥2.5 mm and ≤3.3 mm	≤14 mm	Single 3.0×18 mm
	>14 mm and ≤22 mm	Single 3.0×28 mm
	>22 mm and ≤28 mm	Two overlapping 3.0×18 mm
≥2.0 mm and ≤2.5 mm (distal Dmax)	>22 mm and ≤28 mm	Overlapping 2.5×18 with 3.0×18 mm
≥3.0 mm and ≤3.3 mm (proximal Dmax)		

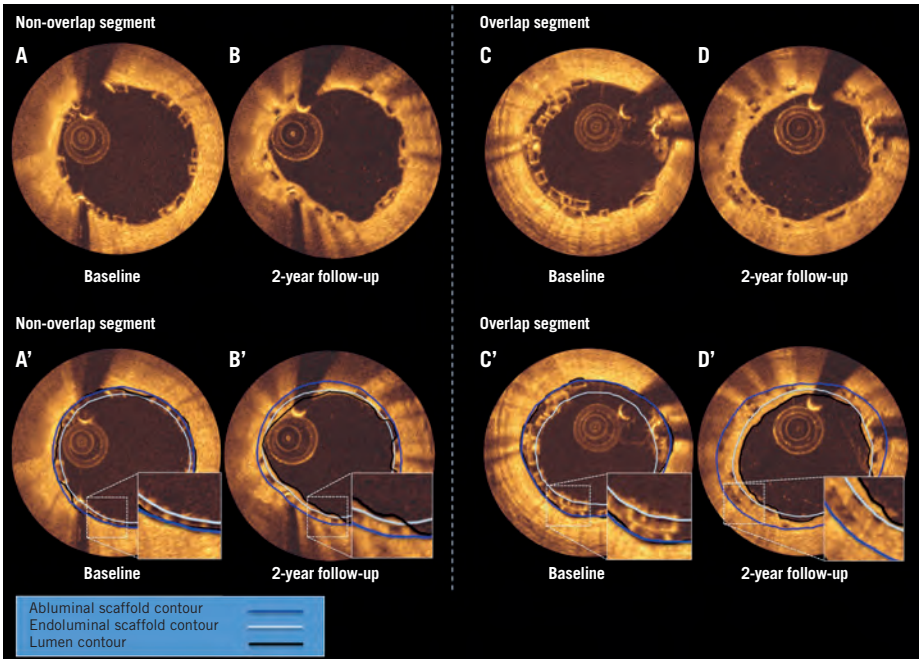

Figure 1. *OCT methodology. A) – D) Baseline and follow-up OCT images in the non-overlap and overlap segments, respectively. In the non-overlap segment, the previously published methodology was applied (A', B')[4]. In the overlap segment, the endoluminal scaffold contour was drawn using the midpoint of the endoluminal black core border of "inner struts" at baseline (C') and follow-up (D'). The abluminal scaffold contour was drawn using the midpoint of the abluminal black core border of "outer struts" at baseline (C') and follow-up (D').*

abluminal (endoluminal) border of the outer (inner) struts was used to define the abluminal (endoluminal) scaffold contour **(Figure 1)**.

With respect to coverage analysis, when the coverage thickness (the shortest distance from the lumen contour to the endoluminal border of the strut black core) was ≥30 µm in polymeric struts, the strut was defined as a covered strut. To allow full visualisation of the spatial distribution of neointimal thickness and coverage status in the overlapping devices, "spread-out-vessel graphs" – a visual representation of the vessel as if it had been cut along the reference angle (0°) and spread out on a flat surface – were created based upon previously described methodologies[7].

CLINICAL FOLLOW-UP

Definitions of all clinical endpoints have been described elsewhere[3]. All study endpoint events were adjudicated by an independent clinical events committee (CEC), according to either protocol definitions and/or the Academic Research Consortium (ARC) definitions. All adverse events were reported to an independent data and safety monitoring board (DSMB), which reviewed the data to identify any safety issues related to the conduct of the study.

STATISTICAL ANALYSIS

The normality of distribution of continuous data was examined with the Shapiro-Wilk test. Continuous variables with normal distribution are expressed as means±standard deviations and those with unequal variance are expressed as medians and interquartile ranges (25th and 75th percentiles). Categorical variables are expressed as numbers and frequencies. Group means for continuous variables with normal and non-normal distributions were compared using the Student's t-test and the Mann-Whitney U test, respectively. Categorical variables were compared using the χ^2 test or Fisher's exact test, where appropriate. A mixed linear model with an assumed Gaussian distribution was used for the comparisons of continuous variables to take into account the clustered nature of >1 struts and cross-sections analysed from the same lesion, which might result in unknown correlations among measurements within the clusters. Statistical significance was assumed at a probability (p)-value of <0.05. All statistical analyses were performed with SPSS, Version 22.0.0 (IBM Corp., Armonk, NY, USA).

Results

In the whole ABSORB EXTEND trial (N=812), a total of 14 patients were enrolled in the planned overlap population (OCT subgroup). In these 14 patients, one patient died due to a non-cardiac cause, and 13 patients underwent two-year clinical follow-up. The median duration of follow-up was 748 (729-755) days. The baseline OCT data of one patient were not analysable due to the poor image quality. Two-year invasive OCT follow-up was performed in only seven patients.

PATIENT DEMOGRAPHIC DATA AND PROCEDURAL DATA

The baseline characteristics of the patients and procedural data are summarised in **Table 2**. A sensitivity analysis comparing the baseline characteristics of patients with and without OCT surveillance at follow-up demonstrated that there was no significant difference between these cohorts.

Table 2. Patient characteristics.

Variables	N=14
Baseline characteristics	
Age (years)	62±9
BMI (kg/m^2)	27.3±4.3
Male sex, n (%)	12 (85.7)
Current smoker, n (%)	2 (14.3)
Any diabetes, n (%)	1 (7.1)
Diabetes treated with insulin, n (%)	0 (0)
Hypertension requiring medication, n (%)	7 (50.0)
Hypercholesterolaemia requiring medication, n (%)	7 (50.0)
Prior MI, n (%)	2 (14.3)
Stable angina, n (%)	13 (92.9)
Unstable angina, n (%)	1 (7.1)
Lesion data	
Lesion location LAD/LCX/RCA	5/5/4
Lesion class (ACC/AHA) A/B1/B2/C	0/6/7/1
Angulation (≥45°), n (%)	1 (7.1)
Calcification (moderate or severe), n (%)	2 (14.3)
Bifurcation, n (%)	3 (21.4)
Eccentric, n (%)	14 (100)
Pre-procedure thrombus, n (%)	0 (0)
Procedural data	
Predilatation, n (%)	14 (100)
Balloon diameter (mm)	2.61±0.28
Balloon pressure (atm)	13.7±3.2
Post-dilatation, n (%)	9 (64.3)
Compliant balloon, n (%)	4 (29)
Non-compliant balloon, n (%)	5 (36)
Balloon diameter (mm)	3.14±0.17
Balloon pressure (atm)	17.3±4.0
Device, n (%)	
2.5×18; 2.5×18 mm	1 (7.1)
3×18; 3×18 mm	12 (85.7)
3.5×18; 3.5×18 mm	1 (7.1)
Bail-out with XIENCE PRIME (3.5×18 mm), n (%)	2 (14.3)
Side branch occlusion, n (%)	1 (7.1)
Overlap length (mm) by post-procedural OCT	4.0 [2.0, 7.4]
Acute success, n (%)	14 (100)
QCA data	
Pre-procedural lesion length (mm)	15.1 [8.2, 21.0]
Pre-procedural RVD (mm)	2.5 [2.26, 2.55]
Pre-procedural DS%	56.9±14.8
Post-procedural in-device DS%	18.0±6.3
In-device acute gain (mm)	0.99±0.39

Data are expressed as mean±standard deviation, number (frequency), and median [interquartile range]. BMI: body mass index; DS%: percent diameter stenosis; LAD: left anterior descending artery; LCX: left circumflex artery; MI: myocardial infarction; OCT: optical coherence tomography; QCA: quantitative coronary angiography; RCA: right coronary artery; RVD: reference vessel diameter

QUANTITATIVE OCT FINDINGS AT BASELINE AND TWO-YEAR FOLLOW-UP

Table 3 shows the quantitative OCT findings at baseline in 13 patients at lesion level and cross-section level analyses. At cross-section level analysis, no significant difference in endoluminal scaffold area was observed (6.31±1.18 mm^2 vs. 6.29±0.97 mm^2, p=0.568) between overlap and non-overlap segments.

Table 4 tabulates the quantitative OCT findings at baseline and two-year follow-up in seven patients with both baseline and follow-up OCT data. The time interval to OCT follow-up was 742 (724-754) days. At two-year follow-up, both non-overlap and overlap segments presented with a similar lumen area, abluminal scaffold area, endoluminal scaffold area, flow area, and neointimal area in lesion-level analysis.

Serial changes of abluminal/endoluminal scaffold areas and the flow area between the overlap segment and its margin (10 mm) are illustrated in the graph of **Figure 2** (representative case 6 in **Figure 3**). Serial changes of all the cases (margin: 5 mm) are shown in **Figure 3**. Post-dilatation was performed in five out of the seven patients. Abluminal and endoluminal scaffold area ratios were 1.12±0.07 and 1.03±0.06, respectively. Outward vessel enlargement was still maintained at two-year follow-up despite being after the disappearance of scaffold radial strength (12 months).

Regarding the strut coverage analysis, 7,828 struts in non-overlap segments and 1,801 struts in overlap segments were analysed. The neointimal coverage was almost completed in both segments at two-year follow-up (coverage rate in non-overlap segment vs. overlap segment, 99.4±0.8% vs. 99.8±0.4%, p=0.360).

Table 3. Baseline OCT data (13 cases).

	Non-overlap segment (N=13*)	Overlap segment (N=13*)	*p*-value
Baseline			
Total number of struts, n	2,571	4,382	
Number of struts per lesion, n	198±52	337±267	0.077
Lesion level analysis	**N=13**	**N=13**	
Lumen area (mm^2)	7.00±0.92	7.96±1.37	0.046
Abluminal scaffold area (mm^2)	7.30±0.96	8.04±1.19	0.095
Endoluminal scaffold area (mm^2)	6.31±0.86	6.35±1.07	0.926
Strut core area (mm^2)	0.20±0.03	0.43±0.06	<0.001
Flow area (mm^2)	6.80±0.90	7.53±1.36	0.118
Cross-section level analysis	**N=339**	**N=324**	
Lumen area (mm^2)	6.98±1.26	7.94±1.24	<0.001
Abluminal scaffold area (mm^2)	7.29±1.30	8.01±1.10	<0.001
Endoluminal scaffold area (mm^2)	6.31±1.18	6.29±0.97	0.568
Strut core area (mm^2)	0.20±0.08	0.44±0.16	<0.001
Flow area (mm^2)	6.78±1.24	7.50±1.22	<0.001

Data are expressed as mean±standard deviation and number. *The OCT baseline data (case 14) were not analysable due to poor quality of image.

Table 4. Serial OCT data post-procedure and at 2-year follow-up (7 cases).

	Baseline	2-year follow-up	*p*-value
Strut analysis			
Number of struts per lesion, n			
Non-overlap segment	175±59	1,118±197	–
Overlap segment	283±265	257±74	–
p-value¶	0.351	<0.001	
Number of uncovered struts per lesion, n			
Non-overlap segment	–	7.0±9.4	–
Overlap segment	–	0.9±1.7	–
p-value¶	–	0.163	
Coverage rate (%)			
Non-overlap segment	–	99.4±0.8	–
Overlap segment	–	99.8±0.4	–
p-value¶	–	0.360	
Lesion level analysis			
Non-overlap segment	N=7	N=7	
Overlap segment	N=7	N=7	
Lumen area (mm^2)			
Non-overlap segment	6.98±1.18	5.58±2.01	0.138
Overlap segment	8.25±1.73	6.09±2.30	0.071
p-value¶	0.133	0.663	
Abluminal scaffold area (mm^2)			
Non-overlap segment	7.33±1.23	8.02±2.52	0.529
Overlap segment	8.26±1.50	9.23±3.16	0.476
p-value¶	0.233	0.445	
Endoluminal scaffold area (mm^2)			
Non-overlap segment	6.34±1.09	6.81±2.20	0.619
Overlap segment	6.56±1.35	7.48±2.84	0.453
p-value¶	0.744	0.632	
Strut core area (mm^2)			
Non-overlap segment	0.20±0.04	0.21±0.05	0.804
Overlap segment	0.41±0.07	0.36±0.10	0.284
p-value¶	<0.001	0.004	
Flow area (mm^2)			
Non-overlap segment	6.78±1.15	5.58±2.01	0.195
Overlap segment	7.84±1.71	6.09±2.30	0.133
p-value¶	0.197	0.663	

	Baseline	2-year follow-up	*p*-value
Lesion level analysis			
Neointimal area (mm^2)			
Non-overlap segment		2.24±0.63	
Overlap segment		2.78±0.85	
p-value¶		0.206	
Cross-section level analysis			
Non-overlap segment	N=174	N=211	
Overlap segment	N=143	N=142	
Lumen area (mm^2)			
Non-overlap segment	6.89±1.50	5.56±2.20	<0.001
Overlap segment	8.12±1.55	5.69±1.96	<0.001
p-value¶	<0.001	0.735	
Abluminal scaffold area (mm^2)			
Non-overlap segment	7.24±1.56	8.02±2.76	<0.001
Overlap segment	8.18±1.33	8.69±2.68	0.001
p-value¶	<0.001	0.001	
Endoluminal scaffold area (mm^2)			
Non-overlap segment	6.27±1.40	6.81±2.42	<0.001
Overlap segment	6.52±1.21	7.01±2.43	<0.001
p-value¶	0.030	0.834	
Strut core area (mm^2)			
Non-overlap segment	0.20±0.08	0.21±0.09	0.788
Overlap segment	0.40±0.13	0.35±0.15	0.015
p-value¶	<0.001	<0.001	
Flow area (mm^2)			
Non-overlap segment	6.69±1.47	5.56±2.20	<0.001
Overlap segment	7.72±1.54	5.69±1.96	<0.001
p-value¶	<0.001	0.735	
Neointimal area (mm^2)			
Non-overlap segment	–	2.25±0.95	–
Overlap segment	–	2.65±0.81	–
p-value¶	–	<0.001	–
Abluminal scaffold area ratio (overlap vs. non-overlap)	1.12±0.07	–	–

Data are expressed as mean±standard deviation and number.
¶ Non-overlap segment vs. overlap segment

Spread-out-vessel graphs represent the spatial distribution of the neointimal thickness and coverage status along each overlap segment and non-overlap segments at two-year follow-up **(Figure 4)**.

ADVERSE EVENTS

The rate of ischaemia-driven (ID) major adverse cardiac events (all cardiac death, all myocardial infarction, or ischaemia-driven target lesion revascularisation) at two years was 0% in the OCT subgroup. Preprocedural and post-procedural blood sample tests for cardiac enzymes (creatine kinase, creatine kinase-myocardial band, and troponin) were performed in 12 (85%) patients, and the periprocedural myocardial infarction rate (per protocol criteria) was 0%. Of the 14 patients, 13 patients were on dual antiplatelet therapy at one year (one patient discontinued the treatment before one year), and three patients were still on dual antiplatelet therapy at two years. One patient died due to a non-cardiac cause 345 days after the index procedure. Two patients underwent ID non-target vessel revascularisation by PCI 188 days and 409 days after the index procedure, respectively. One patient underwent non-ID target lesion revascularisation by PCI 707 days after the index procedure due to in-scaffold restenosis.

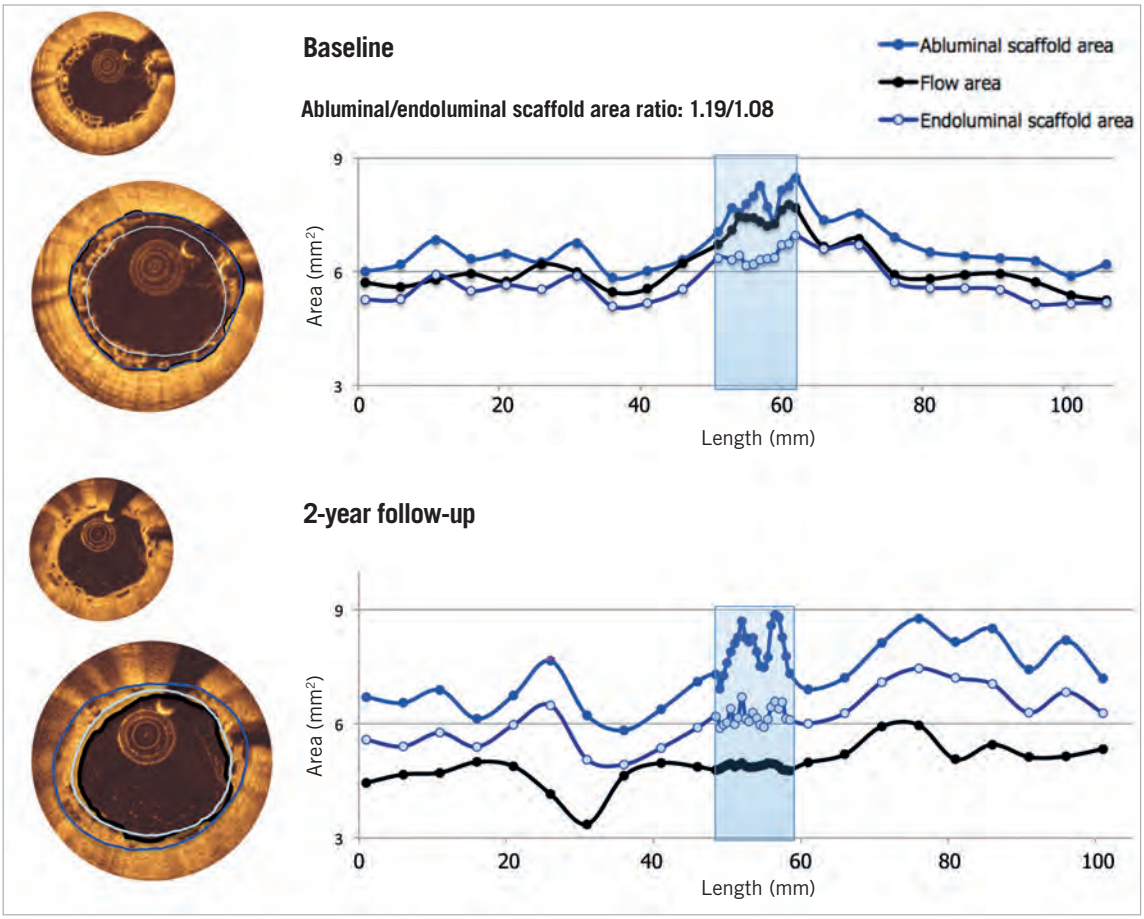

Figure 2. *Vessel-scaffold interaction in overlap and non-overlap segments. Vessel-scaffold interaction in overlap and non-overlap segments of a representative case (case 6 in Figure 3) is indicated with OCT analysis images. The horizontal axis indicates the length of the lesion from distal to proximal. The vertical axis indicates the area of each cross-section (black: flow area; dark blue: abluminal scaffold area; light blue: endoluminal scaffold area). The overlap segment (blue shadow) and both 10 mm margins are illustrated.*

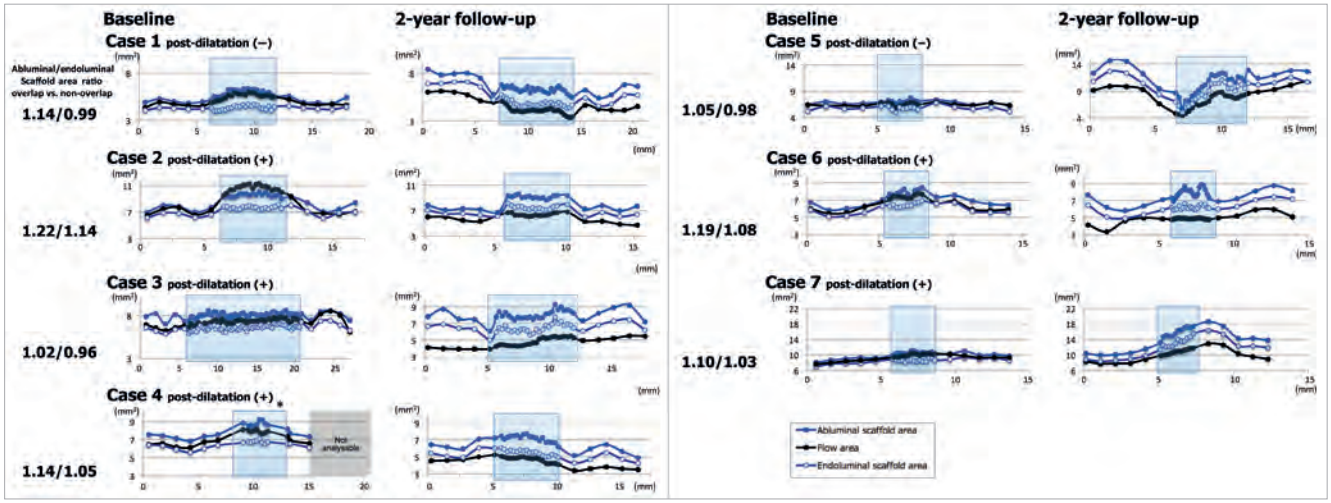

Figure 3. *Vessel-scaffold interaction in all cases. Vessel-scaffold interactions in overlap (blue shadow) and non-overlap segments of all the cases are shown. The horizontal axis indicates the length of the lesion from the distal to proximal. The vertical axis indicates the area of each cross-section (black: flow area; dark blue: abluminal scaffold area; light blue: endoluminal scaffold area). The overlap segments and both 5 mm margins are illustrated. * In case 4, some cross-sections in the overlap segments and proximal site of the scaffolded lesion were not analysable due to insufficient image quality.*

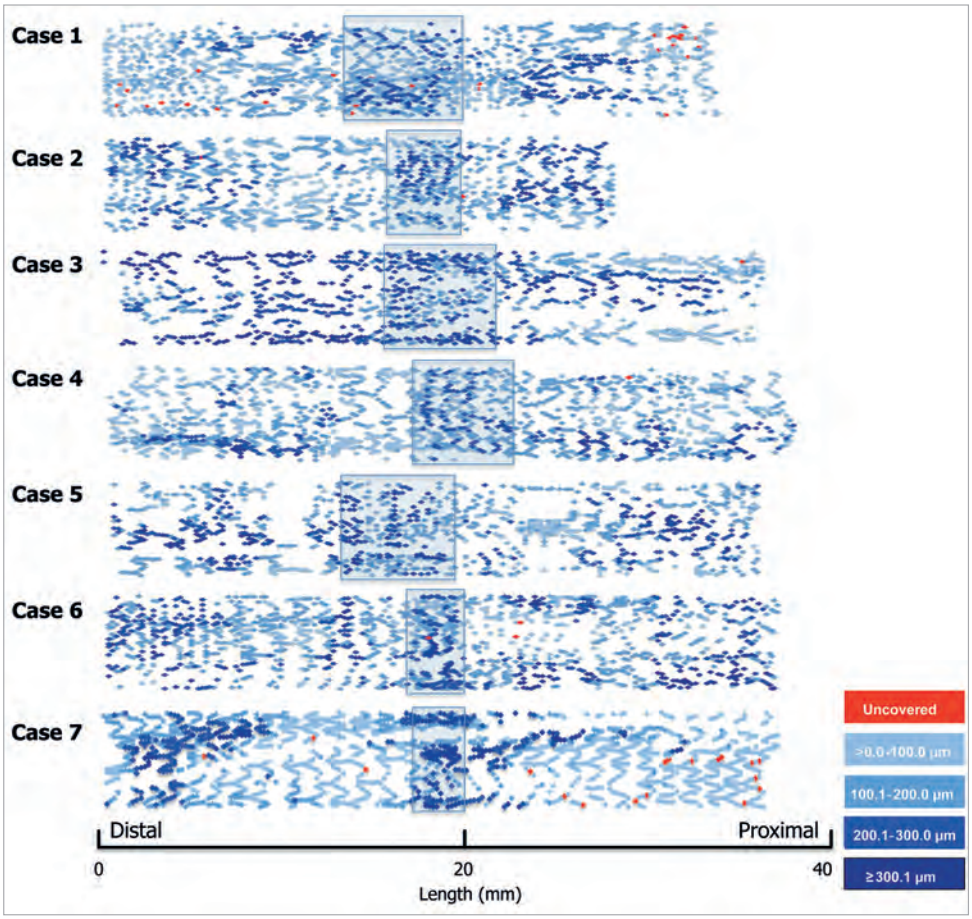

Figure 4. *The spatial distribution of the neointimal thickness and coverage status along each overlap segment and non-overlap segment at two-year follow-up. The horizontal axis indicates the distance from the distal edge of the implanted devices to the struts in the overlap and non-overlap segments. The vertical axis indicates the angle where the strut is located in the circular cross-section with respect to the centre of gravity of the vessel (0° to 360°). The neointimal thickness of each strut is colour-coded as indicated in the figure. Overlap segments (light blue square) show a mixture of light blue and dark blue, indicating the thinner neointima of "inner struts" and thicker neointima of "outer struts".*

Discussion

The major findings of the present study are: 1) post-procedure, both overlap and non-overlap segments presented a similar endoluminal scaffold area; 2) at two-year follow-up, the neointimal coverage of the BVS struts was almost completed both in overlap segments and in non-overlap segments; 3) the flow area in the overlap segments at two-year follow-up was not different from the flow area in the non-overlap segments, despite the neointimal response being greater in the overlap segments. Consequently, the treated segments showed a homogeneous lumen area through the scaffold segment.

LUMINAL DIMENSION AT THE OVERLAP SEGMENT

The lumen area at baseline was larger in the overlap segment than in the non-overlap segment. This could compensate for the greater neointimal growth at the overlap segment than at the non-overlap segment, resulting in the equivalent luminal dimensions at follow-up. As shown in **Figure 3**, post-dilatation aligned the scaffold endoluminal surface at the overlap segments, resulting in greater outward enlargement of the vessel due to double layers of struts compared to non-overlap segments. To maintain equivalent luminal dimension after neointimal coverage at an overlap segment as compared to non-overlap segments, appropriate post-dilatation might be necessary. However, the safety of this technique needs to be evaluated in further trials, since this technique could be a cause of coronary perforation[8].

TECHNICAL ISSUES WITH OVERLAPPING ABSORB SCAFFOLDS

According to a European perspective for BVS use[9], keeping the overlap to a minimum to avoid delays in healing is mandated due to the relatively thick struts of the Absorb scaffold[2]. The thick struts of the Absorb scaffold could also hinder implantation of the second Absorb scaffold, which could result in difficulty in scaffold delivery or disruption of struts.

For an optimal overlapping of Absorb scaffolds, the "marker-to-marker" (~1 mm of overlap) and "scaffold-to-scaffold" (no overlap)

techniques are recommended by the European perspective[9]. In the marker-to-marker configuration, which appears to be the best to avoid gap restenosis, the second scaffold is advanced until the distal balloon markers line up with the proximal marker beads of the implanted scaffold. As such, the markers of the second scaffold will be adjacent to the markers of the deployed scaffold. Enhanced stent visualisation-guided implantation would also be helpful[10]. Attention should be paid to scaffold size selection and placement order (i.e., starting with the distal scaffold is preferred) to avoid damage at the overlap site.

In the ABSORB EXTEND trial, planned overlapping of scaffolds was permitted in lesions with an overlap of 1 mm to 4 mm. As a result, the overlap length obtained by post-procedural OCT was 4.0 mm (2.0, 7.4 mm) in this study population. Despite the overlap length being relatively longer than the expert recommendation, procedure success was achieved in all patients and no strut disruption was observed.

It is noteworthy that the endoluminal scaffold area in the overlap segments was similar to that in the non-overlap segments post-procedure (representative case [case 6] shown in **Figure 2**). Post-dilatation made the transition between overlap and non-overlap smooth, which consequently resulted in outward enlargement of the outer scaffold and vessel wall.

DELAYED COVERAGE AND GREATER NEOINTIMAL RESPONSE IN OVERLAPPING ABSORB SCAFFOLDS

In a juvenile porcine model, overlapping Absorb scaffolds showed more delay in tissue coverage than non-overlapping scaffolds[2]. It is likely that the larger strut thickness of the stacked-like Absorb scaffolds (approximately 300 μm) in overlap segments led to a greater neointimal response compared with that in non-overlap segments. Thicker, rectangular (non-streamlined) struts, characteristic of the Absorb, may theoretically increase the device area exposed to low endothelial oscillatory shear stress areas, leading to the local accumulation of growth factors, mitogenic cytokines, and platelets, which promote neointimal formation until a smooth lumen surface is achieved[11]. The delayed coverage of overlapping struts presumably results from that greater neointimal response which has a longer duration. Despite these concerns raised from the preclinical studies, overall coverage rate of the overlap segments at two-year follow-up was achieved in 99.8% of struts, a figure similar to that of the non-overlap segments. Lumen area was similar between overlap and non-overlap segments despite the greater neointimal response in the overlap segments. Despite a large abluminal scaffold area ratio (overlap segment versus non-overlap segment), exuberant neointima in response to barotrauma was not observed.

Study limitations

The first limitations are the small number of patients included in our study, low imaging follow-up rate (50%) and consequent selection bias, despite the data representing one of the largest early registries. The small sample size did not permit drawing any conclusions on clinical relevance. The second limitation is the follow-up timing. The OCT follow-up in this study was performed two years after the index procedure. The results confirmed the completed strut coverage at least at that time point. However, the serial changes of neointimal coverage of overlapping BVS struts in humans still remain to be elucidated. Lastly, the challenges of OCT assessment for overlapping segments should be acknowledged. Artefacts of OCT such as elongation and repetition could also interfere with the results[12]. Therefore, OCT results should be interpreted with caution.

Conclusions

Despite the expectation that overlapping scaffold struts would occupy more of the luminal area than non-overlapping struts, both overlap and non-overlap segments showed similar endoluminal areas post-implantation and good vessel healing and vascular response at two-year follow-up. The results from this small OCT substudy therefore support the feasibility of overlapping scaffolds when needed for longer lesions if acute lumen expansion is achieved similar to non-overlap segments using good implantation techniques.

Impact on daily practice

Results from the present OCT study might support the feasibility of overlapping scaffolds when needed for longer lesions if acute lumen expansion is achieved similar to non-overlap segments using good implantation techniques. Since the number of patients in our analysis was very limited, the results should be interpreted with caution, and further investigation in a prospective fashion might be necessary to elucidate the impact of overlapped Absorb scaffolds on clinical outcomes.

Funding

This study was sponsored and funded by Abbott Vascular, Santa Clara, CA, USA.

Conflict of interest statement

Y. Sotomi is a consultant for GOODMAN and has received a grant from Fukuda Memorial Foundation for Medical Research and SUNRISE Lab. Y. Onuma and P. Serruys are members of the Advisory Board of Abbott Vascular. W-F. Cheong, W-Y. Zhao and S. Veldhof are employees of Abbott Vascular. The other authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:58-62

In vitro evaluation of the appropriate guidewire for performing the reversed guidewire technique to treat severely angulated bifurcated lesions

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KEYWORDS

- bifurcated lesion
- percutaneous coronary intervention
- PTCA guidewire
- reversed guidewire technique

Abstract

Aims: The aim of this study was to determine which guidewire is best for crossing through severely angulated bifurcation lesions.

Methods and results: Bench test 1 determined which wire could access the orifice of the side branch. A composite coil wire (SION blue), a polymer-coated wire (Fielder FC), a polymer-coated tapered wire (Fielder XT-R), and a polymer-coated composite core wire (SION black) were evaluated. We manipulated all the guidewires with 90° and 45° angles at 3 cm and 1 mm, respectively, from the guidewire tip. The tip of the SION blue and Fielder XT-R wires detached from the main branch and did not turn to the orifice of the side branch. The Fielder FC and SION black wires reached the ostium along the main branch. Bench test 2 measured the wires' crossability with pull force using a double lumen catheter. The Fielder FC and SION black were chosen based on the bench test 1 results. The pullback force was significantly smaller for the SION black than for the Fielder FC (8.14±0.90 cN vs. 12.00±1.29 cN, p=0.0016). The SION black's shape changed, whereas the composite core wire retained its original shape.

Conclusions: When treating severely angulated bifurcated lesions, a polymer-coated composite core guidewire is optimal.

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SUBMITTED ON 11/08/2016 - REVISION RECEIVED ON 16/10/2016 - ACCEPTED ON 14/11/2016

DOI: 10.4244/AsiaInterv_V3I1A13

Introduction

Bifurcated lesions account for 15-20% of percutaneous coronary intervention (PCI) cases[1]. The complexity and wide anatomical spectrum of bifurcated lesions compared to non-bifurcated lesions make treatment difficult and uncertain[2]. In cases of bifurcated lesions, the risk of side branch (SB) occlusion should be considered[3]. The standard treatment of bifurcated lesions is provisional stenting[4], which involves implanting one stent in the main branch (MB) and then stenting the SB if dissection or flow disturbance occurs in the SB[5]. To prevent complications in the SB, guidewire placement in the MB and SB is required. The placement of a guidewire in the SB when a stent is implanted in the MB is the jailed guidewire technique, which has been shown to improve the outcome of bifurcated lesions[6]. However, the complexities of bifurcated coronary anatomy such as the SB take-off angle and different patterns of atherosclerotic lesion distribution make SB wiring challenging[7]. However, when initial wiring of the SB is impossible, plaque modification with a balloon or rotablation may facilitate wire passage[8]. To overcome complex SB wiring, new techniques and guidewires have been developed[8,9]. However, in the case of bifurcation with severe angulation of the SB, wiring is especially challenging.

The reversed guidewire technique was first described by Kawasaki et al in 2008 to cross through severely angulated SBs, and it is now performed with some modifications[10,11]. Although the technique has evolved, there are still some concerns. When performing the reversed guidewire technique, the use of polymer-coated guidewires is recommended. However, the reason why the coil guidewire is not recommended is unclear, so the different kinds of polymer-coated wires that can be selected should be assessed. Therefore, the present study was performed to 1) clarify the reasons why polymer-coated guidewires are recommended more than coil wires, and 2) compare the performance between different polymer-coated wires.

Methods

In vitro bench tests with coronary bifurcation models were used in this study. Bench test 1 was performed to evaluate the wire's accessibility. We selected coil or plastic polymer-coated guidewires to compare the behaviour of the tip of the guidewire and determine which guidewire is most suitable for approaching the orifice of the SB. The SION™ blue (SiBlue; Asahi Intecc, Tokyo, Japan) was used as a composite coil wire, and the Fielder™ FC (FFC; Asahi Intecc) was used as a polymer-coated plastic wire, as in previous reports[10,11]. We also selected the following new guidewires that have never been evaluated in previous reports. The Fielder™ XT-R (FXTR; Asahi Intecc) has a slender tip (0.010-inch) compared to conventional 0.014-inch guidewires, and the SION™ black (SiBlack; Asahi Intecc) has a new composite core structure compared to conventional polymer-coated wires.

We manipulated all the guidewires into the same shape: 90° angle 3 cm from the guidewire tip and 45° angle 1 mm from the guidewire tip **(Figure 1)**. We inserted the wires into an assumed coronary bifurcation model consisting of two different parts

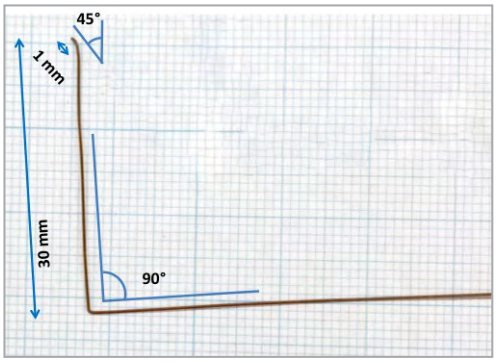

Figure 1. *Guidewire manipulation. All wires were manipulated into the same shapes: 90° angles were created 3 cm from the guidewire tip, and 45° angles were created 1 mm from the tip.*

made of a transparent plastic tube: distal (diameter 2.0 mm, length 21 mm) and proximal (diameter 3.6 mm, length 29 mm) **(Figure 2)**. We recorded the behaviour of each guidewire.

Bench test 2 was performed to measure the pullback force of the guidewire when crossing through a severely angulated and stenotic lesion. We created a severely angulated MB and SB in

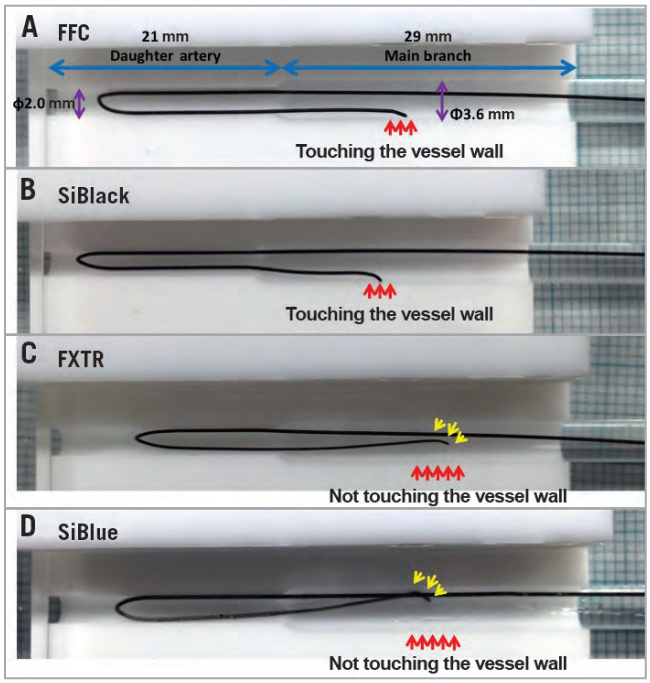

Figure 2. *Vascular bifurcation model. All wires were inserted into the same vascular bifurcation model that was made from a transparent plastic box with two parts: distal (diameter 2.0 mm, length 21 mm) and proximal (diameter 3.6 mm and length 29 mm). The tips of the Fielder FC (A) and SION black (B) faced the side branch along the trunk of the MB. Conversely, the tips of the Fielder XT-R (C) and SION blue (D) did not face the MB wall; instead, the wire tips turned inward towards the vessel wall. FFC: Fielder FC; FXTR: Fielder XT-R; MB: main branch; SiBlack: SION black; SiBlue: SION blue*

a 160° bifurcated coronary model using a plastic tube **(Figure 3A)**. The plastic tube was filled with 0.9% saline. Severe stenosis was simulated by bending the middle part of the plastic tube (i.e., the SB) **(Figure 3B)** to assess the crossability of the guidewires. A microcatheter (SASUKE®; Asahi Intecc) was used to perform the reversed guidewire technique[11] and cross the guidewire through the SB and stenotic lesion. The pull force (cN) was calculated by using a spring balance attached to the torquer of the SB wire **(Figure 4)**. The tests were repeated seven times. Then the shapes of the guidewires were assessed.

Statistical analysis

All data were analysed using the Mann-Whitney U test with SPSS, Version 21.0 statistical software (IBM Corp., Armonk, NY, USA). Data are presented as a mean±standard error of the mean. Values of $p<0.05$ were considered statistically significant.

Results

BENCH TEST 1

All wires were inserted into the same vascular bifurcation model. The tip of the FFC and SiBlack faced the SB along the trunk of the MB **(Figure 2)**. However, the tips of the FXTR and SiBlue did not touch the vessel wall of the MB; instead, the wire tips turned inward towards the vessel wall **(Figure 2)**.

BENCH TEST 2

On the basis of the results of bench test 1, we selected the FFC and SiBlack as the candidate guidewires to perform the reversed guidewire technique. The tips of these guidewires moved along the vessel wall of the MB, which was beneficial when approaching a severely angulated SB ostium. Although the FFC and SiBlack entered the SB ostium easily, the pullback force to cross through the SB ostium and stenotic lesion was significantly higher with the FFC than with the SiBlack (12.00±0.49 cN vs. 8.14±0.34 cN, p=0.0016) **(Figure 5)**. Regarding the shapes of the guidewires, the SiBlack was superior to the FFC, as it retained its original shape. The characteristics of each wire are summarised in **Table 1**.

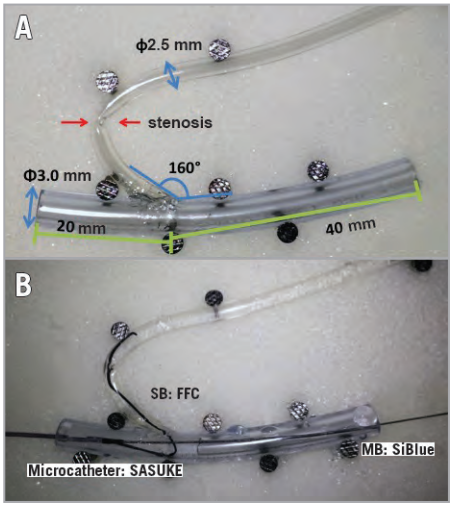

Figure 3. *Angulated bifurcation model. A) The severely angulated MB and SB of the 160° bifurcated coronary model was created using a plastic tube. The diameters of the MB and SB were 3.0 mm and 2.5 mm, respectively. The distal part of the MB from the SB orifice was 40 mm, and the proximal part was 20 mm long. B) The plastic tube was filled with 0.9% saline. Severe stenosis was simulated by bending the plastic tube (i.e., the SB). A SASUKE microcatheter was used to perform the reversed guidewire technique. FFC: Fielder FC; MB: main branch; SB: side branch; SiBlue: SION blue*

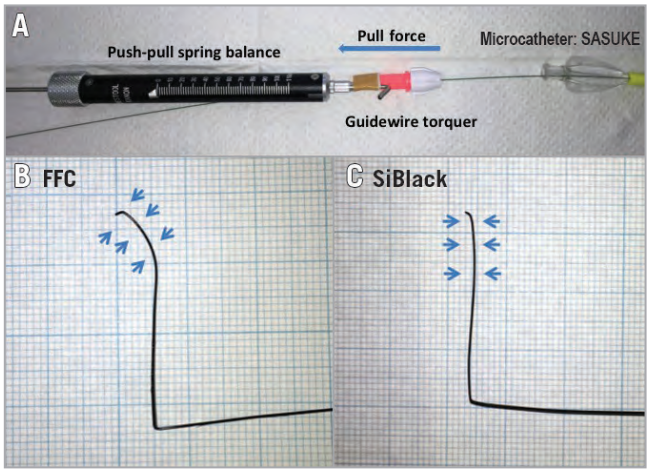

Figure 4. *Measurement of pull force by push-pull balance. A) The pull force required to cross the guidewire through the stenotic SB was calculated by using a push-pull spring balance attached to the wire torquer of the SB. The reversed guidewire technique was performed seven times, and the FFC (B) and SiBlack (C) were removed to assess their shapes. FFC: Fielder FC; SiBlue: SION blue*

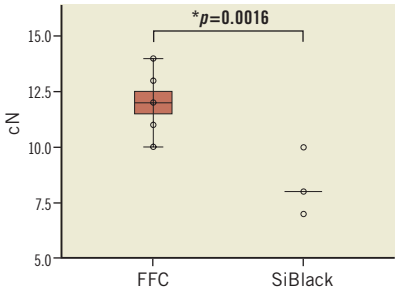

Figure 5. *Pull force of the Fielder FC and SION black wires. Box-and-whisker plot showing the results of the pull force. FFC: Fielder FC; SiBlack: SION black*

Table 1. Accessibility and pull force of the different guidewires.

	FFC	SiBlack	FXTR	SiBlue
Accessibility	yes	yes	no	no
Pull force	big	small	N/A	N/A

N/A: not applicable; FFC: Fielder FC; SiBlack: SION black; FXTR: Fielder XT-R; SiBlue: SION blue

Discussion

Compared to non-bifurcation lesions, PCI for coronary bifurcated lesions is challenging and associated with a higher complication rate[12]. As the placement of the SB wire in the jailed guidewire technique is significantly associated with angiographic success and target lesion revascularisation[6], physicians must consider crossing through the SB when treating bifurcated lesions. However, it is sometimes difficult to place the guidewire in the SB.

In the present study, the results of bench test 1 showed that, in terms of shaping the hairpin curve of the guidewire and performing the reversed guidewire technique[10], the FFC and SiBlack were most suitable. The main difference between the present study and a previous study[11] was the use of more human-like coronary artery bifurcation lesions that consisted of two different vessel diameters. The diameters of the SB and MB are not the same, thus the mother artery is larger than the daughter artery[13]. In the bifurcation vessel model, the FXTR and SiBlue did not move along the vessel wall of the MB. The following factors may have contributed to this result: the wire core of the FXTR is thinner, the SiBlue is not coated with a hydrophilic polymer, and the force of the guidewire to spread in the vessel and track the vessel wall is weaker than the FFC and SiBlack[14]. Therefore, the FFC and SiBlack are suitable for performing the reversed guidewire technique.

Results of bench test 2 showed a difference between the FFC and SiBlack in terms of the pullback force for crossing through the orifice and stenotic lesion before the entry of the SB. The conventional[10] or microcatheter-facilitated reversed guidewire technique[11] involves pulling the guidewires, so there is a risk of coronary dissection or subintimal wiring, which should be avoided when placing a wire into the SB[10]. Interestingly, the FFC required a significantly higher force than the SiBlack, although the diameter and load of their guidewire tips are the same. Moreover, in terms of the shaping memory, the SiBlack was superior to the FFC. Therefore, the shape retention of the guidewires may affect the pullback force, and the SiBlack may be safer than the FFC. Changes in the guidewire tip can lead to unintentional wire handling, which can cause coronary dissection or subintimal wiring. Compared to the FFC, the SiBlack has appropriate lubricity and vessel trackability, making it more durable for performing the reversed guidewire technique.

This is the first study to assess the crossability of the wire by using the handling force of the guidewire and a push-pull spring balance. We think that using the push-pull spring balance is suitable for objectively measuring the operator's handling of the guidewire during challenging manoeuvres.

Limitations

There are some limitations in this study. First, operators may change the bending angle or point to fit the coronary anatomy of each patient in the clinical setting. Although a different bending angle and point, such as a longer tip and acute angle, may solve the problem of lack of contact with the vessel wall noted with some guidewires, we fixed the bending angle and point to the same degree and position to evaluate each wire consistently. Second, this study only performed an *in vitro* evaluation; the behaviour of the guidewires in a human coronary artery may be different. The inner surface of the silicone tube used in this model is much smoother than real coronary arteries. Plaque distribution and calcification in the vessel may affect the behaviour of the guidewires. Third, we did not report the success rate and time taken crossing the SB. The bifurcated vessel model made with a plastic tube inner surface is different from a real coronary artery, and the ostium of the SB was difficult to recognise from the outer surface of the plastic tube, which is different from the contrast-enhanced angiography-guided wiring during real percutaneous coronary intervention (PCI). Lastly, we think the skills or experience of the operators did not affect the results of the experiments.

Conclusions

When treating severely angulated bifurcated lesions, wire selection is the key to successful treatment. Polymer-coated wires are better than composite coil wires for approaching the orifice of the SB and, among polymer-coated wires, a polymer-coated composite core wire has better accessibility, crossability, and shape retention. These factors should be considered when selecting an appropriate guidewire.

Impact on daily practice

Knowledge of the features of each guidewire is essential for every interventional cardiologist. When treating severely angulated bifurcated lesions, several factors should be considered when selecting the appropriate guidewire.

Acknowledgements

We thank Akihisa Nakagawa (Asahi Intecc) for providing valuable technical support and supplying the devices.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:63-69

A prospective, multicentre registry to assess an everolimus-eluting coronary stent system (PROMUS Element™) for coronary revascularisation in an unrestricted Indian population: the PROMUS Element™ India all-comers registry

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KEYWORDS

- all-comers registry
- Indian population
- PROMUS Element coronary stent system

Abstract

Aims: This registry aims to evaluate the safety and effectiveness of an everolimus-eluting, platinum chromium-based coronary stent system, PROMUS Element™, in an all-comers Indian population.

Methods and results: This prospective, open-label, single-arm study recruited 1,000 patients. The primary endpoint was target vessel failure (TVF) at 12 months post procedure, defined as ischaemia-driven revascularisation of the target vessel (TVR), target vessel myocardial infarction (MI) or cardiac death. Patients were followed up to two years. Mean age was 58.2 (±11.2) years; 83.5% were males. Diabetes mellitus and hypertension were prevalent at 41.1% and 56.5%, respectively. The majority of the patients presented with acute coronary syndrome, of whom 28% had prior STEMI. The primary endpoint occurred in 2.4% at one year. The device-oriented composite endpoint (DoCE), defined as cardiac death, target vessel MI and ischaemia-driven target lesion revascularisation (TLR), was 2.2% at one year and 3.0% at two years. Major adverse cardiac events (MACE), a composite of death, Q-wave MI and TLR, were 2.6% at one year and 3.5% at two years. Cardiac death and all MI were 2.3% and 10.3%, respectively. The definite/probable stent thrombosis rate was low (0.6%). At two years, 91.7% continued to be on dual antiplatelet therapy and the patient follow-up rate was 95.8%.

Conclusions: The primary endpoint and follow-up data up to two years demonstrate the safety and efficacy of the PROMUS Element coronary stent system in an Indian patient population.

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SUBMITTED ON 19/07/2016 - REVISION RECEIVED ON 1st 18/11/2016 / 2nd 20/12/2016 - ACCEPTED ON 21/12/2016

DOI: 10.4244/AsiaInterv_V3I1A14

Introduction

India is currently undergoing a rapid epidemiological health transition with a rising burden of non-communicable diseases, such as coronary artery disease (CAD)[1]. In India alone, an estimated 30 million individuals are living with CAD, and 52% of deaths due to CAD occur in people <70 years old[2]. Percutaneous coronary intervention (PCI) is an important way of revascularisation in patients with CAD, including implantation of coronary stents. Drug-eluting stents (DES) provide a controlled localised release of antiproliferative agents over the course of several months, have demonstrated a significant reduction in in-stent restenosis and subsequent repeat revascularisation when compared to bare metal stents (BMS), and have become the standard of care for the treatment of CAD. The PROMUS Element™ everolimus-eluting coronary stent system (Boston Scientific Corporation, Marlborough, MA, USA) is a drug/device combination comprising the following key components: PROMUS Element™ stent composed of a platinum chromium (PtCr) alloy and the drug product (everolimus [40-O-(2-hydroxyethyl)-rapamycin], and two polymers, poly [n-butyl methacrylate] and poly [vinylidene fluoride-co-hexafluoropropylene]). The PROMUS Element uses the same drug and polymer formulation as the PROMUS (Boston Scientific) or XIENCE V (Abbott Vascular, Santa Clara, CA, USA) but combines them with a novel PtCr alloy and flexible stent design, improving deliverability and conformability (88% more conformable), increasing radial strength (136% higher) as well as radiopacity, and reducing recoil (five times lower than cobalt alloy stents) compared with cobalt alloy second-generation stents[3]. Platinum chromium alloys have also shown low thrombogenicity and a high degree of endothelial surface coverage[4]. Several studies have reported the advantages of the PROMUS Element over earlier stents in terms of lower ischaemia-driven target lesion revascularisation (TLR), lower adverse event rates, better safety, and a higher reduction in post-procedure incomplete stent apposition[3,5-7].

We report here the prospective two-year clinical follow-up data of 1,000 Indian patients who underwent coronary revascularisation with the PROMUS Element stent.

Methods

STUDY DESIGN AND PATIENTS

PROMUS Element™ India is a prospective, open-label, observational, multicentre, single-arm registry designed to evaluate the safety and effectiveness of the PROMUS Element stent in 1,000 patients with CAD undergoing revascularisation in a real-world setting. Ethics committee approval was obtained from each participating institution before commencing the study. All consecutive patients who underwent PCI with the PROMUS Element stent from July 2012 to April 2013 from 30 centres across India were enrolled. Patients willing to provide informed consent, who had received the PROMUS Element stent (up to three stents per patient with two stents per artery), and who were willing to comply with all protocol-required follow-up evaluations were included in the study. Patients with a known allergy to the PROMUS Element stent or protocol-required concomitant medications, and any other serious medical illness that may reduce life expectancy below 12 months, were excluded from the study. The study was conducted in compliance with the approved protocol and guidelines. The PROMUS Element received CE mark approval on 30 October 2009 and DCGI approval on 13 April 2010. Stents are available in diameter sizes of 2.25-4.0 mm and lengths of 12-38 mm. The study was registered with the Clinical Trials Registry of India: CTRI/2012/06/003734.

STUDY PROCEDURE

The PCI strategy, procedure and adjuvant medication were determined solely by the investigator according to conventional clinical practice. However, it was suggested that all investigators be familiar with the recommendations in the protocol. Post procedure, all the patients were recommended to be on dual antiplatelet therapy, aspirin for an indefinite duration and either clopidogrel or prasugrel or ticagrelor for at least six months at recommended dosages. The usage of statins and other medication was noted meticulously.

FOLLOW-UP

Clinical follow-up was scheduled for 30 days (±7 days), 180 days (±30 days), 12 months (±30 days) and two years (±30 days), where an office visit was essential for the 12-month follow-up period and the remaining follow-ups were either by telephone contact or by office visit. Patients who were enrolled but who did not receive the PROMUS Element stent were followed for 12 months. At each follow-up, collection of data was carried out regarding any adverse events, angina assessment, laboratory tests performed by the treating physician and medication details. **Figure 1** provides the details of the study flow.

STUDY ENDPOINTS

The safety event dossier and all important clinical endpoints, including serious adverse events (SAE), stent thrombosis (ST), target vessel revascularisation (TVR), myocardial infarction (MI) and death were adjudicated by an independent data safety monitoring committee (DSMC), which also reviewed the cumulative safety data on a regular basis. The steering committee was responsible for the overall study procedures and ensured appropriate actions as per DSMC recommendations, if required.

The primary endpoint was target vessel failure (TVF) of the PROMUS Element at 12 months post procedure, defined as ischaemia-driven TVR, target vessel MI or cardiac death. The secondary endpoints were the TVR rate, the TLR rate, the composite of cardiac death or target vessel MI, all MI (Q-wave and non-Q-wave) rate, cardiac death rate, non-cardiac death rate, all death rate, and major adverse cardiac events (MACE) which is the composite of death, Q-wave MI and TLR. The device-oriented composite endpoint (DoCE) was defined as cardiac death, target vessel MI and ischaemia-driven TLR. Stent thrombosis (ST) was defined using the Academic Research Consortium (ARC) definition and categorised into definite, probable and possible ST and also as

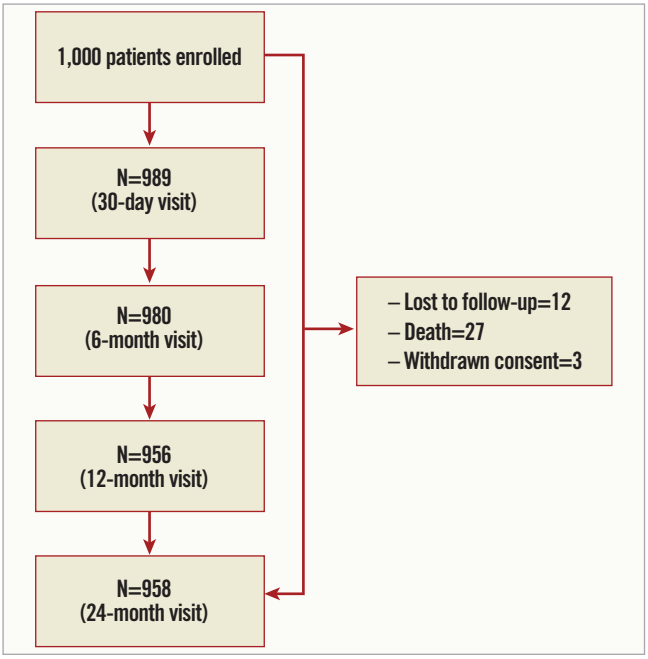

Figure 1. *Patient flow and follow-up of the PROMUS Element registry up to two years.*

Table 1. Baseline patient characteristics and risk factors.

Baseline characteristics & risk factors	ITT population (N=1,000)
Age, years (mean±SD)	58.2±11.23
Male, n (%)	835 (83.5%)
Body mass index, kg/m^2 (mean±SD)	25.8±3.90
Current smoker, n (%)	142 (14.2%)
Family history of CVD, n (%)	127 (12.7%)
Hypertension, n (%)	565 (56.5%)
Dyslipidaemia, n (%)	430 (43.0%)
Diabetes, n (%)	412 (41.2%)
Insulin requiring, n (%)	198 (19.8%)
Previous PCI, n (%)	90 (9.0%)
Previous CABG, n (%)	37 (3.7%)
Left ventricular ejection fraction (mean±SD)	49.9±11.54
Left ventricular ejection fraction <40%, n (%)	302 (30.2%)
Clinical presentation at admission, n (%)	
Acute coronary syndrome	595 (59.5%)
Chronic stable angina	214 (21.4%)
Post-STEMI, n (%)	160 (16.0%)
Asymptomatic ischaemia, n (%)	31 (3.1%)

CABG: coronary artery bypass surgery; CVD: cardiovascular disease; ITT: intention-to-treat; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-elevation myocardial infarction

acute, subacute and late ST based on the time elapsed since stent implantation. The procedural endpoints were the technical success rate and clinical procedural success rate. All study-related definitions are given in the **Appendix**.

STATISTICAL ANALYSIS

No formal sample size calculations were performed as this study was a post-market registry meant for descriptive analyses. One thousand patients who were enrolled in the study after meeting the eligibility criteria constituted the intention-to-treat (ITT) population and safety population. Nine hundred and fifty-eight (95.8%) patients did not have major protocol deviations and completed two-year follow-up and hence constituted the per-protocol (PP) population. Categorical variables were compared with the use of the chi-square test or Fisher's exact test; the Student's t-test was used for comparison of continuous variables. Adverse events (AE) were coded using the Medical Dictionary for Regulatory Affairs, version 17.0.

Results

A total of 1,000 patients were enrolled in the study (the first patient first visit was on 26 July 2012 and the last patient last visit was on 26 June 2015). All the results are presented for the ITT population. Forty-two (4.2%) patients did not complete two-year follow-up, among whom 27 (2.7%) patients died, three (0.3%) withdrew consent, and 12 (1.2%) patients were lost to follow-up at two years. Detailed patient follow-up is illustrated in **Figure 1**.

Baseline demographics and patient characteristics are summarised in **Table 1**. Male patients accounted for 83.5% (835) of the study population and the mean age was 58.2±11.2 years. Diabetes and hypertension were highly prevalent at 41.2% and 56.5%, respectively. The majority of patients presented either with acute coronary syndrome (59.5%) or post STEMI (16%), 30.2% had an ejection fraction (EF) ≤40%. Baseline procedural characteristics are summarised in **Table 2**. The total number of target lesions treated was 1,264. The left anterior descending (LAD) artery was the most commonly involved, LMCA interventions were 0.2%, and 22% of patients had more than one target lesion treated.

The primary endpoint, TVF, was 2.4% at 12 months post procedure and it was 3.3% at two years. At two years, the ST rate was 0.8%, and the definite/probable ST rates were 0.4% and 0.2%, respectively. There were no acute STs reported in the study but subacute and late ST rates were 0.3% and 0.5%, respectively. The timelines of the ST rate are given in **Figure 2**. Regarding secondary endpoints, the death rate was 2.7% (cardiac death: 2.3%; non-cardiac: 0.4%), the TVR rate was 1.1%, and the MACE rate was 3.5%. All revascularisations were considered clinically indicated, and the TLR rate was low at 0.8% at two years. DoCE was 2.2% at one year and 3.0% at two years. **Table 3** lists all the important outcomes of the study. Patients were treated according to standard interventional techniques with high device (post-procedure diameter stenosis <30%, no device malfunction) and procedure success rates of 100% and 99.9%, respectively.

The percentage of patients who remained on dual antiplatelet therapy at one and two years was 98.6% and 91.7%, respectively. More patients were on clopidogrel (69%) than prasugrel or ticagrelor

Table 2. Baseline coronary lesion characteristics.

Baseline lesion characteristics	ITT population (N=1,000)
Total no. of target lesions	1,264
Location of lesions - no. of lesions (%)	
LMCA	3 (0.2%)
LAD	702 (55.5%)
LCX	257 (20.3%)
RCA	300 (23.7%)
Target lesions treated, no. of lesions (%)	
One lesion	780 (78.0%)
Two lesions	195 (19.5%)
Three or more lesions	25 (2.5%)
Target lesions per patient, mm (mean±SD)	1.2±0.48
Reference vessel diameter[a], mm (mean±SD)	2.93±0.398
Diameter stenosis, mm (mean±SD)	88.67±9.167
Lesion length (visual estimate), mm (mean±SD)	21.53±7.652

[a]Visual assessment by the investigator. LAD: left anterior descending artery; LCX: left circumflex artery; LMCA: left main coronary artery; RCA: right coronary artery

Table 3. Clinical outcomes at 2 years - ITT population.

Outcome	12 months (N=1,000)	24 months (N=1,000)
TVF	24 (2.4%)	33 (3.3%)
All death	19 (1.9%)	27 (2.7%)
Cardiac death	15 (1.5%)	23 (2.3%)
Non-cardiac death	4 (0.4%)	4 (0.4%)
Myocardial infarction (MI)	97 (9.7%)	98 (9.8%)
Q-wave MI	2 (0.2%)	3 (0.3%)
Non-Q-wave MI	95 (9.5%)	95 (9.5%)
Stent thrombosis (ST)		
Acute ST (<24 hrs after procedure)	–	–
Subacute ST (24 hrs to 30 days after procedure)	3 (0.3%)	3 (0.3%)
Late ST >30 days after procedure	5 (0.5%)	5 (0.5%)
Definite ST	4 (0.4%)	4 (0.4%)
Probable ST	2 (0.2%)	2 (0.2%)
Possible ST	2 (0.2%)	2 (0.2%)
Cardiac death or target vessel MI	21 (2.1%)	29 (2.9%)
TVR	9 (0.9%)	11 (1.1%)
TLR	7 (0.7%)	8 (0.8%)
Major adverse cardiac events (MACE)	26 (2.6%)	35 (3.5%)
Device-oriented composite endpoint (DoCE)	22 (2.2%)	30 (3.0%)
Device success	1,000 (100%)	1,000 (100%)
Procedure success	997 (99.7%)	997 (99.7%)

TLR: target lesion revascularisation; TVR: target vessel revascularisation

(Table 4). Other details of medication are given in the **Appendix**. Subgroup analysis for the primary endpoint is given in **Table 5**.

Discussion

The results presented show that the PROMUS Element stent is safe and efficacious when used in a real-world patient population in India. The major findings of this study are as follows: 1) the PROMUS Element demonstrated a good performance with lower rates of TVF, DoCE and stent thrombosis in an enriched PCI population of all-comers in India; 2) with the PROMUS Element, the ischaemia-driven revascularisation within two years occurred infrequently, with low two-year rates of cardiac death and MI; 3) there was no reported case of ST after one year, indicating the long-term safety of the PROMUS Element stent in the study population.

The overall results with the PROMUS Element are consistent with the primary endpoint of the PLATINUM study, which demonstrated low rates of cardiac death or MI, TLR, and stent thrombosis with an everolimus-eluting platinum-chromium stent[3]. The PROMUS Element stent was also associated with a significant improvement in two-year event-free survival when the broader composite measures of TVF (3.3%), DoCE (3.0%) and MACE (3.5%) were considered. These benefits were due largely to reductions in MI and ischaemia-driven TLR and TVR, confirming the positive clinical performance of the PROMUS Element, despite the fact that the Indian population is considered to have high rates of restenosis because of a high prevalence of risk factors such as diabetes. TLR estimates the impact of restenosis while TVR clarifies the dispute whether a re-PCI was caused by a stenosis at the stent edge or by a more distally, newly developed stenosis[8]. The two-year TLR rate was 0.8%, and the TVR rate was 1.1%, which were both appreciably lower than the TLR and TVR rates reported elsewhere with similar patient populations[9,10]. This finding may in part be attributed to the higher threshold for repeat revascularisation (TLR/TVR) for Indian patients due to various socioeconomic constraints. Several studies have reported the advantages of the

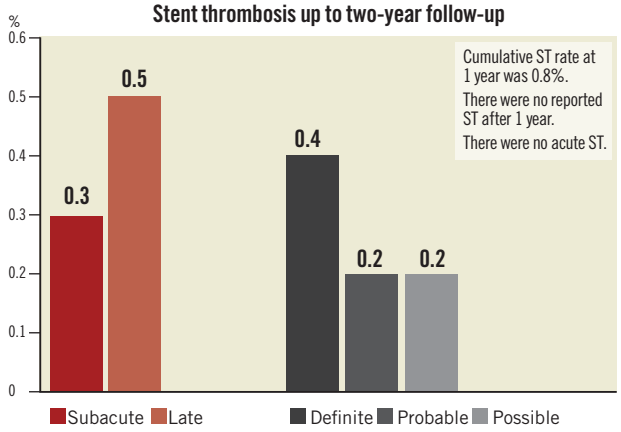

Figure 2. *Stent thrombosis rates in the PROMUS Element™ India all-comers registry up to two-year follow-up.*

Table 4. Summary of antiplatelet therapy up to 2-year follow-up.

Generic name	Pre hospital discharge (N=1,000)	30 days (N=989)	Month 6 (N=980)	Month 12 (N=960)	Month 24 (N=958)
Aspirin	981 (98.1%)	976 (98.7%)	968 (98.8%)	947 (98.6%)	941 (98.2%)
Clopidogrel	649 (64.9%)	637 (64.4%)	638 (65.1%)	663 (69.1%)	661 (69.0%)
Prasugrel	246 (24.6%)	249 (25.2%)	247 (25.2%)	220 (23.0%)	190 (19.8%)
Ticagrelor	105 (10.5%)	95 (9.6%)	86 (8.8%)	77 (8.0%)	65 (6.8%)

PROMUS Element over earlier stents in terms of lower ischaemia-driven TLR: the PLATINUM study reported numerically lower ischaemia-driven TLR (3.5% vs. 4.9%, p=0.21) at three years when compared to the XIENCE V stent[6].

The composite endpoint of cardiac death and target vessel MI was low at 2.9% at two years in this real-world Indian population with CAD. The outcomes of the present study were consistent with the two-year event rates in the XIENCE V® INDIA Study[9]. The low rates of death and target vessel MI were suggested to be due to very few ST reported in this study[11]. DoCE or TLF, the endpoint that supports the characterisation of device effectiveness and safety, was also low in this study at two years (3.0%) and is similar to the reported TLF rates with the XIENCE V stent in an Indian population[9].

The major concerns following DES implantation are non-compliance to antiplatelet therapy and late stent thrombosis. The two-year rate of ST was found to be 0.8%, and ARC definite or probable ST in the present study was 0.6%, consistent with the low thrombosis rates reported in the PLATINUM trial[3]. Late ST was very low at 0.5%, and there were no ST reported after one-year follow-up. The low rates of ST with current-generation DES are reported to be probably due to an optimal combination of a thin fracture-resistant alloy, a low dose of everolimus elution, and the thrombus-resistant non-inflammatory properties of the polymer[12]. This registry also demonstrates that 91.7% of patients continued to be on dual antiplatelet therapy, even at two years. While this practice is not in line with current international guidelines, it is a common practice in India and could possibly be associated with the low ST rates reported in the study.

Table 5. Subgroup analysis for the primary endpoint (target vessel failure) – ITT population.

Category	Subgroup	PROMUS Element (N=1,000)	
		12 months, n (%)	24 months, n (%)
Overall		24/1,000 (2.4)	33/1,000 (3.3)
Age	<65 years	10/720 (1.4)	15/720 (2.1)
	≥65 years	14/280 (5.0)	18/280 (6.4)
Sex	Male	21/835 (2.5)	28/835 (3.4)
	Female	3/165 (1.8)	5/165 (3.0)
eGFR	≤60 mL/min/1.73 m²	7/200 (3.5)	12/200 (6.0)
	>60 mL/min/1.73 m²	17/784 (2.2)	21/784 (2.7)
Angina status	Stable angina	5/342 (1.5)	11/342 (3.2)
	Unstable angina	15/549 (2.7)	18/549 (3.3)
	No angina	4/109 (3.7)	4/109 (3.7)
No. of treated lesions	1	16/780 (2.1)	25/780 (3.2)
	≥2	8/220 (3.6)	8/220 (3.6)
Lesion type	A	–	–
	B	11/489 (2.2)	15/489 (3.1)
	C	24/741 (3.2)	29/741 (3.9)
Reference vessel diameter	≤2.75 mm	21/568 (3.7)	26/568 (4.6)
	>2.75 mm	14/696 (2.0)	18/696 (2.6)
Target vessel	LAD	23/702 (3.2)	29/702 (4.1)
	Non-LAD	12/562 (2.1)	15/562 (2.6)

Conclusions

In conclusion, in this real-world population of Indian patients undergoing coronary revascularisation, PROMUS Element implantation resulted in low two-year rates of TVF, TLR, MI, death, TVR, DoCE, MACE and late ST, suggesting long-term safety and efficacy of the PROMUS Element stent.

Impact on daily practice

This registry of 1,000 patients demonstrated the safety and efficacy of the PROMUS Element™ coronary stent system in an all-comers Indian population. Diabetes and hypertension were highly prevalent at 41.1% and 56.5%, respectively. The majority of the patients presented with ACS, of whom 28% had STEMI. The primary endpoint TVF occurred in 2.4% at one year and in 3.3% at two years. The definite/probable stent thrombosis rate was low at 0.6%. The study was completed by 95.8% of patients, representing a trend towards an improved follow-up rate in Indian patients. Nearly 92% were on DAPT at two years; while this is not in compliance with the current guidelines, it is a common practice in India and could possibly be linked to the low ST rates reported in this study.

Appendix

STUDY DEFINITIONS

INCLUSION CRITERIA

1. Patients receiving PROMUS Element stents
2. Up to:
   3 PROMUS stents per patient
   2 stents per artery
3. Patient (or legal guardian) understood the trial requirements and the treatment procedures and provided written informed consent before any trial-specific tests or procedures were performed

4. Patient was eligible for PCI
5. Patient was willing to comply with all protocol-required follow-up evaluations

EXCLUSION CRITERIA

1. Patient had known allergy to the study stent system or protocol-required concomitant medications (e.g., stainless steel, platinum, chromium, nickel, iron, thienopyridines, aspirin, contrast) that cannot be adequately pre-medicated
2. Patient had any other serious medical illness (e.g., cancer, congestive heart failure - NYHA Class III and IV) that may reduce life expectancy to less than 12 months
3. Patients with a mixture of other drug-eluting stents
4. Pregnant and lactating females or females who had positive pregnancy test (urine or serum)
5. Known/suspected case of Human Immunodeficiency Virus infection
6. Cardiac death
7. Cardiac death was defined as death due to any of the following reasons: acute MI, cardiac perforation/pericardial tamponade, arrhythmia or conduction abnormality, cerebrovascular accident (CVA) through hospital discharge or CVA suspected of being related to the procedure, death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery or any death in which a cardiac cause cannot be excluded. Death not due to cardiac causes is defined as a non-cardiac death.

TARGET VESSEL

The target vessel is any coronary vessel (e.g., left main coronary artery, left anterior descending artery [LAD], left circumflex artery [LCX], or right circumflex artery [RCX]) containing a target lesion. Side branches of a target vessel such as the LAD are also considered part of the target vessel. In this study, the ramus was considered as a branch of the LCX for the purposes of determining eligibility and for determining TVR.

TARGET VESSEL FAILURE

Target vessel failure is any ischaemia-driven revascularisation (TVR), target vessel MI or cardiac death. For the purposes of this protocol, TVF was considered if it could not be determined with certainty whether the MI was related to the target vessel.

TARGET LESION REVASCULARISATION

Target lesion revascularisation is any ischaemia-driven repeat percutaneous intervention, to improve blood flow, of the successfully treated target lesion or bypass surgery of the target vessel with a graft distal to the successfully treated target lesion. A TLR was considered as ischaemia-driven if the target lesion diameter stenosis was ≥50% by quantitative coronary angiography (QCA) in addition to clinical or functional ischaemia which cannot be explained by other coronary or graft lesions. A TLR was considered as ischaemia-driven if the lesion diameter stenosis was ≥70% by QCA even in the absence of clinical or functional ischaemia.

TARGET VESSEL REVASCULARISATION

Target vessel revascularisation is any ischaemia-driven repeat percutaneous intervention, to improve blood flow, or bypass surgery of not previously existing lesions, diameter stenosis ≥50% by QCA in the target vessel, excluding the target lesion. A TVR was considered ischaemia-driven if the target vessel diameter stenosis was ≥50% by QCA and if any of the following were present in the patient: 1) positive functional study corresponding to the area served by the target vessel, 2) ischaemic ECG changes at rest in a distribution consistent with the target vessel, 3) ischaemic symptoms referable to the target vessel. A TVR was also considered as ischaemia-driven if the lesion diameter stenosis was ≥70% even in the absence of clinical or functional ischaemia.

STENT THROMBOSIS

Stent thrombosis was categorised as acute (<1 day), subacute (>24 hours to 30 days), late (>30 days) and very late (>1 year) and was defined as confirmed/definite (acute coronary syndrome and angiographic or pathologic confirmation of ST), probable (unexplained death ≤30 days or TVMI without angiographic information) and possible (unexplained death >30 days after stent placement) as per the Academic Research Consortium guidelines (2007).

TECHNICAL SUCCESS

Technical success is the successful delivery and deployment of the study stent to the target vessel, without balloon rupture or stent embolisation.

CLINICAL PROCEDURE SUCCESS

Clinical procedural success is a mean lesion diameter stenosis <10% in two near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of in-hospital MI, TVR, or cardiac death (MACE).

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:70-80

On-label vs. off-label use of vascular closure devices in Japanese patients undergoing percutaneous coronary intervention

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KEYWORDS

- percutaneous coronary intervention
- vascular closure device

Abstract

Aims: Vascular closure devices (VCD) provide immediate haemostasis and enable early mobilisation for patients undergoing percutaneous coronary intervention (PCI). At present, the use of VCD in Japan is only approved for elective PCI patients who are expected to be discharged within 48 hrs. The aim of this study was to clarify the safety of VCD use in on- and off-label cases.

Methods and results: We analysed 7,901 consecutive patients undergoing a femoral-approach PCI between 2008 and 2014 at 13 hospitals in Japan. We compared in-hospital outcomes of VCD users to VCD non-users (control). In addition, propensity score matching analyses were performed for on- and off-label VCD users, subsequently generating two matched data sets consisting of 2,626 patients (with on-label), and 626 patients (with off-label), respectively. The patients' average age was 67.7±11.1 and 54.5% presented with ACS. Overall, 20.8% used VCD for haemostasis, and the crude in-hospital vascular complication rates were not different between the VCD users and the controls (2.0% vs. 2.1%, p=0.741). Female gender was the only variable associated with a risk of vascular complication among VCD users (OR 3.12, 95% CI: 1.45-6.71, p=0.004). Even after propensity score matching, the incidence of vascular complications did not differ among VCD users and the control group for either the on-label (2.0 vs. 2.1%, p=0.783) or off-label data set (2.2 vs. 1.6%, p=0.560).

Conclusions: VCD users had a similar bleeding complication rate to the controls, including in patients with off-label use. Further studies are necessary to confirm the safety of VCD in different scenarios.

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SUBMITTED ON 05/01/2016 - REVISION RECEIVED ON 08/11/2016 - ACCEPTED ON 07/12/2016

DOI: 10.4244/AsiaInterv_V3I1A15

Abbreviations

AHA	American Heart Association
BMI	body mass index
CPA	cardiopulmonary arrest
CS	cardiogenic shock
DES	drug-eluting stent
IABP	intra-aortic balloon pump
JCD-KiCS	Japanese Cardiovascular Database-Keio interhospital Cardiovascular Studies
PCI	percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction
VCD	vascular closure device(s)

Introduction

Periprocedural bleeding is the most common complication of percutaneous coronary intervention (PCI) and is associated with a risk of early mortality[1-4]. Vascular closure devices (VCD) provide immediate haemostasis and enable early mobilisation for patients undergoing PCI. However, data of bleeding risk with VCD have revealed mixed results; the use of VCD seemed to increase the vascular complication rate in a subset of patients with increased body habitus, complex arterial anatomy, small-sized and non-patent vessel, larger sheath size and systemic disease[5,6]. Further, VCD for emergent cases could potentially lead to an increased rate of bleeding complications when compared with elective PCI[7]. The most recent American Heart Association (AHA) statement provides a class IIa recommendation for faster haemostasis and a shorter duration of bed rest, and a class III recommendation for the routine use of VCD to reduce vascular complications.

In Japan, VCD are approved for use in patients who are expected to be discharged within 48 hrs after the PCI procedure. This application of the device is intended for early mobilisation and, consequently, early discharge. Asian patients are known to have higher rates of bleeding complications compared with patients in Western countries[8], and such concerns and cost issues have led to the limited use of VCD. However, at times, VCD are used off-label[9], such as in cases of ST-elevation myocardial infarction (STEMI).

To date, there has not been any clinical validation of the use of VCD in real-world situations[9]. Hence, the aim of this study was to investigate whether VCD are safe for Japanese patients who undergo PCI, irrespective of VCD indication.

Methods

The Japanese Cardiovascular Database-Keio interhospital Cardiovascular Studies (JCD-KiCS) is a large, ongoing, prospective, multicentre cohort study designed to collect clinical background and outcome data on PCI patients. Participating hospitals were instructed to record data from hospital visits for consecutive PCI patients and to register these data in an internet-based database. Data pertaining to approximately 150 variables are being collected. There are dedicated clinical research coordinators assigned to each site, and a web-based system performs checks to ensure that the reported data are complete and internally consistent. PCI performed using any coronary device may be included. The decision to perform PCI is made based on the attending physician's clinical assessments. The study does not mandate specific interventional or surgical techniques, such as vascular access, sheath size or use of a specific stent or VCD.

Although the sizes of the sheath and guiding catheter were not protocol-mandated in this cohort, the commonly used size was 6-8 Fr in a transfemoral intervention. Since GP IIb/IIIa inhibitors and bivalirudin are not available in Japan, all patients underwent periprocedural anticoagulation via heparin based on institutional dosing instructions during PCI. Usually a bolus dose of 5,000-10,000 IU was given, with additional doses provided based on an activated clotting time of >300 s during PCI[10]. The recommended antiplatelet therapy was long-term aspirin 81 mg daily, along with a thienopyridine (75 mg clopidogrel or 200 mg ticlopidine daily). In general, the loading dose of clopidogrel was 300 mg. Prasugrel was available from March 2014, but ticagrelor was not available in Japan.

Major teaching hospitals within the Tokyo metropolitan area were selected for the study, and the study protocol was approved by an institutional review board committee at each site. In this registry, the data have been collected since September 2008 from 12 Japanese hospitals participating in the JCD[11-16]. Prior to the launch of the JCD, information on the study objectives, social significance, and an abstract were provided to register this clinical trial with the University Hospital Medical Information Network. This network is recognised by the International Committee of Medical Journal Editors as an acceptable registry, according to a statement issued in September 2004 (UMIN R000005598).

Data were analysed from the 7,901 patients who underwent consecutive PCI with a transfemoral approach between September 2008 and March 2014 **(Figure 1)**. We divided all patients into two groups according to the kind of VCD use (on-label indication group and off-label indication group). The on-label use of VCD was defined as the use of VCD for non-urgent/elective patients and those anticipated to be discharged within 48 hrs after PCI. Any use of VCD for critically ill patients (who clearly need to stay at the hospital for >48 hrs after PCI) would be considered off-label (e.g., in those patients with ST-elevation myocardial infarction [STEMI][17], cardiogenic shock [CS], cardiopulmonary arrest [CPA], or use of an intra-aortic balloon pump [IABP]). Thus, we defined the off-label indication group as those with STEMI, CS, CPA, and IABP, while the on-label indication group included the others.

We analysed baseline characteristics and clinical outcomes, and compared VCD use (VCD users) with manual compression (control) in each group. Currently in Japan, Angio-Seal™ (St. Jude Medical, St. Paul, MN, USA), Perclose (Abbott Vascular, Santa Clara, CA, USA) and ExoSeal® (Cordis, Johnson & Johnson, New Brunswick, NJ, USA) are available as VCD for on-label PCI use, albeit ExoSeal was not used in our study since it was introduced into the market very recently.

The majority of the clinical variables in the JCD were defined according to the National Cardiovascular Data Registry, sponsored

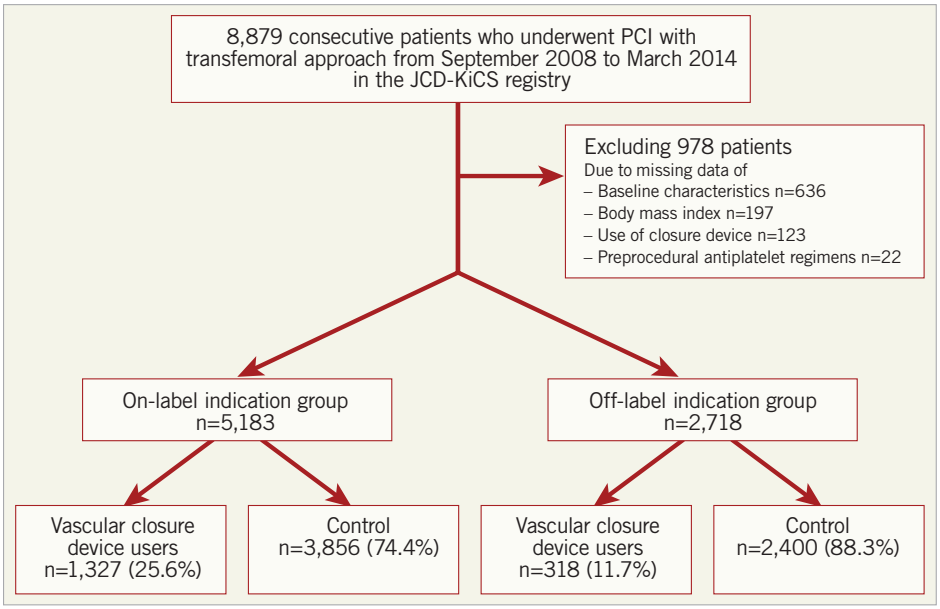

Figure 1. *Patient flow chart.*

by the American College of Cardiology, to conduct comparative research and determine the factors that lead to disparities in PCI management[18,19].

The study endpoints were vascular complications and other complications. Vascular complication was defined as the composite of puncture-site bleeding, puncture-site haematoma, and peritoneal bleeding. Puncture-site bleeding consisted of significant external bleeding that occurred at the access or percutaneous entry site and was associated with any of the following: haemoglobin drop of >3.0 g/dl[20], requiring transfusion, procedural intervention/surgery at the bleeding site to reverse/stop or correct the bleeding, and acute anaemia with a reduction in haemoglobin of >3.0 g/dl without other obvious sources or intraprocedural blood loss. Puncture-site haematoma was defined as haematoma >10 cm. These definitions were in accordance with the National Cardiovascular Data Registry (http://www.ncdr.com/webncdr/cathpci/). Bleeding criteria are also consistent with the Bleeding Academic Research Consortium grades 3A to C[21]. Other complications included in-hospital mortality, heart failure, cardiogenic shock, severe dissection or coronary perforation, myocardial infarction after PCI, cardiogenic shock or heart failure, cerebral bleeding or stroke, gastrointestinal bleeding, genitourinary bleeding, or other bleeding.

STATISTICAL ANALYSIS

Continuous variables are expressed as means and standard deviations, or median (interquartile range), and categorical variables are expressed as percentages. Continuous variables were compared using a Student's t-test or Mann-Whitney U test, and differences between categorical variables were examined using a χ^2 test or Fisher's exact test. A multivariate logistic regression analysis was performed to determine the independent predictors for vascular complications among patients who received VCD. A univariate logistic regression analysis was performed, and factors with a p-value <0.25 and off-label use were included in the multivariate analysis.

For the propensity score matching analysis, the model covariates consisted of sex, body mass index (BMI) <18.5[22], previous myocardial infarction, previous heart failure, diabetes mellitus, dialysis, cerebrovascular disease, peripheral artery disease, chronic lung disease, smoking, hypertension, dyslipidaemia, previous PCI, previous coronary bypass, congestive heart failure at admission, age >80, preprocedural aspirin and clopidogrel for both groups, and STEMI, CS at admission, CPA at admission, IABP insertion for the off-label group, and unstable angina/non-ST-elevation myocardial infarction for the on-label group. A propensity score was developed using a logistic regression conditioned on these covariates. A 1:1 match was performed using a nearest neighbour match within a calliper of 1/5 of the standard deviation of the logit of the propensity model[23]. 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

Among all 7,901 patients, the average age was 67.7±11.1 and 4,308 patients (54.5%) presented with acute coronary syndrome. A total of 1,645 patients (20.8%) received VCD and 1,464 (18.5%) patients received the Angio-Seal (89.0% of patients with the use of VCD). Crude vascular complication rates were not significantly different with different uses of VCD (VCD users vs. control; 2.0% vs. 2.1%, p=0.741). Among all patients who received VCD (n=1,645), patients on off-label use (n=318) were leaner (BMI: 23.8±3.8 vs. 24.5±3.5, p=0.007), and had a higher proportion of

age >80 (17.3% vs. 12.1%, p=0.015) compared with on-label use (n=1,328) **(Table 1)**. The average ages were not significantly different in either group (off-label use vs. on-label use: 66.5±12.7 vs. 67.8±10.6, p=0.106). In-hospital clinical outcomes are shown in **Table 2**. Vascular complications were not significantly different in each group (off-label use vs. on-label use: 2.2% vs. 2.0%, p=0.782). When a logistic regression modelling was performed, after adjustment, female gender was the only variable that was associated with vascular complications in patients in whom a VCD was used (odds ratio [OR] 3.12, confidence interval [CI]: 1.45-6.71, p=0.004). Notably, the off-label use of VCD, along with variables such as lower BMI or age >80, was not associated with an increased risk of vascular complications **(Table 3)**.

Overall, 2,718 (34.4%) patients out of 7,901 presented with STEMI, CS, CPA, and use of IABP, which were thought to be off-label indications with respect to the use of VCD **(Figure 1)**. In the on-label indication group (n=5,183), 1,327 (25.6%) patients received VCD. Baseline characteristics and in-hospital outcomes are shown in **Table 4** and **Table 5**. Vascular complications were not significantly different regardless of the use of VCD (VCD users vs. control: 2.0% vs. 1.9%, p=0.974). In the off-label indication group (n=2,718), 318 (11.7%) patients received VCD. Baseline characteristics and in-hospital outcomes for these patients are shown in **Table 6** and **Table 7**. Vascular complications were not significantly different regardless of the use of VCD (VCD vs. control: 2.2% vs. 2.4%, p=0.848).

Since baseline characteristics were significantly different in VCD users and controls in the on- and off-label indication groups, we performed a propensity score matching analysis in each group

Table 1. Baseline characteristics in vascular closure device users.

		Off-label users n=318 (%)	On-label users n=1,327 (%)	*p*-value
Age (years)		66.5±12.7	67.8±10.6	0.106
Age >80		55 (17.3%)	161 (12.1%)	0.014
Female		74 (23.3%)	275 (20.7%)	0.318
Body mass index		23.8±3.8	24.5±3.5	0.007
Body mass index <18.5		20 (6.3%)	47 (3.5%)	0.026
Previous myocardial infarction		40 (12.6%)	370 (27.9%)	<0.001
Previous heart failure		15 (4.7%)	126 (9.5%)	0.006
Diabetes mellitus		112 (35.2%)	620 (46.7%)	<0.001
Diabetes mellitus with insulin		13 (4.1%)	132 (9.9%)	0.001
Dialysis		8 (2.5%)	104 (7.8%)	0.001
Cerebrovascular disease		26 (8.2%)	141 (10.6%)	0.194
Peripheral artery disease		12 (3.8%)	96 (7.2%)	0.025
Chronic lung disease		7 (2.2%)	44 (3.3%)	0.303
Hypertension		214 (67.3%)	1,001 (75.4%)	0.003
Smoking		132 (41.5%)	382 (28.7%)	<0.001
Dyslipidaemia		181 (56.9%)	925 (69.7%)	<0.001
Previous percutaneous coronary intervention		36 (11.3%)	603 (45.4%)	<0.001
Previous coronary bypass		6 (1.9%)	115 (8.7%)	<0.001
Heart failure at admission		43 (13.5%)	97 (7.3%)	<0.001
ST-elevation myocardial infarction		280 (88.1%)	0 (0%)	<0.001
Cardiogenic shock at admission		29 (9.1%)	0 (0%)	<0.001
Cardiopulmonary arrest at admission		17 (5.3%)	0 (0%)	<0.001
Intra-aortic balloon pump		51 (16.0%)	0 (0%)	<0.001
Unstable angina/ non-ST-elevation myocardial infarction		27 (8.5%)	351 (26.5%)	<0.001
Antiplatelet regimens	Aspirin	313 (98.4%)	1,303 (98.2%)	0.774
	Clopidogrel	246 (77.3%)	1,092 (82.2%)	0.043
	Prasugrel	0 (0%)	0 (0%)	
	Ticlopidine	10 (3.1%)	57 (4.3%)	0.351
	Cilostazol	5 (1.6%)	23 (1.7%)	0.842
Angio-Seal		282 (88.7%)	1,182 (89.1%)	0.840
Perclose		36 (11.3%)	145 (10.9%)	
Drug-eluting stent		183 (58.1%)	1,072 (82.7%)	<0.001
Bare metal stent		116 (36.8%)	190 (14.6%)	<0.001
Balloon angioplasty		54 (17.1%)	225 (17.3%)	0.931
Thrombectomy		178 (56.5%)	128 (9.9%)	<0.001
Rotablator		11 (3.5%)	135 (10.4%)	<0.001

Table 2. In-hospital clinical outcomes in vascular closure device users.

	Off-label users n=318 (%)	On-label users n=1,327 (%)	*p*-value
In-hospital mortality	9 (2.8%)	4 (0.3%)	<0.001
All complications	46 (14.5%)	84 (6.3%)	<0.001
Coronary dissection	9 (2.8%)	16 (1.2%)	0.033
Coronary perforation	0	5 (0.4%)	0.273
Myocardial infarction	5 (1.6%)	20 (1.5%)	0.932
Cardiogenic shock	12 (3.8%)	6 (0.5%)	<0.001
Heart failure	14 (4.4%)	5 (0.4%)	<0.001
Cerebral infarction	0 (0%)	4 (0.3%)	0.327
Intracranial haemorrhage	0 (0%)	0 (0%)	
Cardiac tamponade	4 (1.3%)	0 (0%)	<0.001
Dialysis	3 (0.9%)	3 (0.2%)	0.057
Transfusion	8 (2.5%)	18 (1.4%)	0.137
All bleeding	14 (4.4%)	30 (2.3%)	0.033
Puncture-site bleeding	4 (1.3%)	14 (1.1%)	0.755
Puncture-site haematoma	3 (0.9%)	16 (1.2%)	0.694
Peritoneal bleeding	0 (0%)	3 (0.2%)	0.396
Vascular complications	7 (2.2%)	26 (2.0%)	0.782
Gastrointestinal bleeding	0 (0%)	4 (0.3%)	0.327
Genitourinary bleeding	0 (0%)	0 (0%)	
Other bleeding	6 (1.9%)	3 (0.2%)	<0.001

Table 3. Univariate and multivariate analysis for vascular complications among vascular closure device users.

	Univariate		Multivariate	
Variable	OR (CI)	*p*-value	OR (CI)	*p*-value
Age >80	2.55 (1.17-5.55)	0.015	1.30 (0.54-3.14)	0.564
Female	4.10 (2.05-8.19)	<0.001	3.12 (1.45-6.71)	0.004
BMI <18.5	2.42 (0.72-8.14)	0.141	1.29 (0.34-4.85)	0.710
Previous myocardial infarction	1.13 (0.52-2.46)	0.753		
Previous heart failure	2.97 (1.27-7.00)	0.009	1.81 (0.67-4.89)	0.240
Diabetes mellitus	0.92 (0.46-1.84)	0.809		
Diabetes mellitus with insulin	0.32 (0.04-2.35)	0.236	0.18 (0.023-1.46)	0.109
Haemodialysis	0.42 (0.06-3.12)	0.384		
Cerebrovascular disease	0.57 (0.13-2.39)	0.432		
Peripheral artery disease	2.00 (0.69-5.80)	0.193	1.85 (0.59-5.85)	0.292
Hypertension	2.01 (0.77-5.23)	0.147	1.30 (0.48-3.53)	0.614
Smoking	0.39 (0.15-1.01)	0.044	0.56 (0.20-1.57)	0.272
Dyslipidaemia	2.22 (0.91-5.42)	0.071	2.27 (0.89-5.08)	0.060
Previous percutaneous coronary intervention	0.90 (0.44-1.84)	0.768		
Previous coronary bypass	0.81 (0.19-3.42)	0.773		
Heart failure at admission	4.24 (1.93-9.31)	<0.001	2.55 (0.96-6.77)	0.060
Cardiogenic shock at admission	1.77 (0.23-13.4)	0.576		
Intra-aortic balloon pump	3.26 (0.96-11.0)	0.080	2.42 (0.44-13.2)	0.309
Angio-Seal	0.69 (0.27-1.77)	0.442		
ST-elevation myocardial infarction	0.87 (0.33-2.27)	0.773		
Unstable angina/ non-ST-elevation myocardial infarction	1.70 (0.82-3.53)	0.153	1.35 (0.58-3.13)	0.484
Preprocedural aspirin	1.02 (1.01-1.03)	0.437		
Preprocedural clopidogrel	3.62 (0.86-15.2)	0.061	3.83 (0.88-16.7)	0.074
Off-label use	1.13 (0.48-2.62)	0.782	0.99 (0.31-3.16)	0.987

Table 4. Baseline characteristics in the on-label vascular closure device use group.

		Vascular closure device n=1,327 (%)	Manual compression n=3,856 (%)	*p*-value
Age (years)		67.8±10.6	68.5±10.3	0.028
Age >80		161 (12.1%)	508 (13.2%)	0.329
Female		275 (20.7%)	876 (22.7%)	0.132
Body mass index		24.5±3.5	24.2±3.6	0.020
Body mass index <18.5		47 (3.5%)	175 (4.5%)	0.122
Previous myocardial infarction		370 (27.9%)	1,188 (30.8%)	0.045
Previous heart failure		126 (9.5%)	486 (12.6%)	0.002
Diabetes mellitus		620 (46.7%)	1,812 (47.0%)	0.865
Diabetes mellitus with insulin		132 (9.9%)	434 (11.3%)	0.188
Dialysis		104 (7.8%)	364 (9.4%)	0.079
Creatinine (mg/dl)		0.9 [0.8, 1.1]	0.9 [0.8, 1.2]	0.956
Cerebrovascular disease		141 (10.6%)	375 (9.7%)	0.345
Peripheral artery disease		96 (7.2%)	327 (8.5%)	0.153
Chronic lung disease		44 (3.3%)	103 (2.7%)	0.222
Hypertension		1,001 (75.4%)	2,977 (77.2%)	0.188
Smoking		382 (28.8%)	1,172 (30.4%)	0.270
Dyslipidaemia		925 (69.7%)	2,620 (67.9%)	0.234
Previous percutaneous coronary intervention		603 (45.4%)	1,750 (45.4%)	0.971
Previous coronary bypass		115 (8.7%)	377 (9.8%)	0.234
Heart failure at admission		97 (7.3%)	517 (13.4%)	<0.001
Unstable angina/ non-ST-elevation myocardial infarction		351 (26.4%)	1,324 (34.3%)	<0.001
Antiplatelet regimens	Aspirin	1,303 (98.2%)	3,735 (96.9%)	0.011
	Clopidogrel	1,092 (82.2%)	2,768 (71.8%)	<0.001
	Prasugrel	0 (0.0%)	7 (0.2%)	0.120
	Ticlopidine	57 (4.3%)	153 (4.0%)	0.602
	Cilostazol	23 (1.7%)	82 (2.1%)	0.380
Angio-Seal		1,182 (89.1%)	–	
Perclose		145 (10.9%)		
Drug-eluting stent		1,072 (82.7%)	2,946 (78.6%)	0.002
Bare metal stent		190 (14.6%)	515 (13.8%)	0.410
Balloon angioplasty		225 (17.3%)	897 (23.9%)	<0.001
Thrombectomy		128 (9.9%)	339 (9.0%)	0.373
Rotablator		135 (10.4%)	170 (4.5%)	<0.001

for the use of VCD. After a propensity score matching analysis, two matched control groups were generated for on- (n=1,313) and off-label (n=313) VCD users. Baseline characteristics were similar in VCD users and controls in each group. The incidence of vascular complications did not differ with the use of VCD in the on- or off-label indication groups (2.0 vs. 2.1% in the on-label [p=0.783], and 2.2 vs. 1.6% in the off-label group [p=0.560] for VCD users vs. control) **(Table 8-Table 11, Figure 2)**.

Discussion

In the present study, 20.8% of all transfemoral PCI patients received VCD and the incidence of vascular complications was 2.1%. In this relatively lean Asian population, female gender was the only independent predictor of vascular complications with the use of VCD. When short-term in-hospital outcomes were analysed, the incidence of vascular complications did not differ among VCD users and controls in either the on-label or the off-label data set after a propensity score matching analysis. VCD users had a similar bleeding complication rate to the controls, demonstrating the safety of VCD, including its off-label use for Asian populations who are more vulnerable to bleeding. Our data also raise the question of potential off-label uses of devices in the interventional cardiology field.

Previous studies have revealed mixed results when using VCD. In 2007, the PCI registry showed that the use of VCD was associated with a reduction of the vascular complication

Table 5. Clinical outcomes in the on-label vascular closure device use group.

	Vascular closure device n=1,327 (%)	Manual compression n=3,856 (%)	*p*-value
In-hospital mortality	4 (0.3%)	23 (0.6%)	0.200
All complications	84 (6.3%)	340 (8.8%)	0.004
Coronary dissection	16 (1.2%)	51 (1.3%)	0.745
Coronary perforation	5 (0.4%)	53 (1.4%)	0.003
Myocardial infarction	20 (1.5%)	87 (2.2%)	0.098
Cardiogenic shock	6 (0.5%)	23 (0.6%)	0.543
Heart failure	5 (0.4%)	29 (0.8%)	0.144
Cerebral infarction	4 (0.3%)	11 (0.3%)	0.925
Intracranial haemorrhage	0 (0%)	1 (0.03%)	0.557
Cardiac tamponade	0 (0%)	7 (0.2%)	0.120
Dialysis	3 (0.2%)	26 (0.7%)	0.059
Transfusion	18 (1.4%)	78 (2.0%)	0.120
All bleeding	30 (2.3%)	106 (2.7%)	0.337
Puncture-site bleeding	14 (1.1%)	37 (1.0%)	0.761
Puncture-site haematoma	16 (1.2%)	46 (1.2%)	0.971
Peritoneal bleeding	3 (0.2%)	7 (0.2%)	0.750
Vascular complications	26 (2.0%)	75 (1.9%)	0.974
Gastrointestinal bleeding	4 (0.3%)	10 (0.3%)	0.799
Genitourinary bleeding	0 (0%)	1 (0.03%)	0.557
Other bleeding	3 (0.2%)	25 (0.6%)	0.070
Length of hospital stay after PCI (days)	2 [2, 3]	2 [2, 5]	<0.001

risk[24]. An analysis from the NCDR Cath PCI Registry reported that VCD reduced bleeding complications compared with manual compression[25], although patients at high risk for bleeding were less likely to receive a bleeding avoidance strategy. Another study revealed that emergent PCI could increase bleeding complications with the use of VCD compared with elective PCI[7]. In contrast,

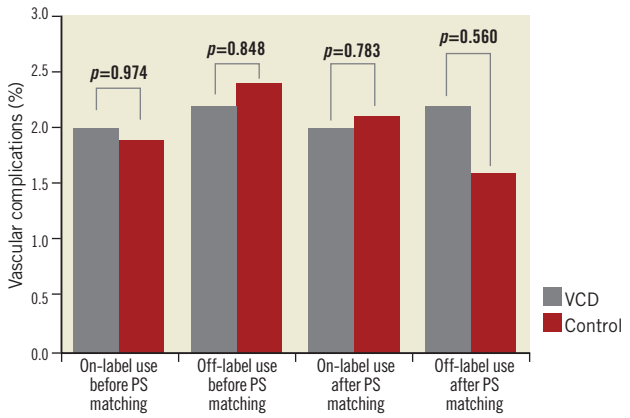

Figure 2. *Vascular complications in on- and off-label use before and after propensity score matching analysis. These graphs show similar vascular complication rates between VCD and control in each group. PS: propensity score; VCD: vascular closure device*

Table 6. Baseline characteristics in the off-label vascular closure device use group.

		Vascular closure device n=318 (%)	Manual compression n=2,400 (%)	*p*-value
Age (years)		66.5±12.7	66.6±12.2	0.958
Age >80		55 (17.3%)	371 (15.5%)	0.397
Female		74 (23.3%)	492 (20.5%)	0.253
Body mass index		23.9±3.8	23.8±3.7	0.891
Body mass index <18.5		20 (6.3%)	144 (6.0%)	0.839
Previous myocardial infarction		40 (12.6%)	279 (11.6%)	0.620
Previous heart failure		15 (4.7%)	138 (5.8%)	0.453
Diabetes mellitus		112 (35.2%)	849 (35.4%)	0.957
Diabetes mellitus with insulin		13 (4.1%)	155 (6.5%)	0.099
Dialysis		8 (2.5%)	64 (2.7%)	0.875
Creatinine (mg/dl)		0.8 [0.7, 1.0]	0.9 [0.7, 1.1]	0.064
Cerebrovascular disease		26 (8.2%)	193 (8.0%)	0.934
Peripheral artery disease		12 (3.8%)	97 (4.0%)	0.819
Chronic lung disease		7 (2.2%)	64 (2.7%)	0.625
Hypertension		214 (67.3%)	1,603 (66.8%)	0.858
Smoking		132 (41.5%)	1,068 (44.5%)	0.313
Dyslipidaemia		181 (56.9%)	1,341 (55.9%)	0.725
Previous percutaneous coronary intervention		36 (11.3%)	282 (11.8%)	0.823
Previous coronary bypass		6 (1.9%)	62 (2.6%)	0.455
Heart failure at admission		43 (13.5%)	470 (19.6%)	0.009
ST-elevation myocardial infarction		280 (88.1%)	2,120 (88.3%)	0.938
Cardiogenic shock at admission		29 (9.1%)	392 (16.3%)	0.001
Cardiopulmonary arrest at admission		17 (5.3%)	229 (9.5%)	0.014
Intra-aortic balloon pump		51 (16.0%)	717 (29.9%)	<0.001
Antiplatelet regimens	Aspirin	313 (98.4%)	2,262 (94.3%)	0.002
	Clopidogrel	246 (73.4%)	1,510 (62.9%)	<0.001
	Prasugrel	0 (0.0%)	0 (0.0%)	
	Ticlopidine	10 (3.1%)	23 (1.0%)	<0.001
	Cilostazol	5 (1.6%)	12 (0.5%)	0.023
Angio-Seal		282 (88.7%)	–	
Perclose		36 (11.3%)		
Drug-eluting stent		183 (58.0%)	1,232 (52.0%)	0.043
Bare metal stent		116 (36.7%)	981 (41.4%)	0.117
Balloon angioplasty		54 (17.1%)	441 (18.6%)	0.522
Thrombectomy		178 (56.5%)	1,405 (59.4%)	0.334
Rotablator		11 (3.5%)	35 (1.5%)	0.010

a meta-analysis in 2010 showed no increase in vascular complications, but a significantly higher risk of infection with VCD[26]. With these data, current AHA guidelines give a class III recommendation for the routine use of VCD to reduce vascular complications[5].

Table 7. Clinical outcomes in the off-label vascular closure device use group.

	Vascular closure device n=318 (%)	Manual compression n=2,400 (%)	*p*-value
In-hospital mortality	9 (2.8%)	177 (7.4%)	0.003
All complications	46 (14.5%)	491 (20.5%)	0.012
Coronary dissection	9 (2.8%)	29 (1.2%)	0.021
Coronary perforation	0 (0%)	27 (1.1%)	0.057
Myocardial infarction	5 (1.5%)	58 (2.4%)	0.347
Cardiogenic shock	12 (3.8%)	143 (6.0%)	0.114
Heart failure	14 (4.4%)	133 (5.5%)	0.399
Cerebral infarction	0 (0%)	21 (0.9%)	0.094
Intracranial haemorrhage	0 (0%)	5 (0.2%)	0.415
Cardiac tamponade	4 (1.3%)	23 (1.0%)	0.613
Dialysis	3 (0.9%)	74 (3.1%)	0.031
Transfusion	8 (2.5%)	156 (6.5%)	0.005
All bleeding	14 (4.4%)	160 (6.7%)	0.121
Puncture-site bleeding	4 (1.3%)	40 (1.7%)	0.587
Puncture-site haematoma	3 (0.9%)	19 (0.8%)	0.777
Peritoneal bleeding	0 (0%)	5 (0.2%)	0.415
Vascular complication	7 (2.2%)	57 (2.4%)	0.848
Gastrointestinal bleeding	0 (0%)	21 (0.9%)	0.094
Genitourinary bleeding	0 (0%)	7 (0.3%)	0.335
Other bleeding	6 (1.9%)	83 (3.4%)	0.139
Length of hospital stay after PCI (days)	9 [6, 15]	11 [8, 16]	<0.001

Table 8. Baseline characteristics in the on-label vascular closure device use group after a propensity matching analysis.

		Vascular closure device n=1,313 (%)	Manual compression n=1,313 (%)	*p*-value
Age (years)		67.7±10.6	68.4±9.8	0.645
Age >80		156 (11.8%)	160 (12.2%)	0.810
Female		275 (20.9%)	286 (21.8%)	0.600
Body mass index		24.5±3.5	24.4±3.6	0.558
Body mass index <18.5		46 (3.5%)	41 (3.1%)	0.586
Previous myocardial infarction		367 (28.0%)	362 (27.6%)	0.828
Previous heart failure		126 (9.6%)	134 (10.2%)	0.601
Diabetes mellitus		613 (46.7%)	616 (46.9%)	0.907
Diabetes mellitus with insulin		132 (10.1%)	152 (11.5%)	0.209
Dialysis		104 (7.9%)	111 (8.5%)	0.618
Creatinine (mg/dl)		0.9 [0.8, 1.1]	0.9 [0.7, 1.1]	0.159
Cerebrovascular disease		134 (10.2%)	127 (9.7%)	0.648
Peripheral artery disease		96 (7.3%)	91 (6.9%)	0.704
Chronic lung disease		35 (2.7%)	38 (2.9%)	0.722
Hypertension		996 (75.9%)	991 (75.5%)	0.820
Smoking		378 (28.8%)	361 (27.5%)	0.461
Dyslipidaemia		916 (69.8%)	945 (72.0%)	0.213
Previous percutaneous coronary intervention		599 (45.6%)	621 (47.3%)	0.389
Previous coronary bypass		114 (8.7%)	128 (9.7%)	0.345
Heart failure at admission		97 (7.4%)	99 (7.5%)	0.882
Unstable angina/ non-ST-elevation myocardial infarction		349 (26.6%)	329 (25.1%)	0.372
Antiplatelet regimens	Aspirin	1,289 (98.2%)	1,285 (97.9%)	0.575
	Clopidogrel	1,078 (82.1%)	1,068 (81.3%)	0.614
	Prasugrel	0 (0.0%)	3 (0.2%)	0.083
	Ticlopidine	57 (4.3%)	39 (3.0%)	0.061
	Cilostazol	22 (1.7%)	24 (1.8%)	0.766
Angio-Seal		1,171 (89.2%)	–	
Perclose		142 (10.8%)		
Drug-eluting stent		1,060 (82.6%)	1,045 (81.8%)	0.603
Bare metal stent		186 (14.5%)	171 (13.4%)	0.419
Balloon angioplasty		225 (17.5%)	290 (22.7%)	0.001
Thrombectomy		128 (10.0%)	98 (7.7%)	0.040
Rotablator		135 (10.5%)	54 (4.2%)	<0.001

In our study, a smaller proportion of critically ill patients received VCD compared to stable patients due to our system of national health insurance. Our study clarified the safety of VCD for both on- and off-label use.

To investigate the safety of off-label use and to expand labelling requires clinical trials and registry data with market forces. Off-label use would include several other devices in the interventional cardiology field. For example, the off-label use of a drug-eluting stent (DES) for coronary artery disease was common before the Food and Drug Administration concluded in 2006 that there was an increased risk of stent thrombosis with DES use, especially for off-label use[27]. After that statement, the percentage of DES use was reduced. However, registry data in 2008 showed that DES use for off-label indications did not increase the risk of adverse outcomes compared with bare metal stent use[28] and, subsequently, the percentage of DES use has recovered. Unlike DES, expanding the labelling of VCD might be difficult. Due to higher rates of vascular complications compared to Western countries[8], the use of VCD has been limited to patients who would be likely to be discharged within 48 hours in Japan. In contrast, our data showed the safety of VCD, including off-label use. However, we cannot recommend the off-label use of VCD with these data because there was a selection bias and a problem of cost. Since the VCD market would be small, compared with the market for DES use, due to the increased number of transradial PCI, it might be difficult to expand the labelling of VCD. Furthermore, several issues, such as informed consent for patients, hospital policy on whether to admit off-label use and to react in cases of complications due to device failure, manufacturer support, and operator training for use (including off-label use) would occur in off-label use[9]. Although a manufacturer may be unwilling to support the additional clinical

Table 9. In-hospital clinical outcomes in the on-label vascular closure device use group after a propensity matching analysis.

	Vascular closure device n=1,313 (%)	Manual compression n=1,313 (%)	*p*-value
In-hospital mortality	4 (0.3%)	2 (0.2%)	0.414
All complications	84 (6.4%)	115 (8.8%)	0.022
Coronary dissection	16 (1.2%)	18 (1.3%)	0.730
Coronary perforation	5 (0.4%)	22 (1.7%)	0.001
Myocardial infarction	20 (1.5%)	41 (3.1%)	0.054
Cardiogenic shock	6 (0.5%)	6 (0.5%)	1.00
Heart failure	5 (0.4%)	8 (0.6%)	0.404
Cerebral infarction	4 (0.3%)	4 (0.3%)	1.00
Intracranial haemorrhage	0 (0%)	0 (0%)	
Cardiac tamponade	0 (0%)	2 (0.2%)	0.157
Dialysis	3 (0.2%)	8 (0.6%)	0.131
Transfusion	18 (1.4%)	20 (1.5%)	0.744
All bleeding	30 (2.3%)	35 (2.7%)	0.530
Puncture-site bleeding	14 (1.1%)	13 (1.0%)	0.847
Puncture-site haematoma	16 (1.2%)	18 (1.4%)	0.730
Peritoneal bleeding	3 (0.2%)	1 (0.08%)	0.317
Vascular complication	26 (2.0%)	28 (2.1%)	0.783
Gastrointestinal bleeding	4 (0.3%)	3 (0.2%)	0.705
Genitourinary bleeding	0 (0%)	0 (0%)	
Other bleeding	3 (0.2%)	4 (0.3%)	0.705
Length of hospital stay after PCI (days)	2 [2, 3]	2 [2, 3]	<0.001

Table 10. Baseline characteristics in the off-label vascular closure device use group after a propensity score matching analysis.

		Vascular closure device n=313 (%)	Manual compression n=313 (%)	*p*-value
Age (years)		66.5±12.7	67.5±11.8	0.282
Age >80		53 (16.9%)	55 (17.6%)	0.832
Female		72 (23.0%)	66 (21.1%)	0.563
Body mass index		23.8±3.7	23.9±3.6	0.856
Body mass index <18.5		20 (6.4%)	19 (6.1%)	0.869
Previous myocardial infarction		37 (11.8%)	39 (12.5%)	0.807
Previous heart failure		15 (4.8%)	12 (3.8%)	0.555
Diabetes mellitus		112 (35.8%)	104 (33.2%)	0.501
Diabetes mellitus with insulin		13 (4.2%)	14 (4.5%)	0.844
Creatinine (mg/dl)		0.8 [0.7, 1.0]	0.9 [0.7, 1.1]	0.084
Dialysis		8 (2.6%)	9 (2.9%)	0.806
Cerebrovascular disease		26 (8.3%)	28 (8.9%)	0.776
Peripheral artery disease		12 (3.8%)	11 (3.5%)	0.832
Chronic lung disease		7 (2.2%)	3 (1.0%)	0.202
Hypertension		211 (67.4%)	212 (67.7%)	0.932
Smoking		129 (41.2%)	129 (41.2%)	1.00
Dyslipidaemia		180 (57.5%)	169 (54.0%)	0.376
Previous percutaneous coronary intervention		35 (11.2%)	39 (12.4%)	0.620
Previous coronary bypass		6 (1.9%)	7 (2.2%)	0.779
Heart failure at admission		43 (13.7%)	40 (12.8%)	0.724
ST-elevation myocardial infarction		278 (88.8%)	278 (88.8%)	1.00
Cardiogenic shock at admission		27 (8.6%)	34 (10.9%)	0.345
Cardiopulmonary arrest at admission		16 (5.1%)	16 (5.1%)	1.00
Intra-aortic balloon pump		51 (16.3%)	50 (16.0%)	0.913
Antiplatelet regimens	Aspirin	308 (98.4%)	308 (98.4%)	1.00
	Clopidogrel	241 (77.1%)	242 (77.3%)	0.924
	Prasugrel	0 (0.0%)	0 (0.0%)	
	Ticlopidine	10 (3.2%)	2 (0.6%)	0.020
	Cilostazol	5 (1.6%)	0 (0%)	0.025
Angio-Seal		277 (88.5%)	–	
Perclose		36 (11.5%)		
Drug-eluting stent		180 (58.0%)	171 (52.0%)	0.439
Bare metal stent		114 (36.7%)	120 (41.4%)	0.641
Balloon angioplasty		53 (17.1%)	44 (18.6%)	0.312
Thrombectomy		177 (56.5%)	188 (59.4%)	0.396
Rotablator		11 (3.5%)	3 (1.5%)	0.030

trials in Japan due to the associated costs[9], prospective studies to confirm the safety of VCD in various situations are needed.

For further understanding of bleeding problems, we must focus on the differences in bleeding rates in different races and genders. According to a previous study, Asian patients with coronary artery disease have higher rates of bleeding complications compared with patients in Western countries[8]. Previous studies have reported that patients with lower BMI and the elderly could lose the benefit of reducing vascular complications with the use of VCD[6,29-31]. Warren et al reported that heavier patients had more subcutaneous fat that served as a tamponade in the space around the femoral artery and/or that these patients were relatively less anticoagulated compared to thinner patients who were given approximately the same dose of heparin and antiplatelet medicines[29]. Since Asian populations are typically leaner and have higher bleeding rates than Western populations, we speculated that our data would show higher complication rates with the use of VCD in a Japanese population than those of Western countries. In contrast, we demonstrated the safety of VCD compared to manual compression, irrespective of VCD indications. Moreover, off-label use of VCD, lower BMI and age >80 were not predictors of vascular complications with VCD. However, a gender difference for vascular complications with VCD use was present in our study. Previous studies did not show a gender difference[6,29]. Our registry previously showed that female gender was an independent predictor of bleeding complications[32], and we suggest that being an Asian female might be a risk factor for vascular complications with VCD.

Table 11. Clinical outcomes in the off-label vascular closure device use group after a propensity score matching.

	Vascular closure device n=313 (%)	Manual compression n=313 (%)	*p*-value
In-hospital mortality	10 (3.2%)	16 (5.1%)	0.229
All complications	46 (14.7%)	36 (11.5%)	0.236
Coronary dissection	9 (2.9%)	4 (1.3%)	0.161
Coronary perforation	0 (0%)	4 (1.3%)	0.045
Myocardial infarction	5 (1.6%)	4 (1.3%)	0.737
Cardiogenic shock	12 (3.8%)	11 (3.5%)	0.832
Heart failure	14 (4.5%)	7 (2.2%)	0.120
Cerebral infarction	0 (0%)	1 (0.3%)	0.317
Intracranial haemorrhage	0 (0%)	0 (0%)	
Cardiac tamponade	4 (1.3%)	4 (1.3%)	1.00
Dialysis	3 (1.0%)	3 (1.0%)	1.00
Transfusion	8 (2.6%)	10 (3.2%)	0.632
All bleeding	14 (4.5%)	10 (3.2%)	0.405
Puncture-site bleeding	4 (1.3%)	3 (1.0%)	0.704
Puncture-site haematoma	3 (1.0%)	2 (0.6%)	0.653
Peritoneal bleeding	0 (0%)	0 (0%)	
Vascular complication	7 (2.2%)	5 (1.6%)	0.560
Gastrointestinal bleeding	0 (0%)	0 (0%)	
Genitourinary bleeding	0 (0%)	0 (0%)	
Other bleeding	6 (1.9%)	5 (1.6%)	0.761
Length of hospital stay after PCI (days)	9 [6, 15]	10 [8, 13]	0.048

Limitations

There were several limitations in this study. First, this was an observational clinical trial and not a randomised trial. The use of VCD depended on the decision of the operator. We could not eliminate all confounding factors or the selection bias with the propensity score matching analysis. However, a randomised trial could not have revealed the safety of off-label VCD use. Second, we did not collect data on vascular injury, such as pseudoaneurysm, fistula, dissection, and stenosis/obstruction, collagen plug distal embolisation, neurological injury, infection, delayed VCD-related bleeding complications, and time to haemostasis. However, the incidence rates of these events were low, and objective definitions were extremely difficult and can potentially distort the results of the analysis. Our definition of puncture-site bleeding included bleeding requiring transfusion and procedural intervention/surgery. Thus, pseudoaneurysm and femoral artery occlusion requiring intervention were objectively recorded as a puncture-site bleeding. Besides, we showed the length of hospital stay after PCI. Third, bivalirudin, which is thought to be a part of a bleeding avoidance strategy[33], is not available in Japan. Since we mainly use unfractionated heparin to achieve a target activated clotting time, we could investigate the pure efficacy of VCD, regardless of the pharmacological effects in other studies[25]. Finally, we did not have data on preprocedural oral anticoagulation, liver function, size of the sheaths, and the operators' skill. These factors would affect vascular complications[5,6,29].

Conclusions

In conclusion, the use of VCD showed a similar rate of bleeding complications compared with the control, including in patients with off-label use. Although we must remain cautious about the use of VCD for female patients, our results demonstrate the safety of using VCD for Japanese patients. More studies are necessary to confirm the safety of VCD in different scenarios.

Impact on daily practice

Although Japanese patients are vulnerable to bleeding and the use of vascular closure devices was restricted to stable patients, we revealed the safety of vascular closure devices for on-label and off-label use in a large multicentre registry. Moreover, we found that female gender was an independent predictor of vascular complications with the use of vascular closure devices. Further studies, such as randomised studies, are needed to confirm the safety of VCD in different scenarios and to expand the labelling.

Funding

This research was supported by a grant from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (KAKENHI No. 25460630 and 25460777).

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:81-89

Clinical impact of revascularisation of chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation acute myocardial infarction undergoing primary percutaneous coronary intervention (from the CREDO-Kyoto AMI registry)

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KEYWORDS

- chronic coronary total occlusion
- multiple vessel disease
- ST-elevation myocardial infarction

Abstract

Aims: This study aimed to investigate the clinical effect of percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) in a non-infarct-related artery (IRA) on long-term cardiovascular outcomes in ST-elevation myocardial infarction (STEMI) patients.

Methods and results: The study population consisted of 134 STEMI patients undergoing primary PCI who received PCI for CTO in a non-IRA in the CREDO-Kyoto AMI registry. The patients were divided into two groups: 83 patients who underwent successful CTO-PCI (success group) and 51 patients who underwent failed CTO-PCI (failure group). We performed a landmark analysis set at 90 days to compare clinical outcomes in the groups. The cumulative five-year incidence of all-cause death was not significantly lower in the success group than in the failure group (19.8% vs. 15.4%, log-rank p=0.65). Similarly, the adjusted risk for all-cause death was not statistically different between the groups (adjusted hazard ratio: 1.64, 95% confidence interval: 0.63-5.05, p=0.32). No significant difference was observed between the groups in the cumulative incidence of cardiac death, non-cardiac death, myocardial infarction, heart failure hospitalisation, and any coronary revascularisation.

Conclusions: Successful PCI of CTO in non-IRA was not associated with improved five-year mortality in STEMI patients. Further larger studies are warranted to confirm the present findings.

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SUBMITTED ON 23/09/2016 - REVISION RECEIVED ON 1st 15/12/2016 / 2nd 22/12/2016 - ACCEPTED ON 31/12/2016

DOI: 10.4244/AsiaInterv_V3I1A16

Abbreviations

AMI	acute myocardial infarction
CABG	coronary artery bypass grafting
CI	confidence interval
CTO	chronic total occlusion
HR	hazard ratio
IRA	infarct-related artery
MI	myocardial infarction
MVD	multivessel disease
PCI	percutaneous coronary intervention
RCT	randomised controlled trial
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction

Introduction

ST-elevation myocardial infarction (STEMI) patients with multivessel disease (MVD), particularly with chronic total occlusion (CTO) in a non-infarct-related artery (IRA), have the worst prognosis according to several studies[1-4]. The reason is plausibly explained by several hypotheses, such as the presence of silent myocardial infarction (MI) and greater ischaemia in decreased collateral circulation as in acute coronary syndrome (ACS). However, those observational studies only suggested a close association between the presence of concurrent CTO and increased mortality, but did not prove a cause-and-effect relationship. Although intuitively plausible, it cannot be concluded that CTO in a non-IRA directly increases mortality in STEMI patients. To date, only a few reports are available about whether revascularisation of CTO in the non-IRA improves long-term outcomes in STEMI patients undergoing primary percutaneous coronary intervention (PCI)[5-7]. Hence, to assess the prognostic effect of CTO revascularisation, we sought to elucidate the clinical effectiveness of CTO-PCI in a non-IRA on long-term outcomes of STEMI patients in a large Japanese observational database of STEMI patients undergoing coronary revascularisation.

Methods

STUDY POPULATION

The Coronary Revascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto) AMI registry is a physician-initiated, non-company sponsored, multicentre registry. This study enrolled consecutive acute myocardial infarction (AMI) patients undergoing coronary revascularisation within seven days of symptom onset in 26 centres in Japan between January 2005 and December 2007 **(Appendix 1)**. The relevant review boards or ethics committees in all participating centres approved the research protocol. Written informed consent from the patients was waived because of retrospective enrolment. However, we excluded those patients who refused to participate in the study when contacted at follow-up. This strategy is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor and Welfare of Japan.

Among 5,429 AMI patients enrolled in the registry, 4,436 STEMI patients were treated by PCI. After excluding 3,935 patients who had no concurrent CTO and 55 patients who had a prior history of coronary artery bypass grafting (CABG), 446 patients had concurrent CTO in a non-IRA. Among the remaining 446 patients with CTO in the non-IRA, the current study population consisted of 134 STEMI patients who received CTO-PCI after excluding 31 patients who underwent CABG within 90 days of the index PCI, and 281 patients who did not receive CTO-PCI **(Figure 1)**. They were divided into two groups according to the status of CTO in the non-IRA: 83 patients who had successful PCI of a CTO in the non-IRA (61.9% initial patient success rate for CTO) (success group) and 51 patients who had failed CTO-PCI (38.1%) (failure group). Moreover, CTO revascularisation was attempted simultaneously with primary PCI for 42 out of the 134 patients (31.3%).

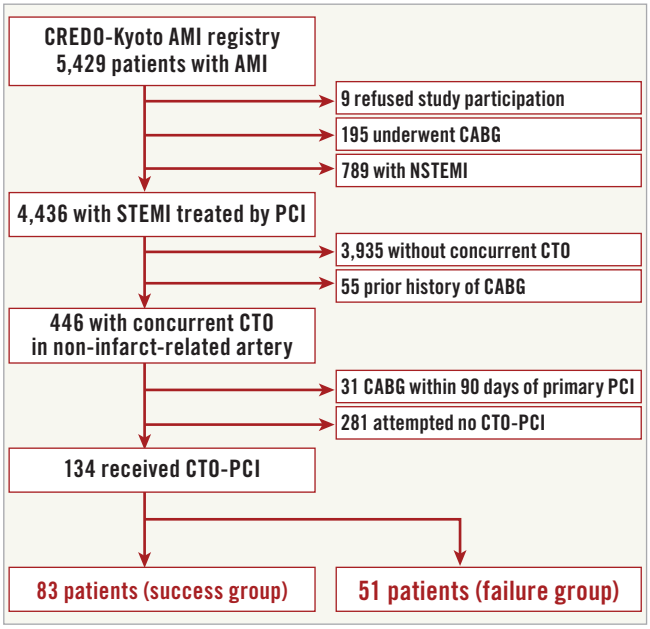


Figure 1. *Study flow chart. CABG: coronary artery bypass grafting; CREDO-Kyoto AMI registry: Coronary Revascularization Demonstrating Outcome Study in Kyoto Acute Myocardial Infarction registry; CTO: chronic total occlusion; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention*

DEFINITIONS AND ENDPOINTS

Definitions of baseline clinical characteristics were previously described in detail[8,9]. The initial perfusion status of the IRA was evaluated according to the Thrombolysis In Myocardial Infarction (TIMI) study classification. CTO was defined as complete obstruction of the vessel with a TIMI flow of 0 or 1 with an estimated duration of the occlusion >1 month or in the presence of collateral flow[10]. The duration of occlusion was evaluated by the investigators in each participating centre based on the interval from the last episode of MI in the target vessel territory, the previous coronary angiography, or changes in electrocardiographic findings. Staged PCI was pre-specified as PCI scheduled during the index hospitalisation and performed within 90 days of the index PCI.

The primary outcome measure for the current analysis was all-cause death. Secondary outcome measures included cardiac death, non-cardiac death, MI, heart failure hospitalisation, and any coronary revascularisation. Death was regarded as cardiac in origin unless evident non-cardiac causes could be identified. MI was defined according to the definition in the Arterial Revascularization Therapies Study[11]. Any coronary revascularisation was defined as either PCI or CABG for any reason.

DATA COLLECTION FOR BASELINE CHARACTERISTICS AND FOLLOW-UP EVENTS

Demographic, angiographic, and procedural data were collected from hospital charts or hospital databases according to the pre-specified definitions by experienced clinical research coordinators from the study management centre (Research Institute for Production Development, Kyoto, Japan) **(Appendix 2)**. In this retrospective cohort study, data collection for follow-up events was performed in 2010 and 2012. Collection of follow-up information was mainly conducted through review of in-patient and out-patient hospital charts by the clinical research coordinators. Additional follow-up information was collected through contact with patients, relatives, and/or referring physicians by sending mail with questions regarding vital status, subsequent hospitalisations, and status of antiplatelet therapy. Death, MI, ST, and stroke were adjudicated by the clinical events committee **(Appendix 3)**. Median follow-up duration was 1,709 (interquartile range [IQR]: 1,092-2,122) days.

STATISTICAL ANALYSIS

Categorical variables were expressed as numbers and percentages, and continuous variables as mean±standard deviation. Categorical variables were compared with the χ^2 test when appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared with the Student's t-test or the Wilcoxon rank-sum test based on their distributions. The Kaplan-Meier method was used to estimate cumulative incidences of clinical events, and the difference was evaluated with the log-rank test. We performed a landmark analysis at 90 days after primary PCI to compare the clinical outcomes between the success and the failure groups. Consistent with our previous reports, we used a multivariable Cox proportional hazards model to estimate the effect of the success group relative to the failure group for the primary and secondary outcome measures[8,9]. Given the small number of events, we selected the following three clinically relevant risk-adjusting variables for the Cox models: successful CTO-PCI, diabetes mellitus requiring insulin therapy, and haemodialysis. Adjusted hazard ratios (HR) and their 95% confidence intervals (CI) were calculated. Multivariable adjustment could not be conducted for several endpoints due to the small number of events. As in our previous reports, we dichotomised continuous variables by using clinically relevant reference values or median values. Statistical analyses were performed with the use of JMP 10.0 (SAS Institute Inc., Cary, NC, USA) software. All statistical analyses were two-tailed. P-values <0.05 were considered statistically significant.

Results

BASELINE CHARACTERISTICS

Baseline characteristics were very analogous except for only one aspect between the success and failure groups **(Table 1)**. More patients in the failure group received haemodialysis than in the success group. Similarly, few differences were found in the procedural and lesion characteristics between the two groups. In CTO-PCI, intravascular ultrasound was more often used in the success group than in the failure group. Moreover, more patients in the success group received complete revascularisation **(Table 2)**.

LONG-TERM CLINICAL OUTCOMES

Landmark analysis at 90 days showed that the cumulative incidence of all-cause death beyond 90 days and up to five years was not significantly lower in the success group than in the failure group (19.8% vs. 15.4%, log rank p=0.65) **(Table 3, Figure 2)**. Even after adjusting for confounders, no significant difference was observed in the adjusted risk of the success group relative to the failure group for all-cause death beyond 90 days and up to five years (HR 1.64, 95% CI: 0.63-5.05, p=0.32) **(Table 3)**.

The cumulative five-year incidences of cardiac death, non-cardiac death, MI, and heart failure hospitalisation and any coronary revascularisation were not significantly different between the success and failure groups **(Table 3)**. The adjusted risk of the success group as compared to the failure group for any coronary revascularisation was not significantly different **(Table 3)**.

Discussion

The main findings in the current analysis were as follows. First, only approximately two thirds of STEMI patients with CTO in the non-IRA received successful CTO-PCI. Second, successful PCI of CTO in the non-IRA was not associated with improved all-cause mortality in STEMI patients who underwent primary PCI.

Whether revascularisation of a CTO could improve mortality in STEMI patients remains unknown due to a paucity of data. No randomised controlled trials (RCT) have been conducted to assess the clinical effect of staged revascularisation of a CTO in a non-IRA to date. Three observational studies have demonstrated the clinical efficacy of staged PCI for CTO in a non-IRA in AMI patients[5-7]. However, these studies had varied population sizes and were confounded by the small sample size and low patient success rate of CTO-PCI. Yang et al compared successful CTO-PCI and failed CTO-PCI. They reported that successful CTO-PCI (87 patients) improved cardiac mortality in 136 STEMI patients (patient success rate: 64%) at two-year follow-up[5]. Valentine et al compared successful CTO-PCI and failed/non-attempted CTO-PCI. They showed that successful CTO-PCI (58 patients) was statistically significantly associated with improved mortality in 169 AMI patients (patient success rate: 78%) at one-year follow-up[7]. In the current study, the cumulative incidence of all-cause death beyond 90 days and up to five years was not significantly different between the success and the failure groups. Similarly, the adjusted risk for all-cause death was similar between the groups.

Table 1. Baseline patient characteristics.

Variables	Success group N=83	Failure group N=51	*p*-value
Clinical characteristics			
Age (years)	66.4±12.4	66.9±11.6	0.82
>75 years	29 (34.9%)	14 (27.5%)	0.36
Male	66 (79.5%)	42 (82.4%)	0.69
Body mass index (kg/m²)	24.4±3.6	24.9±3.5	0.44
<25.0 kg/m²	54 (65.1%)	29 (56.9%)	0.34
Hypertension	63 (75.9%)	44 (86.3%)	0.14
Diabetes mellitus	32 (38.6%)	14 (27.5%)	0.19
requiring insulin therapy	5 (6.0%)	3 (5.9%)	0.97
Current smoking	35 (42.2%)	24 (47.1%)	0.58
Prior and current heart failure	36 (43.4%)	25 (49.0%)	0.52
Mitral regurgitation 3-4/4	2 (2.4%)	4 (7.8%)	0.15
Prior myocardial infarction	8 (9.6%)	9 (17.7%)	0.18
Prior stroke	9 (10.8%)	2 (3.9%)	0.14
Peripheral vascular disease	2 (2.4%)	2 (3.9%)	0.62
eGFR <30, without haemodialysis	2 (2.4%)	4 (7.8%)	0.15
Haemodialysis	0	2 (3.9%)	0.048
Left ventricular ejection fraction	49.0±13.8 (67)	48.4±13.9 (36)	0.82
<40%	16/67 (23.9%)	9/36 (25.0%)	0.90
Atrial fibrillation	8 (9.6%)	7 (13.7%)	0.47
Anaemia (haemoglobin <11.0 g/dl)	2 (2.4%)	3 (5.9%)	0.31
Thrombocytopaenia (platelet <100*109/L)	2 (2.4%)	0	0.16
Liver cirrhosis	2 (2.4%)	1 (2.0%)	0.86
Malignancy	5 (6.0%)	2 (3.9%)	0.59
Peak creatinine phosphokinase (IU/L)	2,466 (1,312-5,261)	1,683 (828-4,590)	0.12
Presentation of STEMI			
Killip class ≤II	61 (73.5%)	35 (68.6%)	0.55
Killip class IV	19 (22.9%)	12 (23.5%)	0.93
Anterior MI	37 (44.6%)	15 (29.4%)	0.08
Onset-to-presentation time (hours)	1.9 (1.1-5.9) (82)	3.1 (1.5-7.4) (49)	0.12
Onset-to-balloon time (hours)	4.3 (2.8-8.7) (74)	4.7 (3.5-12.3) (43)	0.12
Door-to-balloon time (hours)	1.5 (1.0-2.4) (74)	1.6 (1.1-2.8) (43)	0.59
Medication at discharge			
Aspirin	82 (98.8%)	48 (94.1%)	0.13
Thienopyridine	80 (96.4%)	48 (94.1%)	0.54
Cilostazole	34 (41.0%)	14 (27.5%)	0.11
Statin	47 (56.6%)	27 (52.9%)	0.68
ACE-I/ARB	63 (75.9%)	43 (84.3%)	0.24
ß-blocker	33 (39.8%)	24 (47.1%)	0.41
Calcium channel blocker	14 (16.9%)	11 (21.6%)	0.50
Nitrate	23 (27.7%)	18 (35.3%)	0.36
Nicorandil	23 (27.7%)	15 (29.4%)	0.83
Warfarin	6 (7.2%)	8 (15.7%)	0.13
PPI	34 (41.0%)	18 (35.3%)	0.51
H2 blocker	21 (25.3%)	16 (31.4%)	0.45

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean±SD or median (interquartile range). ACE-I/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; PPI: proton pump inhibitor; STEMI: ST-segment elevation myocardial infarction

Table 2. Angiographic and procedural characteristics.

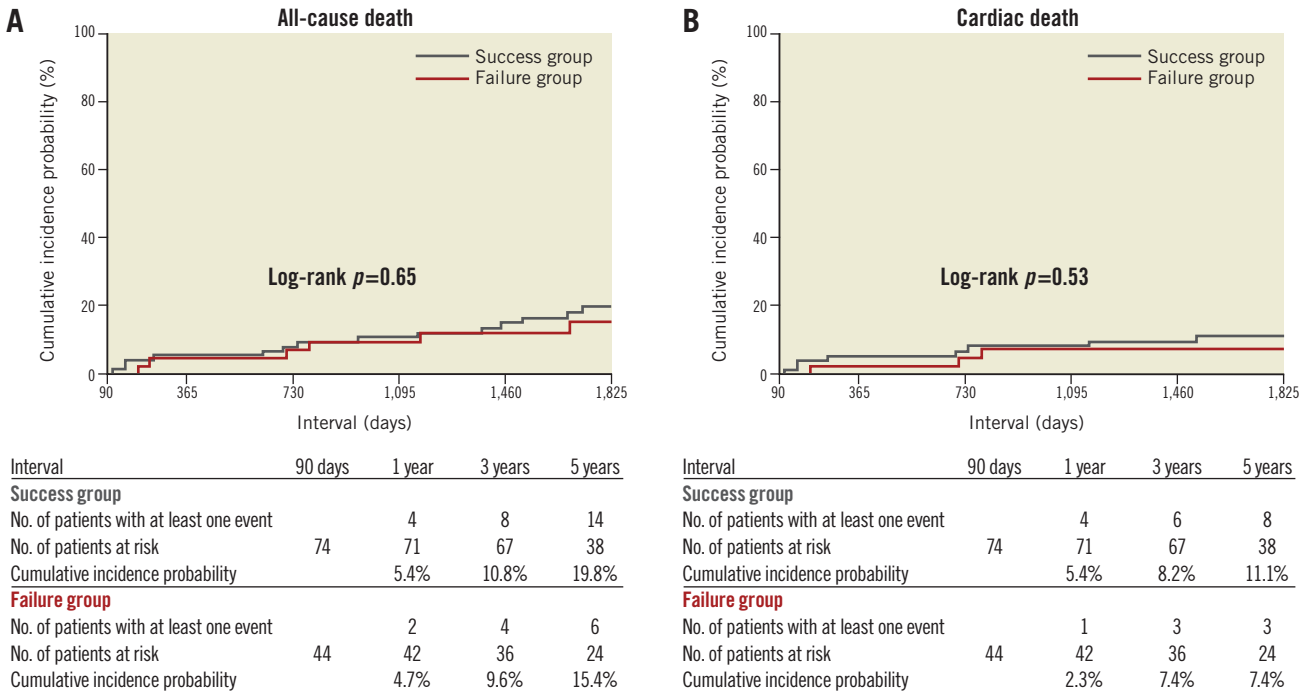
Variables		Success group N=83	Failure group N=51	*p*-value
Primary PCI				
Infarct-related artery	Proximal LAD	32 (38.6%)	14 (27.5%)	0.19
	LAD	35 (42.2%)	16 (31.4%)	0.21
	LCX	11 (13.3%)	7 (13.7%)	0.94
	RCA	34 (41.0%)	27 (52.9%)	0.18
	Unprotected LMCA	3 (3.6%)	1 (2.0%)	0.57
DES use		50 (60.2%)	–	–
Contrast media (ml)		189 (144-266) (70)	200 (132-251) (41)	0.81
Implanted stents		1 (1-2) (77)	1 (1-1) (40)	0.40
Total stent length (mm)		23.5 (18-30.75) (76)	23 (18-30) (39)	0.95
>28 mm		23/76 (30.3%)	11/39 (28.2%)	0.82
Minimal stent diameter (mm)		3.0 (3.0-3.5) (76)	3.0 (3.0-3.5) (39)	0.56
<3.0 mm		16/76 (21.1%)	6/39 (15.4%)	0.46
Thrombectomy		42 (50.6%)	26 (51.0%)	0.97
Distal protection		5 (6.0%)	2 (3.9%)	0.59
IVUS use		15 (18.1%)	8 (15.7%)	0.72
IABP use		33 (39.8%)	19 (37.3%)	0.77
PCPS use		6 (7.2%)	4 (7.8%)	0.90
CTO-PCI				
Number of CTO (interquartile range)		1 (1-1)	1 (1-1)	0.36
Location of CTO	LAD	36 (43.4%)	23 (45.1%)	0.85
	LCX	31 (37.4%)	15 (29.4%)	0.34
	RCA	26 (31.3%)	18 (35.3%)	0.64
Location of target CTO	LAD	31 (37.4%)	22 (43.1%)	0.51
	LCX	28 (33.7%)	13 (25.5%)	0.31
	RCA	25 (30.1%)	17 (33.3%)	0.70
IVUS use		23 (27.7%)	4 (7.8%)	0.003
Contrast media		249±107	234±106	0.49
Interval of CTO-PCI after primary PCI (days)		11 (0-17)	6 (0-16)	0.11
CTO-PCI on Day 0		21(25%)	21(41%)	0.06
DES use		50 (60.2%)	–	–
Implanted stents		1 (1-2) (76)	–	–
Total stent length (mm)		33 (23-56) (65)	–	–
>28 mm		35/65 (53.9%)	–	–
Minimal stent diameter (mm)		2.5 (2.5-3.0) (65)	–	–
<3.0 mm		42/65 (64.6%)	–	–
Procedural complication	Slow flow	3 (3.6%)	0	0.09
	Acute occlusion	1 (1.2%)	0	0.33
	Coronary perforation	0	1 (2.0%)	0.16
Overall procedures				
PCI for LMT		4 (4.8%)	1 (2.0%)	0.38
Non-IRA, non-CTO-PCI		28 (33.7%)	16 (31.4%)	0.78
Complete revascularisation		60 (72.3%)	0	<0.001

Categorical variables are expressed as number (%) unless otherwise indicated. Continuous variables are shown as mean±SD or median (interquartile range). CTO: chronic total occlusion; DES: drug-eluting stent; IABP: intra-aortic balloon pumping; IRA: infarct-related artery; IVUS: intravascular ultrasound; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LMCA: left main coronary artery; PCI: percutaneous coronary intervention; PCPS: percutaneous cardiopulmonary support; RCA: right coronary artery

Table 3. Crude and adjusted 5-year clinical outcomes: success group versus failure group.

Variable	Success group No. of patients with events (cumulative incidence) N=83	Failure group No. of patients with events (cumulative incidence) N=51	Crude HR (95% CI)	*p*-value (log-rank)	Adjusted HR (95% CI)	*p*-value
All-cause death	14 (19.8%)	6 (15.4%)	1.23 (0.52-3.23)	0.65	1.64 (0.63–5.05)	0.32
Cardiac death	8 (11.1%)	3 (7.4%)	1.52 (0.44-6.93)	0.53	–	–
Non-cardiac death	6 (9.8%)	3 (8.7%)	1.01 (0.31-3.88)	0.98	–	–
Myocardial infarction	3 (5.2%)	3 (10.0%)	0.53 (0.10-2.87)	0.43	–	–
Heart failure hospitalisation	7 (10.3%)	4 (10.2%)	1.01 (0.30-3.84)	0.99	–	–
Any coronary revascularisation	38 (56.4%)	16 (48.7%)	1.03 (0.59-1.86)	0.93	1.08 (0.61-1.99)	0.79

Cumulative incidence was estimated by the Kaplan-Meier method. CABG: coronary artery bypass grafting; CI: confidence interval; HR: hazard ratio



Interval	90 days	1 year	3 years	5 years
Success group				
No. of patients with at least one event		4	8	14
No. of patients at risk	74	71	67	38
Cumulative incidence probability		5.4%	10.8%	19.8%
Failure group				
No. of patients with at least one event		2	4	6
No. of patients at risk	44	42	36	24
Cumulative incidence probability		4.7%	9.6%	15.4%

Interval	90 days	1 year	3 years	5 years
Success group				
No. of patients with at least one event		4	6	8
No. of patients at risk	74	71	67	38
Cumulative incidence probability		5.4%	8.2%	11.1%
Failure group				
No. of patients with at least one event		1	3	3
No. of patients at risk	44	42	36	24
Cumulative incidence probability		2.3%	7.4%	7.4%

Figure 2. *Crude Kaplan-Meier curves for the cumulative incidence of all-cause death and cardiac death in the success and failure groups.*

The current study mainly focused on the analysis of the long-term effect of successful CTO revascularisation. The effect of CTO revascularisation in STEMI patients should be evaluated according to clinical settings. On the one hand, in the acute setting, emergent multivessel revascularisation was sometimes unavoidable, as in AMI patients complicated by cardiogenic shock (CS). The purpose of this strategy is the restoration of haemodynamic stability because of ongoing large ischaemia, which often involves CTO revascularisation. The clinical efficacy of acute multivessel PCI in the CS setting was assessed in several observational studies, but remains controversial due to inconsistent results[12,13]. On the other hand, in the subacute and chronic phases, the presumed advantage of CTO-PCI was recovery of contraction in hibernating viable myocardium.

Given that low left ventricular ejection fraction (LVEF) was a strong prognostic indicator, CTO revascularisation based on adequate assessment of myocardial viability was expected to result in better clinical outcomes. The EXPLORE trial, assessing the effect of early CTO-PCI on LVEF and left ventricular end-diastolic volume (LVEDV) at a four-month follow-up,

demonstrated that the staged PCI of non-IRA CTO within a week of primary PCI was not associated with improvement of LVEF or LVEDV (44.1±12.2% vs. 44.8±11.9%, p=0.60)[14]. However, a subgroup analysis suggested the clinical benefit from LAD-CTO revascularisation, which was endorsed by previous observational studies[15,16]. Thus, further investigations should be performed on this topic. Staged revascularisation of CTO in the non-IRA was part of a staged multivessel PCI strategy in STEMI patients. Recent RCT have suggested that a multivessel revascularisation strategy is a safe and acceptable alternative compared with a culprit-only PCI strategy[17-19]. Complete revascularisation was the prerequisite of a staged multivessel revascularisation strategy in most previous observational and randomised studies. However, numerous studies with positive results excluded patients with CTO in the non-IRA due to the difficulty in achieving complete revascularisation.

One of the latest randomised studies, CvLPRIT (Complete Versus culprit-Lesion only PRimary PCI Trial), which excluded STEMI patients with CTO in the non-IRA, randomised 296 STEMI patients to complete versus culprit lesion-only revascularisation. It resulted in significant reduction in the primary endpoint of MACE (mortality, recurrent MI, heart failure, or ischaemia-driven revascularisation within 12 months [10.0% vs. 21.2%; HR 0.45; p=0.009])[19].

As the techniques and devices for CTO revascularisation have evolved over time, more data about revascularisation of CTO in the non-IRA should be obtained to elucidate its clinical relevance in STEMI patients with MVD.

Limitations

The current study has several limitations. First, this retrospective observational study could not exclude unmeasured confounders despite multivariable adjustment. Second, compared with the results in CTO revascularisation in stable coronary disease, the procedural success rate of CTO-PCI was very low in this study and does not reflect the contemporary success rate of CTO-PCI. The main strategy of CTO-PCI in the study period was only antegrade wiring. The second-generation DES and other supplementary devices, including newly developed CTO guidewires and channel dilation microcatheters, many of which were not available in the study period, have been widely used in the current CTO-PCI. Therefore, the current study result cannot be directly applied to contemporary CTO-PCI. Finally, the number of study patients was too small to draw solid conclusions. Furthermore, the study population in our current analysis included those who received CTO-PCI simultaneously with primary PCI. Multivessel revascularisation at the primary PCI had a different clinical role because it was often performed due to haemodynamic instability, such as in cardiogenic shock.

Conclusions

Successful PCI of CTO in a non-IRA was not associated with a better five-year mortality rate in STEMI patients who underwent primary PCI.

Impact on daily practice

Our analysis shows real data about the management of non-infarct-related CTO in STEMI patients who underwent primary PCI. When we evaluated the advantage of CTO-PCI in STEMI patients, meticulous discussion was required according to the clinical situation. CTO-PCI should play a pivotal role both in emergency situations such as cardiogenic shock, and in the chronic phase where the recovery of lost LVEF is indispensable. Larger sample-size cohort studies and randomised trials are warranted on this topic.

Appendix 1

LIST OF PARTICIPATING CENTRES AND INVESTIGATORS FOR THE CREDO-KYOTO PCI/CABG REGISTRY COHORT-2

CARDIOLOGY

Kyoto University Hospital: Takeshi Kimura; *Kishiwada City Hospital:* Mitsuo Matsuda, Hirokazu Mitsuoka; *Tenri Hospital:* Yoshihisa Nakagawa; *Hyogo Prefectural Amagasaki Hospital:* Hisayoshi Fujiwara, Yoshiki Takatsu, Ryoji Taniguchi; *Kitano Hospital:* Ryuji Nohara; *Koto Memorial Hospital:* Tomoyuki Murakami, Teruki Takeda; *Kokura Memorial Hospital:* Masakiyo Nobuyoshi, Masashi Iwabuchi; *Maizuru Kyosai Hospital:* Ryozo Tatami; *Nara Hospital, Kinki University Faculty of Medicine:* Manabu Shirotani; *Kobe City Medical Center General Hospital:* Toru Kita, Yutaka Furukawa, Natsuhiko Ehara; *Nishi-Kobe Medical Center:* Hiroshi Kato, Hiroshi Eizawa; *Kansai Denryoku Hospital:* Katsuhisa Ishii; *Osaka Red Cross Hospital:* Masaru Tanaka; *University of Fukui Hospital:* Jong-Dae Lee, Akira Nakano; *Shizuoka City Shizuoka Hospital:* Akinori Takizawa; *Hamamatsu Rosai Hospital:* Masaaki Takahashi; *Shiga University of Medical Science Hospital:* Minoru Horie, Hiroyuki Takashima; *Japanese Red Cross Wakayama Medical Center:* Takashi Tamura; Shimabara Hospital: Mamoru Takahashi; *Kagoshima University Medical and Dental Hospital:* Chuwa Tei, Shuichi Hamasaki; *Shizuoka General Hospital:* Hirofumi Kambara, Osamu Doi, Satoshi Kaburagi; *Kurashiki Central Hospital:* Kazuaki Mitsudo, Kazushige Kadota; *Mitsubishi Kyoto Hospital:* Shinji Miki, Tetsu Mizoguchi; *Kumamoto University Hospital:* Hisao Ogawa, Seigo Sugiyama; *Shimada Municipal Hospital:* Ryuichi Hattori, Takeshi Aoyama, Makoto Araki; *Juntendo University Shizuoka Hospital:* Satoru Suwa.

CARDIOVASCULAR SURGERY

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Mitsuomi Shimamoto, Fumio Yamazaki; *Hamamatsu Rosai Hospital:* Junichiro Nishizawa; *Japanese Red Cross Wakayama Medical Center:* Masaki Aota; *Shimabara Hospital:* Takafumi Tabata; *Kagoshima University Medical and Dental Hospital:* Yutaka Imoto, Hiroyuki Yamamoto; *Shizuoka General Hospital:* Katsuhiko Matsuda, Masafumi Nara; *Kurashiki Central Hospital:* Tatsuhiko Komiya; *Mitsubishi Kyoto Hospital:* Hiroyuki Nakajima; *Kumamoto University Hospital:* Michio Kawasuji, Syuji Moriyama; *Juntendo University Shizuoka Hospital:* Keiichi Tanbara.

Appendix 2

LIST OF CLINICAL RESEARCH COORDINATORS

RESEARCH INSTITUTE FOR PRODUCTION DEVELOPMENT

Kumiko Kitagawa, Misato Yamauchi, Naoko Okamoto, Yumika Fujino, Saori Tezuka, Asuka Saeki, Miya Hanazawa, Yuki Sato, Chikako Hibi, Hitomi Sasae, Emi Takinami, Yuriko Uchida, Yuko Yamamoto, Satoko Nishida, Mai Yoshimoto, Sachiko Maeda, Izumi Miki, Saeko Minematsu.

Appendix 3

LIST OF CLINICAL EVENTS COMMITTEE MEMBERS

Mitsuru Abe, *Kyoto Medical Center*; Hiroki Shiomi, *Kyoto University Hospital*; Tomohisa Tada, *Kyoto University Hospital*; Junichi Tazaki, *Kyoto University Hospital*; Yoshihiro Kato, *Kyoto University Hospital*; Mamoru Hayano, *Kyoto University Hospital*; Akihiro Tokushige, *Kyoto University Hospital*; Masahiro Natsuaki, *Kyoto University Hospital*; Tetsu Nakajima, *Kyoto University Hospital*.

Acknowledgements

We appreciate the collaboration of the co-investigators in the CREDO-Kyoto PCI/CABG Registry Cohort-2.

Funding

The CREDO-Kyoto AMI registry was supported by the Ministry of Health, Labor and Welfare, and the Pharmaceuticals and Medical Devices Agency in Japan.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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AsiaIntervention 2017;3:90-92

Buddy wire technique for successful transfemoral transcatheter aortic valve implantation through an extremely tortuous abdominal aorta: a basic technique in Asian patients?

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Abstract

Recent papers have reported better outcomes in transfemoral (TF) transcatheter aortic valve implantation (TAVI) than with transapical and direct aortic approaches. However, TF TAVI is challenging in a case with an extremely tortuous access route. Our case highlights the feasibility of TF TAVI in the presence of extreme tortuosity in the abdominal aorta if the "buddy wire technique" is appropriately utilised. Asian operators should become familiar with this technique, as the angle of the abdominal aorta may be more acute in Asians than in Caucasians.

Introduction

Recently, the Placement of Aortic Transcatheter Valves (PARTNER) 2 trial demonstrated that the rate of death or disabling stroke was similar between transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (sAVR), even in intermediate-risk patients with severe aortic stenosis (AS)[1]. In this trial, transfemoral (TF) TAVI resulted in a lower rate of this endpoint than sAVR at two years. In addition, recent papers have reported better outcomes in TF TAVI than with the transapical and direct aortic approaches[2-4]. One of the potential anatomical issues encountered with TF TAVI is severe tortuosity of the access route. A "buddy wire technique" using stiff wires is a potential solution for this situation by straightening a tortuous access route; however, to the best of our knowledge, this has never been reported in Asian patients. Herein, we report a case with an extremely tortuous abdominal aorta which was successfully treated with TF TAVI using the buddy wire technique.

Case report

A frail, 89-year-old woman was diagnosed with symptomatic severe AS. Transthoracic echocardiography revealed severe degenerative AS with an area of 0.3 cm^2 and a mean aortic valve pressure gradient (AVPG) of 104 mmHg. Moderate aortic regurgitation was also detected, with a decreased left ventricular ejection fraction (40%). Multislice computed tomography showed an aortic annulus perimeter of 67.0 mm and an extremely tortuous abdominal aorta **(Figure 1A, Figure 1B)**. Minimum lumen diameters in the bilateral iliac to femoral arteries were at least 6.0 mm, but only 4.6 mm in the left subclavian artery. Furthermore, the ascending aorta was dilated (45 mm). In view of the high surgical risk based on the logistic European System

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SUBMITTED ON 30/07/2016 - REVISION RECEIVED ON 24/10/2016 - ACCEPTED ON 14/11/2016

DOI: 10.4244/AsiaInterv_V3I1A17

AsiaIntervention 2017;3:90-92

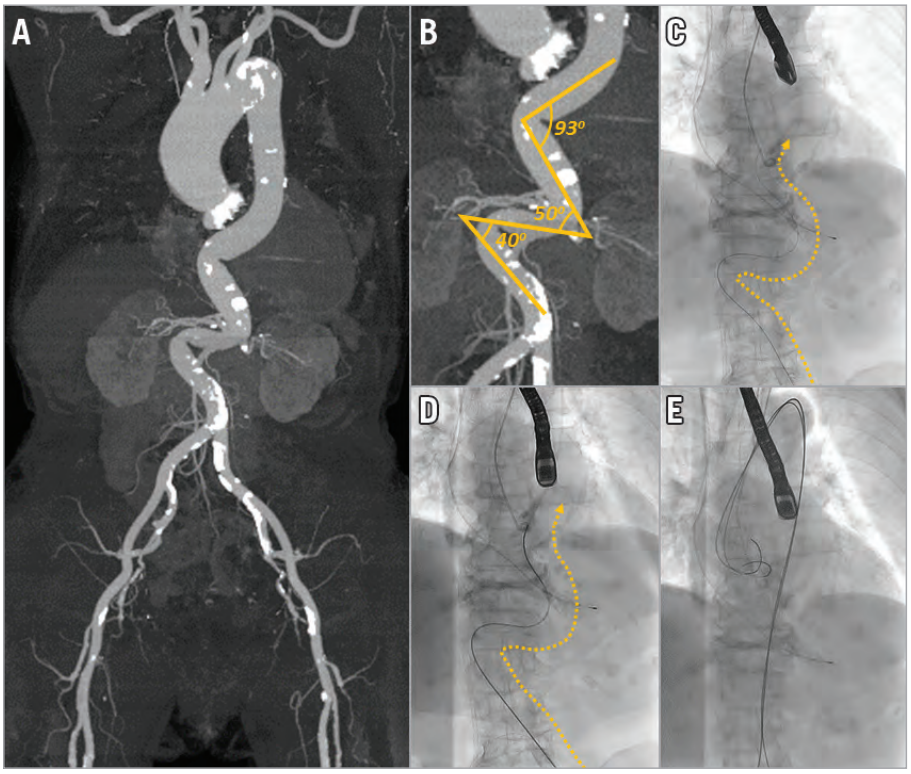

Figure 1. *Extremely tortuous abdominal aorta. A) & B) Computed tomography showing extremely tortuous abdominal aorta. C) Radifocus guidewire M with a 4 Fr Judkins right 4.0 catheter from the left femoral artery (dotted arrow). D) Lunderquist wire through the 4 Fr Judkins right 4.0 catheter from the left femoral artery (dotted arrow). E) Buddy wire technique with two Lunderquist wires from the bilateral femoral arteries.*

for Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgeons (STS) scores of 51.6% and 12.2%, respectively, a decision was made to perform TAVI. The procedure was performed via the right transfemoral approach, because of dissection risk in the dilated ascending aorta with a direct aortic approach and too small a lumen diameter for a trans-subclavian approach. First, a 300 cm Radifocus® guidewire M (Terumo Corp., Tokyo, Japan) was advanced from the left femoral artery towards the sinus of Valsalva with a 4 Fr Judkins right 4.0 catheter **(Figure 1C)**. This was replaced with a 260 cm Lunderquist® wire (Cook Medical, Bloomington, IN, USA) **(Figure 1D)**. However, a single Lunderquist wire was not adequate to straighten the tortuous abdominal aorta. Only after this manoeuvre was repeated from the right side using the buddy wire technique was the tortuosity completely straightened **(Figure 1E)**. Next, an 18 Fr 40 cm Check-Flo® sheath (Cook Medical) was smoothly advanced from the right femoral artery until the tip of the sheath was proximal to the bends in the aorta **(Figure 2A)**. After placing the sheath, a 26 mm CoreValve® (Medtronic, Minneapolis, MN, USA) was successfully advanced and deployed following predilatation with an 18 mm balloon **(Figure 2B, Figure 2C)**. There were no vascular complications **(Figure 2D)**. Transthoracic echocardiography at one week showed a well-seated prosthesis with an acceptable AVPG (9 mmHg) and a trivial paravalvular leak.

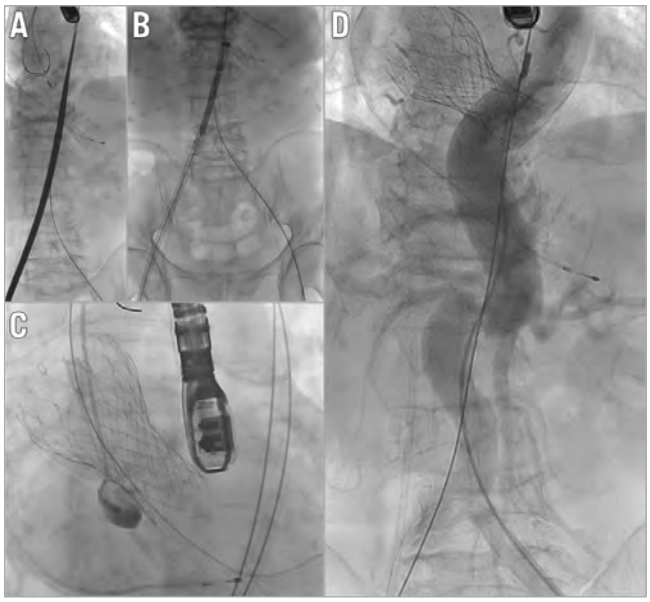

Figure 2. *Successful CoreValve implantation with the buddy wire technique. A) Smooth advancement of an 18 Fr 40 cm Check-Flo sheath on the right-side Lunderquist wire. B) Smooth delivery of a 26 mm CoreValve. C) Successful implantation of a 26 mm CoreValve. D) Post-procedural aortography showing no evidence of aortic injuries.*

Discussion

Asian operators should become familiar with this technique, as the angle of the abdominal aorta may be more acute in Asians than in Caucasians[5]. Since the flexural modulus of the Lunderquist wire has been reported to be the largest among commercially available wires (158.4 gigapascals)[6], it should be chosen to straighten aortic and/or iliac bends. We recommend using a long sheath for such cases because once the tip of the sheath has been advanced and placed proximal to the aortic and/or iliac bends it should be easy to deliver a TAVI system. By using these manoeuvres and straightening the access route through the aortic and iliac arteries, it is possible that even devices with relatively inflexible delivery systems can be used. A potential complication of this technique may be injury to the access route if a shortcut is used for placement of these extremely stiff wires. Therefore, post-procedural assessments with aortography and/or echo may be required.

Conclusions

Our case highlights the feasibility of TF TAVI in the presence of extreme tortuosity in the abdominal aorta if the buddy wire technique is utilised appropriately.

Impact on daily practice

TF TAVI is feasible even in the presence of extreme tortuosity in the abdominal aorta if the buddy wire technique is appropriately utilised.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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