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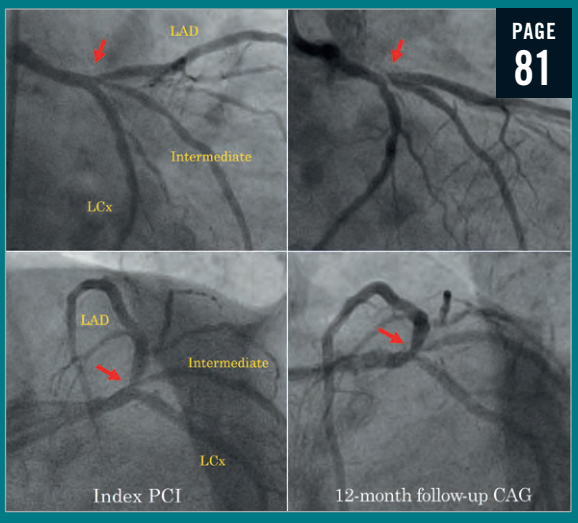

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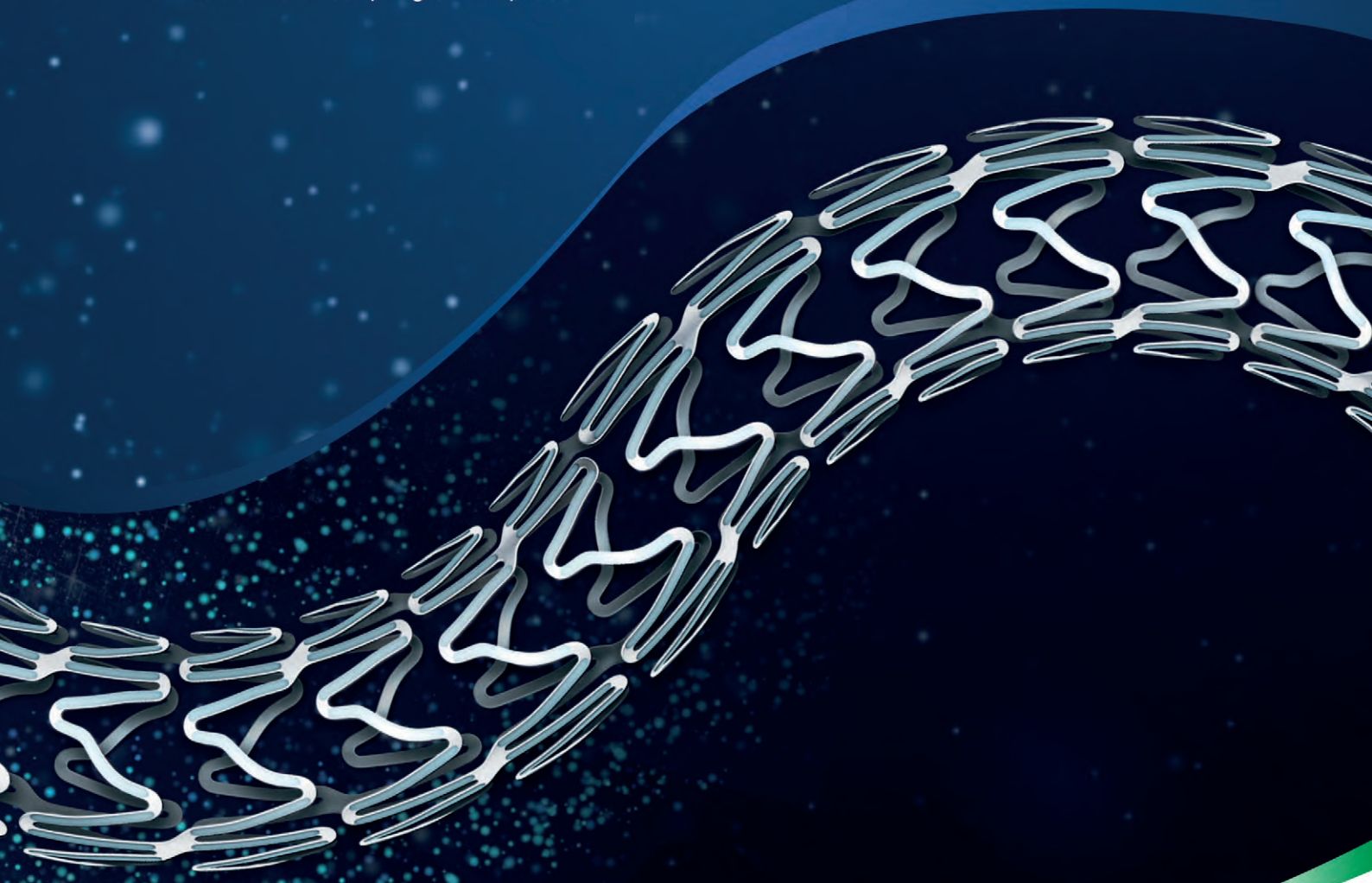

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AsiaIntervention, a new Journal dedicated to interventional cardiology in the Asia-Pacific Rim

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AsiaIntervention 2015;1:5-7

The official launch of AsiaIntervention

Runlin Gao, Uprenda Kaul, Takeshi Kimura, Seung-Jung Park, *Chief Editors, AsiaIntervention*

Congratulations to the Asia-Pacific interventional cardiology community

Runlin Gao, MD

Department of Cardiology, FuWai Hospital, National Center for Cardiovascular Diseases, Beijing, China

AsiaIntervention, a new journal dedicated to the field of cardiovascular intervention with particular emphasis on scientific contributions from the Asia-Pacific region, is officially launched with this inaugural issue. The Asia-Pacific interventional cardiology community ought to be congratulated for this achievement.

Alongside its formidable economic development, the Asia-Pacific region, which accounts for over 60% of the world population, has experienced the most rapid expansion in interventional cardiology worldwide. This new era for the region has witnessed an ever growing number of percutaneous coronary interventions (PCI), and the introduction in many Asian countries of transcatheter aortic valve replacement (TAVR) and novel technologies, such as a mitral clip and parachute device to isolate the malfunctioning portion of the left ventricle in ischaemic heart disease, among others.

Take China for example. After the first percutaneous transluminal coronary angioplasty (PTCA) was performed in 1985, its adoption was very slow during the first 10 years with only 11,735 cases treated in 110 hospitals by the year 2000. However, the last decade has witnessed an exponential growth in the number of PCI cases: in 2013, for instance, a total of 454,505 procedures were performed in more than 1,000 hospitals. Expansion of the PCI case-load also fuelled research and development of, for instance, new drug-eluting stents, including fully bioabsorbable ones, and TAVR devices. To this end, the pre-marketing clinical trial of a Chinese manufactured polymer bioabsorbable sirolimus-eluting stent is ongoing, while patient enrolment has been completed in a trial on a Chinese manufactured self-expandable TAVR device.

The expansion in interventional cardiology is also reflected in the many high-quality papers originating from the Asia-Pacific region which have been published in world-renowned journals. Expanded clinical practice has also promoted academic exchanges and educational programmes. There are currently many high-level academic conferences in the Asia region, such as AsiaPCR/SingLive, TCTAP, CCT, IndiaLive and CIT. These meetings play an important role in promoting scientific exchanges through lectures, oral presentations of late-breaking trials and live demonstrations. Obviously, this body of knowledge needs to be captured in the more enduring medium of the written word. Although there are quite a number of journals in the Asia-Pacific region, either in native languages or in English, none is dedicated to publishing work in the interventional cardiology field primarily originating from within our Asia-pacific region. This is why we launched AsiaIntervention as a journal dedicated specifically to the region.

Credit is due to Professor Patrick Serruys, the Editor-in-Chief of EuroIntervention, for the idea of launching this new journal. Professor Serruys will be Senior Consulting Editor to the Chief Editors. He will be assisted by Dr Christoph Naber. The Editorial Office of EuroIntervention will help to manage administrative affairs in the initial stage. I would like to express my sincere thanks to Prof. Serruys, Dr Naber, Mr Paul Cummins, Ms Sylvie Lhoste and all the staff from EuroIntervention. It is my conviction that, with their strong support and guidance, AsiaIntervention will quickly flourish.

I would like to invite colleagues from the Asia-Pacific region as well as from other parts of the world to submit to AsiaIntervention high-quality research and educational work in the field of percutaneous and surgical cardiovascular interventions. Let us come together to make this journal a great success and to help it quickly develop from a newborn to an adult, measuring up to and exceeding the best.

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A new journal is with us: AsiaIntervention

Upendra Kaul, MD

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

A new journal, AsiaIntervention, is with us. Is it yet another journal for interventional cardiologists of the region or does it add some additional value over the existing forums?

The Asian region has peculiarities in cardiovascular diseases and the risk factors associated with these, such as diffuse vascular disease and small vessels with earlier onset of presentation. This is often associated with a very high prevalence of diabetes mellitus and dysmetabolic syndrome, making interventional treatment challenging in several situations. Valvular heart disease with rheumatic heart disease involving younger patients as well as the burden of degenerative valve disease in the elderly which is increasingly seen, pose a dual challenge at both ends of the spectrum. Special mention should be made of aortoarteritis, a unique problem of this region rarely seen in industrialised countries in Europe and the American continent.

Uneven distribution of healthcare delivery systems in some highly populated countries such as India, China, Indonesia, etc., requires innovative methods of delivering cost-effective therapies. These then need to be proven for their efficacy and safety and reported in the scientific literature. The region also has countries like Japan and Korea which have excelled in treatment strategies in focused areas of coronary artery disease, giving the world a lead in PCI of chronic total occlusions and left main disease.

There are all sufficient reasons – among others – for starting a journal with a focus on Asia, and for this new journal to become a forum perfectly complementary with EuroIntervention, which is, itself, gaining recognition and popularity at a rapid pace. I am very optimistic that it will in time become a widely quoted and read journal of interventional cardiologists of the region.

Greetings for the launch of AsiaIntervention

Takeshi Kimura, MD

Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

I am very pleased and honoured to be one of the Editors-in-Chief of the new journal AsiaIntervention. It is really remarkable to see the marked increase in the number of scientific articles in the international cardiology journals from Asian countries. Also, the recent contributions of Asian cardiologists to international cardiology meetings, such as ACC, AHA, ESC, EuroPCR, and TCT, are unprecedented. Global trials in cardiovascular medicine are of course very important, and we should actively participate in these trials. At the same time, we should have clinical studies dedicated to Asian patients, because the risks for thrombosis and bleeding of Asian patients might be different from those of European and American patients. The new journal AsiaIntervention will be a relevant journal in which to publish cardiovascular studies dedicated to Asian patients, and to discuss the optimal treatment strategies for Asian patients. Many young cardiologists in Asia are highly motivated to publish original articles. We would particularly welcome submissions from young Asian investigators in interventional cardiology and related fields. Finally, we appreciate the kind support for AsiaIntervention from the Consulting Editors, P.W. Serruys and C. Naber.

AsiaIntervention: the beginning of a new future

Seung-Jung Park, MD, PhD

Department of Cardiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Today, interventional cardiology, which encompasses coronary intervention, peripheral vascular intervention, structural heart disease and congenital heart disease, has realised tremendous growth in a considerable number of Asian countries. An incredible number of Asian colleagues, institutes, and countries have participated in major international scientific evaluations and meetings, and have contributed to worldwide dissemination of the latest developments in interventional cardiology. Along with this increase in our participation, a premier journal focusing on the large and growing field of interventional cardiology in Asia has long been needed. At this most appropriate time, I am proud to introduce the launch of AsiaIntervention which I believe will fill this important unmet need and provide the greater interventional Asian community with a reliable source of high-quality articles in the field. As long as the members of the Asian-Pacific Society of Cardiology join forces to work together, AsiaIntervention will definitely grow into a global indexed journal in the near future. The window of opportunity is finally wide open to us all, so let us all enjoy the beginning of our new future.

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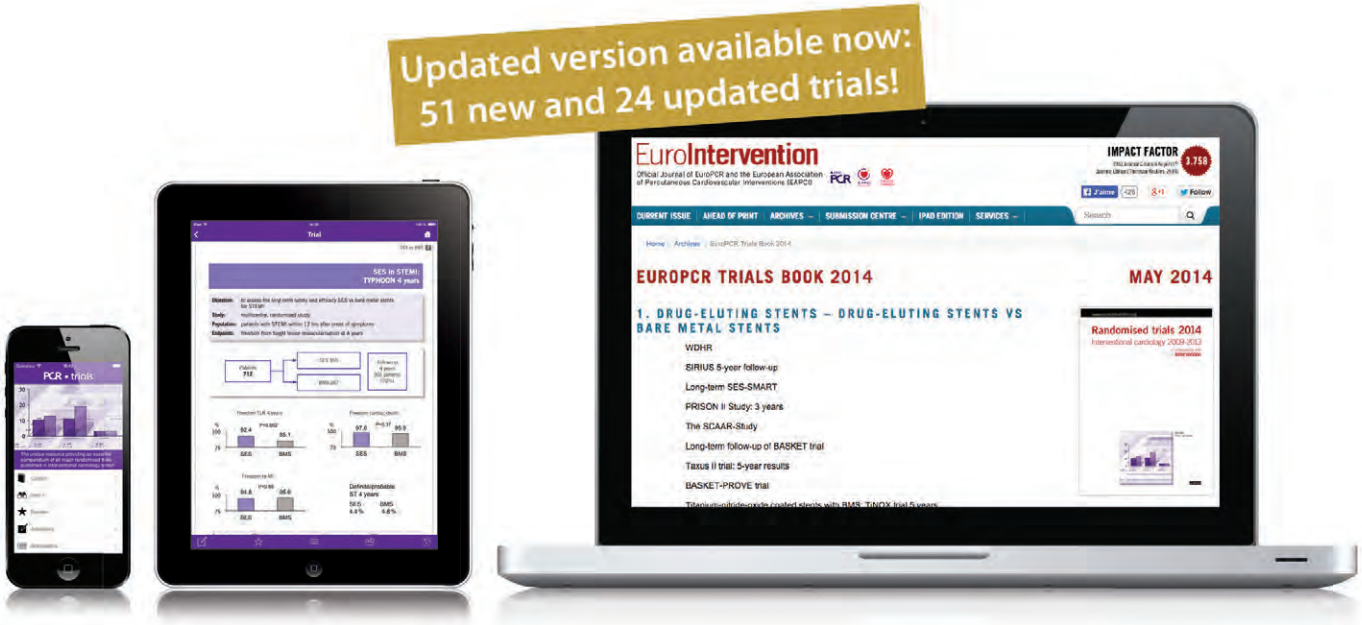

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PCR Innovation in education at work

AsiaIntervention 2015;1:9

AsiaIntervention – "you cannot open a book without learning something"

Patrick W. Serruys

Senior Consulting Editor, AsiaIntervention

In 2005, together with a small team of dedicated individuals, we started EuroIntervention. In the subsequent years, the journal has evolved into an important academic publication within the field of interventional cardiology. Today, EuroIntervention's submissions continue to grow and the journal has a more than respectable impact factor with its website frequently visited and PDF's downloaded. The Journal is present not only at EuroPCR but also at other international meetings. Two aspects come to mind when assessing the success of the Journal – the concept of teamwork, and achieving and maintaining a solid and esteemed reputation.

We have been lucky to have been supported by a great team not only "front stage" but also "behind the scenes". These are colleagues who trust the journal with their papers when submitting and those who advise and guide us in the review process. This great team effort has ensured that the Journal is not only well regarded but also respected within the field and for this we remain sincerely grateful.

A recent paper in EuroIntervention from Rodgriguez-Granillo et al reported the relationship between economic variables such as gross domestic output (GDP) and scientific output in cardiovascular medicine[1]. The authors concluded that "economies with higher rates of GDP growth and increasingly larger expenditures on R&D and healthcare are expected to show a visible escalation in the scientific global picture in the near future". This so-called "escalation" is borne out when, on assessing annually the geographical origin of EuroIntervention's submissions, we have seen a remarkable and steady increase in submissions from the Asian-Pacific Rim. In fact, last year this region accounted for 22% of all submissions. These encouraging developments have led our publishers, Europa Digital & Publishing, to develop and launch a journal for interventional cardiology for the Asian-Pacific Rim. Last year saw the publication of a pilot issue of AsiaIntervention, which met with great success, including articles on the local national societies as well as abstracts from AsiaPCR. This year sees the official launch of AsiaIntervention with original papers predominately from the region. AsiaIntervention has been placed in the capable hands of Runlin Gao, Upendra Kaul, Takeshi Kimura and Seung-Jung Park. I am personally delighted that they are the Chief Editors since they are not only fantastic interventionalists with a great understanding of science, but they also possess great visionary and leadership talents for promoting and improving healthcare in the region. They are, above all, committed team players, fostering cultures that value collaboration. It is for me, a tremendous honour to be invited and to be involved in the birth of another new journal, this time as a Consulting Editor to AsiaIntervention. It will be a privilege to serve Runlin, Upendra, Takeshi and SJ in this exciting new chapter of interventional cardiology. After all, the great philosopher Confucius once said "you cannot open a book without learning something".

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AsiaIntervention 2015;1:10-11

The role of the Asian-Pacific Society of Interventional Cardiology (APSIC) in the future of interventional cardiology

Huay Cheem Tan*, MBBS, MMed, FRCP, FAMS, FACC, FSCAI, President, APSIC

Department of Cardiology, National University Heart Centre, Singapore, Republic of Singapore

The Asian-Pacific Society of Interventional Cardiology (APSIC) was officially formed during the third live demonstration course held in Singapore in July 1993, in the presence of 35 representatives from the region. Founded initially by 11 eminent cardiologists who were convinced that the growth in interventional cardiology in the 21st century would be in Asia, the group had the vision to provide a forum in which Asia-Pacific experts could share knowledge and expertise in the field of catheter-based therapies, and to develop a joint academic research and education programme. Membership of APSIC was to be conducted through their national cardiac societies. It would come under the umbrella of the Asian-Pacific Society of Cardiology (APSC) and the President would be a member of the APSC Council.

Drs Richard Ng and Arthur Tan were elected to be the first President and Secretary General of APSIC, respectively, for a term of three years. An APSIC newsletter was first published on 29 September 1993, designed to feature regular updates of scientific development, and to share interesting cases and literature reviews among the interventional cardiology fraternity. The APSIC website (http://www.apsic.net) was set up in 2006 to facilitate information flow among members and others.

In the 20 years of its existence, the APSIC has made progress in its growth and development. The APSIC now boasts membership from 20 Asian-Pacific countries, with 273 fully-fledged fellows, including members from Australia and New Zealand, and Gulf States such as Saudi Arabia and Kuwait. It has a permanent secretariat based in Hong Kong.

Under the current APSIC Board **(Figure 1)**, the Society has embarked on two broad initiatives. The first of these is to raise the standard of catheter-based therapies in the region through scientific and training activities, and to connect with the rest of the world through collaborative educational opportunities. The Society has its own official scientific meeting called Asian Interventional Cardiovascular Therapeutics (AICT). In the recent, 10th AICT meeting held in Jakarta, Indonesia, from 17th to 29th November 2014, a total of 881 delegates from 35 countries attended, supported by 151 regional and international faculties. It was a resounding success, as delegates had the opportunity to interact closely with the faculties

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Figure 1. *APSIC Board members at 10th AICT Meeting in Jakarta, Indonesia, 2014.*

in a congenial environment marked by true Asian hospitality. The learning experience for delegates was greatly enhanced by the presence of many societies and organisations, such as the Society of Cardiovascular Angiography & Intervention (SCAI) which runs the Fellows course, the LUMEN Global on STEMI, EuroPCR, Korea TCTAP and the India National Intervention Council (NIC). It is this spirit of sharing that APSIC will be embracing in the coming years. We intend to participate actively in all international meetings whenever the opportunity arises. The 11th AICT meeting will be held in Dhaka, Bangladesh, from 13th to 15th November 2015.

There is already an increasing flurry of research publications and trials originating from Asia. Not surprisingly, therefore, the second initiative of the APSIC is to promote collaborative research activities among member countries, and to bring together the strengths, resources and know-how of the Asia-Pacific region as a single entity. Most of the research studies are either single-centre or single-country based. The APSIC Research Committee, ably led by Dr Michael Lee from Queen Elizabeth Hospital, Hong Kong, started the first initiative, namely the Asian Pacific Transcatheter Aortic Valve Implantation (APTAVI) Registry. This initiative is supported by 10 centres from eight countries. The framework of collaboration has been developed based on analyses of outcomes, cost-effectiveness, quality of care, transparency in data analyses and equity among collaborators, so as to facilitate access and publication of relevant analyses. It is hoped that the APTAVI registry will set the template for future collaboration in the region.

As I enter my second year as President of the APSIC, I am optimistic about the growing presence of APSIC in the global arena and look forward to engaging members and the various world bodies for the common good of providing excellent cardiac endovascular care to our patients.

Conflict of interest statement

The author has no conflicts of interest to declare.

AsiaIntervention 2015;1:12-14

Peri-stent contrast staining: a stain on the long-term safety of DES?

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Drug-eluting stents (DES) have contributed to lowering rates of repeat revascularisation due to a reduction in the occurrence of in-stent restenosis (ISR)[1]. However, the risk of stent thrombosis (ST) remains prevalent in the DES era, with several studies associating the use of DES with an increased occurrence of late and very late stent thrombosis (VLST)[2,3]. Delayed healing of the stented arterial segment which involves chronic inflammation with persistent fibrin deposition, and ultimately incomplete stent strut coverage, has been recognised as one of the underlying mechanisms for the late occurrence of ST[4]. Vessel remodelling, with a larger diameter of the stented segment, predisposes to incomplete stent apposition (ISA), a known risk factor for VLST[5,6]. Recently, Imai et al described the angiographic phenomenon of peri-stent contrast staining (PSS), defined as contrast staining outside the stent struts insufficient to fulfil the definition of a coronary artery aneurysm, as an angiographic correlate of ISA[7] that may help identify patients with higher risk of VLST.

In this issue of AsiaIntervention, Ozaki et al[8] investigated the impact of PSS on the occurrence of adverse events during a median clinical follow-up of five years in 807 patients who underwent follow-up angiography a minimum of six months after implantation of sirolimus-eluting stents (SES). PSS was defined as contrast staining outside the stent struts of >20% of the reference diameter and was observed in 20 patients (2.48%), of whom seven had persistent and 13 late acquired PSS. The reported incidence was low and is in accord with previous studies on the occurrence of PSS after implantation of the first-generation DES[7,9]. However, it was nonetheless significantly associated with a higher rate of the combined primary endpoint of death, myocardial infarction (MI), ST and/or target lesion revascularisation (TLR), in the PSS versus the non-PSS group (35.0% vs. 14.9%, p=0.013, HR: 2.94, p=0.006) and a higher rate of VLST, which occurred in three (15.0%) patients with PSS versus 13 (1.7%) in those without (p=0.006). Current smoking, stent fracture and a larger reference vessel diameter were significantly associated with the development of PSS. Multivariable analysis, after adjusting for potential confounding variables, including stent fracture, showed PSS to be an independent predictor of MACE, along with the presence of diabetes, renal failure, saphenous vein graft, longer total stent length and unstable angina.

Article, see page 48

There seem to be two important issues when evaluating the potential of PSS to predict the occurrence of long-term adverse events after DES implantation. First, it is important to delineate

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pathophysiological mechanisms which lead to the angiographic finding of PSS. Second, the assessment of the true impact of PSS on the long-term prognosis appears to depend on the definition of the adverse events in accord with the underlying pathophysiology. The pathophysiological background of PSS may be characterised by the following three observations: the temporal nature of PSS, the lack of linear correlation with intravascular imaging of ISA, and the discrepancy in the reported incidence with different stent types. First, positive vessel remodelling after stent implantation may generate incomplete apposition of the acutely well-apposed stent struts, as evidenced by the results of several studies, showing that roughly half of observed PSS cases are late acquired and/or progressive[7,8,10]. In the other half of cases, PSS persists throughout the reported angiographic follow-up or is lost over time. Second, studies using intravascular ultrasound (IVUS) have shown much higher rates of ISA, as compared with the rates of angiographically detectable PSS[7]. Based on this finding, PSS was seen as a more severe form of ISA[7]. However, studies comparing the association of IVUS-defined ISA versus angiographically visible PSS with clinical outcomes are needed to support this hypothesis. Third, different stent types may account for inherent discrepancies in the pattern of arterial wall healing and thus result in different rates of PSS, as evidenced in several studies[7,9,11]. A study with a mixed population of patients who received BMS or paclitaxel-eluting stents (PES) documented PSS in 2.1% of patients at follow-up angiography and no difference between BMS and PES[9]. A more contemporary DES study reported a lower rate of PSS in patients after implantation of newer-generation everolimus-eluting stents (EES), as compared to the first-generation SES (1.2% vs. 4.5%, p=0.045)[11]. Of note, recent research has challenged the hypothesis that durable polymer is the premier component to provoke hypersensitivity reaction leading to delayed healing and increased risk of ST[12]. It seems rather that polymer, drug and scaffold all have a role in the vessel response, and the combined effect of the three produces a different healing pattern per stent type[13].

When assessing the true impact of PSS on long-term DES safety, two aspects may be important. First, the combined endpoint that includes TLR might neglect the above-described pathophysiological background that PSS as an angiographic entity relies on. Second, alternative causes of ST, independent of ISA and thus potentially unrelated to PSS, should be carefully considered.

Like the pivotal study by Imai et al[7], Ozaki et al use a combined primary endpoint to evaluate the association of PSS with long-term adverse events, a strategy that seems warranted in the light of the low occurrence rate of both PSS and its proposed dire consequence, VLST. Along with ST and hard clinical endpoints, such as death and MI, TLR was also included. Therefore, it appears that a distinction between the occurrence of ST and clinically relevant ISR, which appears mandated due to the different pathophysiological backgrounds, becomes neglected. Stent thrombosis has been associated with positive remodelling, incomplete stent strut apposition and coverage, while ISR is characterised by excessive proliferation of neointima. Both of these events appear to be mingled when TLR is reported. The use of TLR additionally obscures the true impact of PSS on the long-term safety of DES, by potentially misconstruing primary PCI, an accepted treatment strategy for thrombotic stent occlusion, as an adverse event.

Importantly, other mechanisms which contribute to late occurring ST, such as neoatherosclerosis[14], do not correlate with the angiographically visible PSS. Thus, the use of intravascular imaging modalities such as IVUS and optical coherence tomography (OCT) may be essential in adjudicating adverse events and establishing the relationship between PSS and late occurring ST.

In summary, PSS is a rare angiographic finding and, even though it could potentially be applicable as a marker of the delayed healing of the stented segment and thus a predictor of long-term events after DES implantation, only a thorough risk adjustment for the described distinct pathophysiological aspects of PSS can overcome the lack of a satisfactory mechanistic explanation.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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New-generation drug-eluting stents in patients with complex coronary artery disease: still a "work in progress"?

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Treatment of complex obstructive coronary artery disease remains a challenge for physicians in practice around the globe. However, drug-eluting stent (DES) therapy represents an important breakthrough technology which has enabled cardiologists to offer percutaneous intervention to patients with complex disease patterns who were formerly precluded from such treatment due to a high rate of stent failure, mainly as a result of in-stent restenosis[1,2]. Nevertheless, rates of certain adverse clinical events after stenting remain higher in patients with complex disease and in those where the indication for stenting is deemed "off-label" in comparison to patients with more straightforward disease[3,4].

Early-generation DES were associated with some important limitations, including very late stent thrombosis and late catch-up restenosis. The basis for these problems seems to be systematic delayed healing of the stented arterial segment[5]. Although undoubtedly multifactorial in aetiology, persistent inflammatory response to the durable polymer coatings used on these stents plays a central role[6]. However, iterative development of newer-generation DES has resulted in improved healing after stent implantation[7] and has further improved patient outcomes with reduced rates of restenosis and stent thrombosis in comparison to early-generation DES[8,9].

The zotarolimus-eluting Resolute stent (Medtronic CardioVascular, Santa Rosa, CA, USA) is a newer-generation thin-strut durable polymer-based DES. The key difference in relation to its predecessor zotarolimus-eluting Endeavor stent (Medtronic CardioVascular) is its durable polymer coating, which facilitates more controlled drug elution. This has been shown in translational investigation to be the key factor in determining antirestenotic efficacy[10], and clinical trials have demonstrated that this iterative change results in improved clinical outcomes with the Resolute ZES in comparison with the Endeavor ZES[11,12]. Moreover, large-scale randomised trials with wide inclusion criteria have shown broadly comparable results between the Resolute ZES and the initial benchmark durable polymer everolimus-eluting XIENCE stent (Abbott Vascular, Santa Clara, CA, USA) in both industry-initiated and investigator-initiated studies[13-16].

In the current issue of AsiaIntervention, Zambahari and the RESOLUTE Asia Investigators report the results of a multicentre registry enrolling a total of 311 patients undergoing multivessel stenting or those with lesions requiring implantation of long stents (>38 mm)[17]. Patients were included across nine Asian countries and analysis of baseline characteristics of treated patients is notable for a young mean age (under 60 years) and a high prevalence of diagnosed diabetes mellitus (over 40%). The main finding of the investigators was that rates of target lesion failure, the composite of cardiac death, target vessel myocardial infarction or target lesion revascularisation, were low, around 5% at one year in both subgroups of patients. These excellent rates are in line with the results of randomised trials with new-generation durable polymer DES in recent years, many of which included patients with multivessel stenting **(Figure 1)**[13-16]. In addition, the results in patients treated with long stents are very encouraging: the acute performance is excellent with a high rate of device success, in line with what we have come to expect in terms of deliverability from current-generation DES. The advantages in treating long lesions with a single stent are obvious in view of the known unfavourable healing profile of overlapping DES layers[18].

However, the data must be interpreted in the light of some important limitations. Firstly, the impact of patient selection must be considered. With data from 25 centres and an enrolment period of 21 months it can be estimated that in crude terms fewer than one patient per month was recruited at each centre. This suggests that only selected patients were enrolled and impacts on the external validity of the findings. In addition, in terms of disease complexity, patients with interventions for chronic total occlusions and in-stent restenosis are not represented. Secondly, event rates in registry studies are very sensitive to the rigour and completeness of data acquisition and follow-up. In this respect, however, the high

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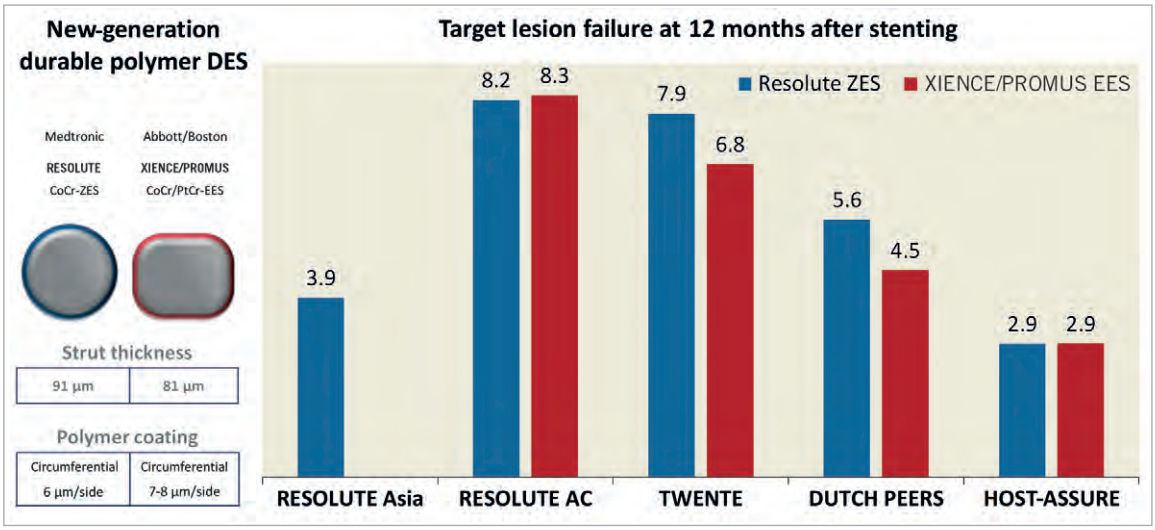

Figure 1. *Key features of current durable polymer drug-eluting stents and rates of target lesion failure at 12 months after implantation from the RESOLUTE Asia registry and selected large-scale randomised clinical trials with primary comparison of outcomes between durable polymer DES. CoCr: cobalt chromium; EES: everolimus-eluting stent; PtCr: platinum chromium; RESOLUTE AC: Resolute All Comers; ZES: zotarolimus-eluting stent*

rate of monitoring and the use of an independent events adjudication committee and angiographic core lab are reassuring. Thirdly, in general terms, the impact of publication bias must always be considered: registry studies are perhaps more susceptible to this than randomised clinical trials. Finally and importantly, the follow-up in this present report is limited to two years. Longer-term surveillance of these patients up to five years should be undertaken.

Overall, the data reported by Zambahari and colleagues with this current-generation durable polymer DES are encouraging and consistent with recent registry and randomised clinical trial reports in showing excellent patient outcomes even with relatively complex disease patterns and lesion subsets at short to medium-term follow-up[13-16]. At the same time, we need to remember that unmet needs continue to exist, particularly with regard to late adverse events after DES implantation, which continue to accrue with time even with newer-generation platforms[19]. In addition, recent autopsy reports suggest that hypersensitivity reactions to durable polymer coatings, a problem well described with the first-generation durable polymer sirolimus-eluting stent (Cypher; Cordis, Miami Lakes, FL, USA), continue to be observed with newer-generation durable polymer DES[20]. Indeed, this is not entirely unexpected, as current-generation durable polymer stents also include methacrylate components, which may well be the trigger for such reactive processes[21]. Moreover, preliminary reports suggest that the rates of neoatherosclerosis, an important, and perhaps the dominant, cause of late stent failure, seem to be similar between early and newer-generation durable polymer DES[20]. For these and other reasons, it is our belief that novel stent solutions, including biodegradable polymer and polymer-free as well as fully bioresorbable DES[22], present attractive alternatives to durable polymer devices and should continue to be pursued. While recently reported initial long-term data comparing biodegradable polymer DES with newer-generation durable polymer DES at five years are encouraging[23], further results from long-term comparative efficacy data are awaited with great interest. With this in mind, in spite of ever improving patient outcomes, we contend that DES technology remains very much a "work in progress".

Conflict of interest statement

R. Byrne reports receiving lecture fees from B. Braun Melsungen AG, Biotronik and Boston Scientific. A. Kastrati reports patent applications related to drug-eluting stent coatings.

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Resolute zotarolimus-eluting coronary stent implantation in Asian patients with multivessel disease and long lesions: clinical outcomes in RESOLUTE Asia

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KEYWORDS

- complex lesions
- coronary artery disease
- drug-eluting stent
- zotarolimus-eluting stent

Abstract

Aims: To examine two-year clinical outcomes after implantation of the Resolute zotarolimus-eluting stent (R-ZES) for the treatment of multivessel disease and long lesions in the RESOLUTE Asia (R-Asia) study.

Methods and results: The R-Asia study includes two cohorts: R-Asia Dual Vessel (≥2 vessels treated with R-ZES) and R-Asia 38 mm (at least one lesion stented with a 38 mm R-ZES). Patients were enrolled simultaneously at 25 centres across Asia from June 2010 to March 2012. A total of 311 patients were enrolled in R-Asia Dual Vessel (n=202) and R-Asia 38 mm (n=109). Device success was 99% in R-Asia Dual Vessel and 97% in R-Asia 38 mm. At two years, clinically driven target lesion revascularisation was 2.5% in R-Asia Dual Vessel and 1.9% in R-Asia 38 mm, and target lesion failure was 5.5% and 4.6%, respectively. There were no cases of ARC definite/probable stent thrombosis in R-Asia Dual Vessel, and a single case (0.9%) of early stent thrombosis in R-Asia 38 mm.

Conclusions: R-Asia demonstrates good long-term safety and efficacy of R-ZES when used for treatment of multivessel disease and for long lesions in an Asian population. Trial registration: ClinicalTrials.gov identifier: NCT01132456.

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Introduction

Two thirds of patients treated with drug-eluting stents (DES) for coronary artery disease in all-comers studies underwent percutaneous coronary intervention (PCI) of complex lesions[1-4]. Long lesions (>18 mm) and multivessel treatment accounted for 20% and 60% of patients in the RESOLUTE All Comers study, respectively[2]. Longer stent length is associated with higher risk for restenosis[5]. In a study comparing single-vessel and multivessel treatment with DES, the six-month incidence of major adverse cardiac events was more than double among patients undergoing multivessel stenting[6]. The objective of the RESOLUTE Asia (R-Asia) study is to assess outcomes in Asian patients treated with the Resolute™ zotarolimus-eluting stent (R-ZES; Medtronic Inc., Santa Rosa, CA, USA) for multivessel treatment (R-Asia Dual Vessel cohort) and in long lesions (R-Asia 38 mm cohort).

The pooled one-year outcomes of patients treated with the 38 mm R-ZES in the R-Asia 38 mm cohort and the RESOLUTE US (R-US) 38 mm cohort (n=269) have been previously published[7]. Target lesion failure (TLF) at one year was 5.4% and comprised 1.4% clinically driven target lesion revascularisation (TLR), 0.9% cardiac death, and 3.6% target vessel myocardial infarction (MI)[7]. Outcomes in the R-Asia Dual Vessel cohort have not been published.

This report provides the two-year outcomes in both R-Asia Dual Vessel and R-Asia 38 mm. The R-Asia study also extends the RESOLUTE Global Program to include more clinical outcome data in Asian patients. Differences in patient characteristics between Asian and Caucasian populations could affect clinical outcomes. As compared to Caucasian populations, Asian populations tend to have a smaller body habitus and therefore smaller coronary arteries[8,9], a lower body mass index, and different associations of body mass index and health risks[10-12]. R-Asia builds on the clinical results available in an Asian population, including RESOLUTE China (R-China) Randomised Controlled Trial (RCT)[13] and R-China Registry[14], conducted in China, and RESOLUTE Japan[15], conducted in Japan. This report also discusses differences in clinical outcomes from those observed in other studies, including in primarily Caucasian patients.

Methods

R-Asia was a closed-cohort, observational study which enrolled patients implanted with R-ZES from June 2010 to March 2012 at 25 centres in Bangladesh, Hong Kong, India, Indonesia, Korea, Malaysia, Singapore, Taiwan, and Thailand. The study was registered at ClinicalTrials.gov (NCT01132456).

Patients enrolled in R-Asia were adults eligible for PCI due to clinical evidence of ischaemic heart disease, stable/unstable angina, or silent ischaemia, or who had a positive functional study, and stenotic lesions (≥50% and <100%) in *de novo* native coronary arteries with a reference vessel diameter of 3.0 to 4.0 mm (assessed visually by the site) and lesion length ≤35 mm in the 38 mm length cohort, and reference vessel diameter of 2.25 mm to 4.0 mm and lesion length of ≤27 mm in the Dual Vessel cohort. Thrombolysis In Myocardial Infarction (TIMI) flow score ≥2 was required. The R-Asia 38 mm cohort enrolled patients with one or two lesions, in which at least one lesion met the reference vessel diameter and lesion length requirements and could be treated with the 38 mm length R-ZES. Dual target lesions required separate vessels in both cohorts.

Stent usage determined cohort assignment **(Figure 1)**. Exclusion criteria included hypersensitivity to study materials and drugs, serious cardiovascular or circulatory comorbidities, planned PCI of any vessel within 30 days post-index procedure and/or planned PCI of the target vessel(s) within 12 months post-procedure, inability to comply with the dual antiplatelet regimen, acute MI within 72 hours, severe calcification, and unprotected left main disease. Physicians implanted R-ZES according to the instructions for use. Patients in both cohorts with >1 target lesion underwent treatment of all lesions during the index procedure.

The hospital's routine standard of care was followed in line with applicable guidelines and the R-ZES instructions for use, in conjunction with dual antiplatelet therapy: 75 to 100 mg of aspirin for three days prior to the index procedure or a periprocedural loading dose of 250 to 500 mg; 75 mg of clopidogrel for three days prior to the procedure or a periprocedural loading dose between 300 and 600 mg. Following the index procedure, the following dual antiplatelet therapy (DAPT) was recommended: 75 to 100 mg of aspirin daily indefinitely and 75 mg of clopidogrel daily for six to 12 months or longer as per physician's decision.

Follow-up visits (telephone or in-clinic evaluation) were scheduled at 30 days, six months, nine months, and annually up to three years in the Dual Vessel cohort and through five years in the 38 mm length cohort. Monitoring (100%) of case report forms and informed consent documentation was conducted on all patients and will continue up to the end of follow-up.

The primary endpoint was one-year target vessel failure (TVF: cardiac death, target vessel MI, or clinically driven target vessel revascularisation [TVR]) for the Dual Vessel cohort, and one-year TLF (cardiac death, target vessel MI, or clinically driven TLR) for the 38 mm cohort. Secondary endpoints included TVF, TLF, and major adverse cardiac events (MACE: death, MI, emergent coronary bypass surgery, or clinically driven TLR), the components of the composite endpoints, death, cardiac death or target vessel MI, and Academic Research Consortium (ARC)[16] definite/probable stent thrombosis. All deaths were considered cardiac unless unequivocally documented otherwise. MI was adjudicated according to the extended historical definition[17]. Revascularisations could be performed either by PCI or by surgery.

Additional endpoints included the attainment of <50% residual stenosis of the target lesion using any percutaneous method (lesion success), using only the assigned device (device success), or with no in-hospital MACE (procedure success).

Event adjudication was performed by an independent clinical events committee composed of cardiologists not involved in the study. Clinical event definitions were harmonised across the RESOLUTE Global Clinical Trial Program, a process that was validated in a prior study[18]. A similarly independent data safety

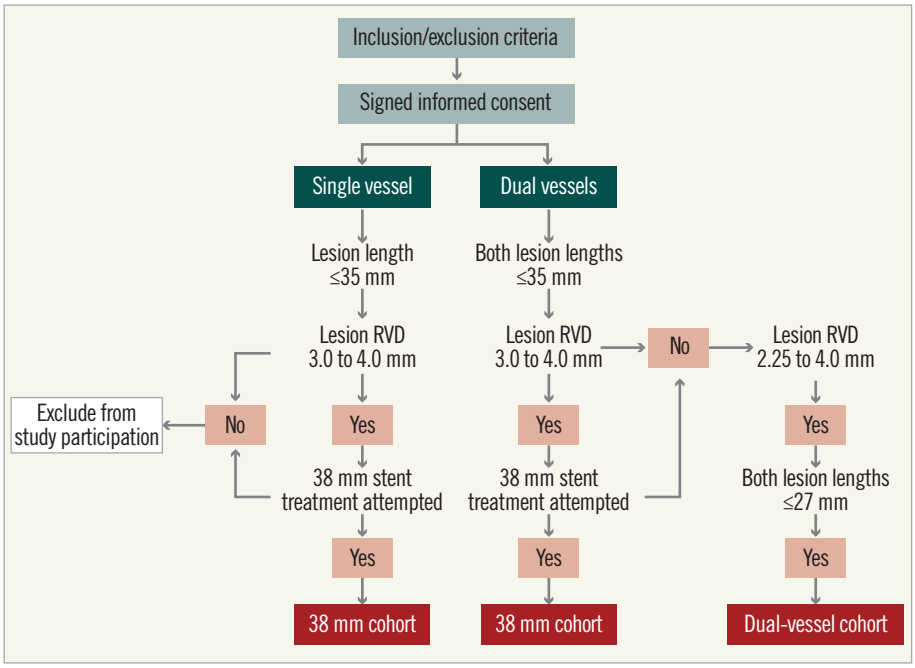

Figure 1. *Enrolment process for the RESOLUTE Asia study. Stent usage determined cohort assignment to either RESOLUTE Asia Dual Vessel cohort or RESOLUTE Asia 38 mm cohort. If the lesion length was ≤35 mm it was at the physician's discretion to consider the patient for 38 mm length RESOLUTE zotarolimus-eluting stent treatment. If no 38 mm length stent treatment was attempted, the patient was considered for enrolment to the Dual Vessel cohort if each vessel had a lesion with length ≤27 mm. RVD: reference vessel diameter*

monitoring board of cardiologists and at least one biostatistician reviewed the study throughout follow-up and could recommend early termination to the sponsor. Angiograms were analysed by an angiographic core laboratory (Cardiovascular Research Foundation, New York, NY, USA).

All patients provided written informed consent. Ethics committee approval was obtained at all sites where it was required, and the protocol complied with the Declaration of Helsinki and local regulations. An independent data safety monitoring board provided guidance on the progress of the trial.

STATISTICAL ANALYSIS

All analyses were conducted based on the intention-to-treat principle. Baseline and outcome data are provided descriptively: categorical variables are reported using counts and percentages, and continuous variables are reported using means and standard deviations. The Kaplan-Meier method was used to calculate time-to-event within each cohort. All analyses were performed using SAS software version 9.1 or later (SAS Institute, Cary, NC, USA).

Results

The R-Asia study enrolled 311 patients (544 lesions): 202 patients (408 lesions) in the Dual Vessel cohort and 109 patients (136 lesions) in the 38 mm cohort. Baseline characteristics are shown in **Table 1**. Mean age was 60±10 and 57±10 years in the R-Asia Dual Vessel and 38 mm cohorts, respectively. In both cohorts, 84% of the patients were men; history of diabetes was present in 46% of the Dual Vessel cohort and 31% of the 38 mm cohort patients. In the 38 mm cohort, only 28% of patients presented with stable angina. Multivessel treatment with R-ZES was performed in 24% of the 38 mm length cohort. **Table 2** provides lesion characteristics and success rates. One third of the lesions in the Dual Vessel cohort

Table 1. Baseline patient characteristics.

	Dual Vessel cohort (N=202 patients)	38 mm cohort (N=109 patients)
Age (yrs)	60.1±9.8	56.9±10.1
Male sex	84.7% (171/202)	84.4% (92/109)
Prior MI	29.4% (58/197)	35.2% (38/108)
Prior PCI	9.4% (19/202)	11.9% (13/109)
Diabetes mellitus	46.0% (93/202)	31.2% (34/109)
Insulin-dependent	6.4% (13/202)	5.5% (6/109)
Hyperlipidaemia	41.1% (83/202)	30.3% (33/109)
Hypertension	69.3% (140/202)	61.5% (67/109)
History of stroke or TIA	3.0% (6/202)	2.8% (3/109)
Current smoker	15.3% (31/202)	18.3% (20/109)
Revascularisation for angina or MI		
Stable angina	41.2% (82/199)	27.5% (30/109)
Unstable angina	47.2% (94/199)	54.1% (59/109)
Myocardial infarction	11.6% (23/199)	18.3% (20/109)

Values are reported as mean±SD or percent of patients (no. of patients/total patients). MI: myocardial infarction; PCI: percutaneous coronary intervention; TIA: transient ischaemic attack

Table 2. Baseline lesion characteristics.

Lesion characteristics	Dual Vessel cohort (n=408 lesions)	38 mm cohort (n=136 lesions)
Vessel location (per lesion)		
LAD	37.6% (142/378)	51.1% (68/133)
LCX	31.2% (118/378)	19.5% (26/133)
RCA	31.2% (118/378)	29.3% (39/133)
RVD, mm	2.69±0.52	2.80±0.34
MLD, mm	0.84±0.39	0.77±0.34
Diameter stenosis, %	68.97±12.71	72.78±11.15
Lesion length, mm	15.26±6.59	26.25±8.50
Total stent length per lesion, mm	21.0±7.1	35.1±10.5
Number of stents per lesion	1.0±0.2	1.0±0.3
Thrombus	4.2% (16/378)	3.8% (5/133)
Calcification		
None/mild	86.8% (328/378)	78.9% (105/133)
Moderate	11.4% (43/378)	19.5% (26/133)
Severe*	1.9% (7/378)	1.5% (2/133)
Pre-procedure TIMI score 0 or 1	2.9% (11/378)	7.5% (10/133)
ACC/AHA modified lesion class B2/C	61.1% (231/378)	87.2% (116/133)
Bifurcation lesion (any)	33.1% (125/378)	45.1% (60/133)
	Dual Vessel cohort (n=202 patients)	**38 mm cohort (n=109 patients)**
Number of lesions treated per patient	2.0±0.2	1.3±0.5
Total stent length per patient, mm	42.5±11.8	44.7±13.7
Number of stents per patient	2.1±0.3	1.3±0.6
Success rates	**Dual Vessel cohort (n=378 lesions)**	**38 mm cohort (n=133 lesions)**
Lesion success, %	100% (377/377)	100% (132/132)
Device success, %	99% (376/378)	97% (129/133)
Procedure success, %	97% (183/188)	97% (103/106)

Values are reported as mean±SD (no. of lesions) or percent of lesions (no. of lesions/total lesions). *Patients enrolled in the study with severe calcification were protocol deviations. ACC/AHA: American College of Cardiology/American Heart Association; LAD: left anterior descending; LCX: left circumflex; MLD: minimum lumen diameter; RCA: right coronary artery; RVD: reference vessel diameter; TIMI: Thrombolysis In Myocardial Infarction

and nearly half in the 38 mm length cohort had bifurcations, and lesion length was 15.26±6.59 and 26.25±8.50 mm, respectively. The lesion length and reference vessel diameter among lesions treated in the R-Asia 38 mm cohort with R-ZES 38 mm (i.e., after excluding any secondary lesions treated with a differently sized stent) were 29.06±6.50 mm and 2.82±0.32 mm, respectively. Both studies attained 100% lesion success, and similarly high rates of device success (99% and 97%) and procedure success (97% and 97%) in the R-Asia Dual Vessel and 38 mm cohorts, respectively.

Table 3 presents clinical outcomes at one and two years in both the Dual Vessel and 38 mm cohorts. In the Dual Vessel cohort, the one-year incidence of TVF was 4.5% (the primary endpoint), TLF 4.0%, clinically driven TLR 1.0%, and target vessel MI 2.5% (all of which occurred in-hospital and were non-Q-wave MI). At two years, the incidence of TVF was 6.5% **(Figure 2A)**, TLF was 5.5% **(Figure 2B)** and clinically driven TLR 2.5%. There were no additional MI events from one to two years, and ARC definite/probable ST remained 0%.

In the 38 mm cohort, the one-year incidence of TLF was 3.7% (primary endpoint) and comprised four target vessel MI events (three of which occurred in-hospital and were non-Q-wave MI, and one of which was a clinically driven TLR in a patient who also had a target vessel MI) in the first 30 days. Between one and two years, there was one additional clinically indicated TLR but no additional target vessel MI events. At two years, the incidence of TLF was 4.6% **(Figure 3A)**, and TVF 5.6% **(Figure 3B)**.

ARC definite/probable stent thrombosis was low in both studies. There were no events in the Dual Vessel cohort and one early stent thrombosis in the 38 mm cohort. DAPT use in the Dual Vessel and 38 mm cohorts was 91% and 94%, respectively, at one year, and 66% and 78%, respectively, at two years.

Discussion

The main findings of our study are the good procedure success and the long-term clinical outcomes in both the R-Asia Dual Vessel and the R-Asia 38 mm study cohorts. Procedure success was 97% in both cohorts. Clinical events remained low. In the Dual Vessel

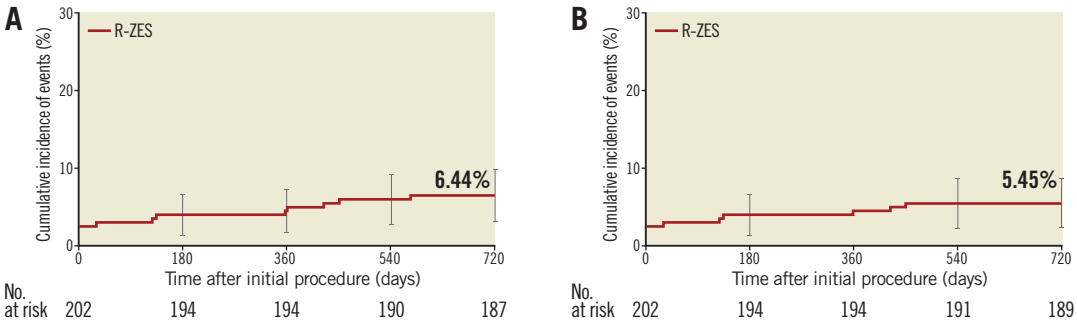

Figure 2. *Cumulative incidence of TVF and TLF at two years in RESOLUTE Asia Dual Vessel cohort. Cumulative incidence of TVF (A) and TLF (B) for all patients assigned to the Dual Vessel cohort. The cumulative incidence of clinical events was calculated using the Kaplan-Meier method and compared using the log-rank test. R-ZES: Resolute zotarolimus-eluting stent; TLF: target vessel failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularisation; TVF: target vessel failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularisation*

Table 3. One- and two-year clinical outcomes in the RESOLUTE Asia Dual Vessel and 38 mm cohorts.

	Dual Vessel cohort 1 year (N=202 patients)	Dual Vessel cohort 2 years (N=200 patients)	38 mm cohort 1 year (N=109 patients)	38 mm cohort 2 years (N=108 patients)
TLF	4.0% (8)	5.5% (11)	3.7% (4)	4.6% (5)
Death	0.5% (1)	0.5% (1)	0.0% (0)	0.0% (0)
Cardiac death	0.5% (1)	0.5% (1)	0.0% (0)	0.0% (0)
Target vessel MI	2.5% (5)	2.5% (5)	3.7% (4)	3.7% (4)
Clinically driven TLR	1.0% (2)	2.5% (5)	0.9% (1)	1.9% (2)
Clinically driven TVR	1.5% (3)	3.5% (7)	0.9% (1)	2.8% (3)
Cardiac death or target vessel MI	3.0% (6)	3.0% (6)	3.7% (4)	3.7% (4)
MACE	4.0% (8)	5.5% (11)	3.7% (4)	3.7% (4)
TVF	4.5% (9)	6.5% (13)	3.7% (4)	5.6% (6)
ARC definite/probable stent thrombosis	0.0% (0)	0.0% (0)	0.9% (1)	0.9% (1)
Early (≤30 days)	0.0% (0)	0.0% (0)	0.9% (1)	0.9% (1)
Late (31-360 days)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Very late (>360 days)	NA	0.0% (0)	0.0% (0)	0.0% (0)

Values are reported as percent of patients (no. of patients). MACE: major adverse cardiac events (a composite of death, MI, emergent coronary artery bypass surgery, or clinically driven TLR); MI: myocardial infarction; TLF: target lesion failure (a composite of cardiac death, target vessel MI, or clinically driven TLR); TLR: target lesion revascularisation; TVF: target lesion failure (composite of cardiac death, target vessel MI, or clinically driven TVR); TVR: target vessel revascularisation

and 38 mm cohorts, the two-year incidence of TLF was 5.5% and 4.6%, and of TVF was 6.5% and 5.6%, respectively. ARC definite/probable ST was 0% in the Dual Vessel and 0.9% (n=1 early) in the 38 mm cohort. These low adverse event rates were achieved in spite of a complex patient population. In the Dual Vessel and 38 mm cohorts, 59% and close to 72% presented with acute coronary syndrome, and treatment of a bifurcation lesion was 33% and 45%, respectively. Additionally, in the R-Asia 38 mm cohort, lesion length was 26.25±8.50 mm.

Multivessel PCI is associated with a higher risk for repeat revascularisation, target vessel MI and other lesion-specific clinical outcomes. Nevertheless, the R-Asia Dual Vessel cohort showed low adverse events, and compared favourably to everolimus-eluting stent (EES) patients at two years **(Table 4)**[19-21]. In an analysis of the SPIRIT III clinical trial of the XIENCE V everolimus-eluting coronary stent system in patients undergoing multivessel PCI with EES, at two years TLR was 6.1%[19] as compared to 2.5% in the R-Asia Dual Vessel cohort.

Additionally, the R-ZES 38 mm allows for long lesions to be treated with a single stent, thereby reducing the need for stent overlap, which can result in higher neointimal hyperplasia and restenosis rates, even with DES[22]. However, even with a single stent, longer lesions have a greater likelihood of covering a bifurcation, which can lead to side branch jailing and increase the risk of periprocedural myocardial infarction[23]. The design of the R-ZES, with thin, round struts[24] may have decreased emboli dislodgement and might help explain the low rate of target vessel MI (3.7% at 30 days and no events thereafter). Additionally, a concern with long

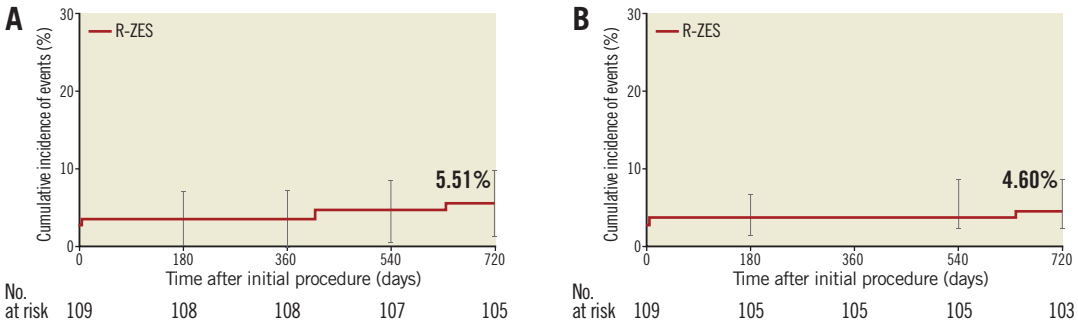

Figure 3. *Cumulative incidence of TVF and TLF at two years in the RESOLUTE Asia 38 mm vessel cohort. Cumulative incidence of TVF (A) and TLF (B) for all patients assigned to the 38 mm cohort. The cumulative incidence of clinical events was calculated using the Kaplan-Meier method and compared using the log-rank test. R-ZES: Resolute zotarolimus-eluting stent; TLF: target lesion failure, a composite of cardiac death, target vessel MI, or clinically driven target lesion revascularisation; TVF: target vessel failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularisation*

Table 4. Clinical outcomes for treatment of multivessel disease and long lesions.

		Multivessel PCI		Coronary revascularisation of long lesions		
		R-Asia Dual Vessel cohort (R-ZES)	SPIRIT III analysis on 2-vessel treatment (XIENCE V EES arm)	R-Asia 38 mm cohort (R-ZES)	P38 (XIENCE PRIME EES)	PLATINUM Long Lesion (PROMUS Element EES)
No. at baseline		202	103	109	203	102
One-year outcomes	TLF	4.0 (8)		3.7 (4)		3.1 (3)
	Cardiac death	0.5 (1)	0.0 (0)	0.0 (0)	3.0 (6)	0.0 (0)
	MI		5.0 (5)		3.4 (7)	0.0 (0)
	Target vessel MI	2.5 (5)		3.7 (4)		0.0 (0)
	TLR	1.0 (2)	4.0 (4)	0.9 (1)		3.1 (3)
	TVR	1.5 (3)		0.9 (1)	3.9 (8)	4.1 (4)
	MACE*	4.0 (8)	8.0 (8)	3.7 (4)	10.3 (21)	
	ST	0.0 (0)	~2%	0.9 (1)	1.0 (2)	0.0 (0)
Two-year outcomes	TLF	5.5 (11)		4.6% (5)		8.8 (8)
	Cardiac death	0.5 (1)	1.0 (1)	0.0 (0)		3.6 (3)
	MI		7.1 (7)			0.0 (0)
	Target vessel MI	2.5 (5)		3.7 (4)		0.0 (0)
	TLR	2.5 (5)	6.1 (6)	1.9 (2)		5.2 (5)
	TVR	3.5 (7)		2.8 (3)		7.2 (7)
	MACE*	5.5 (11)	12.2 (12)	3.7 (4)		
	ST	0.0 (0)	~4%	0.9 (1)		0.0 (0)

Values are reported as percent of patients (no. of patients). * MACE was defined in the RESOLUTE Clinical Trial Program, including R-Asia, as the composite of death, myocardial infarction, emergent coronary bypass surgery, or clinically driven TLR; in SPIRIT III as the composite of cardiac death, MI, or TLR. MACE was defined in P38 as the composite of cardiac death, MI, and TVR. MACE: major adverse cardiac events; MI: myocardial infarction; ST: ARC definite/probable stent thrombosis; TLF: target vessel failure; TLR: clinically driven target lesion revascularisation; TVR: clinically driven target vessel revascularisation

stents is tractability in tortuous coronary anatomy; however, the 38 mm R-ZES was delivered successfully in 97% of patients in the R-Asia 38 mm cohort.

The clinical outcomes in R-Asia 38 mm also compared favourably to those observed in other studies **(Table 4)**. In the P38 global study (which had different inclusion and exclusion criteria, including a required lesion length of ≥35 mm), in which XIENCE PRIME™ (Abbott Vascular, Santa Clara, CA, USA) EES was implanted, at one year TVR was 3.9%[20] (as compared with 0.9% TVR in R-Asia 38 mm). Additionally, two-year TLF in the PLATINUM Clinical Trial to Assess the PROMUS Element Stent System for Treatment of Long *De Novo* Coronary Artery Lesions (PLATINUM LL) study (32 mm and 38 mm PROMUS Element™ EES; Boston Scientific, Marlborough, MA, USA) was 8.8%[21], as compared with 4.6% in R-Asia 38 mm.

A RESOLUTE 38 mm substudy of R-Asia 38 mm and R-US 38 mm was prospectively designed to analyse one-year TLF using one vessel per patient and compared with a performance goal (19%) derived from historical data[7]. Even at two years, TLF in R-Asia 38 mm (including patients treated for dual vessel that included R-ZES 38 mm) was 4.6% and well below the one-year historical performance goal of 19%.

The clinical outcomes in R-Asia are also similar to those observed in "non-complex" populations treated with R-ZES. In the R-US main cohort (stent lengths 8-30 mm implanted), two-year TLF was 7.3% and clinically driven TLR was 4.3% (data on file at Medtronic, Inc.) (as compared to 5.5% and 2.5%, respectively, in R-Asia Dual Vessel, and 4.6% and 1.9%, respectively, in R-Asia 38 mm).

The outcomes in R-Asia were similar to those observed with R-ZES in other Asian populations. R-China RCT and R-China Registry both enrolled "all-comer" populations that included multivessel treatment. At one year, in patients treated with R-ZES, TLF was 5.6% in R-China RCT[13], and 3.5% in R-China Registry[14], and by comparison was similar to that in R-Asia: 4.0% TLF in R-Asia Dual Vessel and 3.7% TLF in R-Asia 38 mm.

Given the low adverse event rates in multivessel disease, R-ZES will be used in the "A Comparison of fractional flow reserve-guided percutaneous coronary intervention and coronary artery bypass graft surgery in patients with multivessel coronary artery disease" (FAME 3) trial. FAME 3 (NCT02100722) will randomise patients with multivessel coronary artery disease to PCI with R-ZES implantation assessed using fractional flow reserve vs. coronary artery bypass graft surgery (CABG), and is currently enrolling patients.

Limitations

Our study has important limitations. The R-Asia Dual Vessel and R-Asia 38 mm cohorts were observational studies. However, 100% monitoring was performed in the entire patient population at all clinical follow-up time points. Also, there was no minimum lesion length required in the R-Asia 38 mm cohort. However, the

lesion length was 29.06±6.50 mm in lesions treated with R-ZES 38 mm, and appropriate for treatment with a 38 mm stent length. Furthermore, the R-Asia 38 mm cohort did not exclude dual vessel treatment, and could therefore have created a bias in the R-Asia Dual Vessel cohort, which did not include lesions amenable to a 38 mm stent, as these patients were enrolled in the R-Asia 38 mm cohort. Additionally, SYNTAX score was not common practice at all study sites and was not calculated for all patients as part of the screening process. Lastly, both studies were relatively small, and both studies were specific to an Asian population. However, the clinical outcomes were consistent with those observed across the RESOLUTE Global Clinical Trial Program.

Conclusion

R-Asia Dual Vessel and R-Asia 38 mm demonstrate low two-year repeat revascularisation rates and good long-term safety and efficacy with R-ZES for treatment of multivessel disease and long lesions. R-Asia also extends the evidence supporting the safety and efficacy of R-ZES in the RESOLUTE Global Clinical Trial Program, specifically in an Asian population.

Impact on daily practice

Most patients undergoing percutaneous coronary intervention have complex disease, including multivessel disease or diffuse atherosclerosis. Treating these lesions can be technically challenging and is often associated with higher rates of major adverse cardiac events. There are limited long-term data in multivessel disease and long lesion treatment, in particular among Asian patients. RESOLUTE Asia (R-Asia), comprising R-Asia Dual Vessel (≥2 vessels treated with the Resolute zotarolimus-eluting stent [R-ZES]) and R-Asia 38 mm (at least one lesion stented with a 38 mm R-ZES), demonstrates good procedural outcomes and long-term safety and efficacy of R-ZES for the treatment of both multivessel disease and long lesions.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Impact of thrombus aspiration in patients with ST-elevation versus non-ST-elevation acute coronary syndrome: a report from a multicentre Japanese PCI registry

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KEYWORDS

- acute coronary syndrome
- complications
- non-ST-elevation myocardial infarction
- ST-elevation myocardial infarction
- thrombus aspiration
- unstable angina

Abstract

Aims: Our aim was to determine whether manual thrombus aspiration (TA) is associated with improved patient outcomes in patients with acute coronary syndrome (ACS) in Japan, where a high number of TA procedures has been performed.

Methods and results: We analysed patient data from the multicentre all-comer PCI registry in Japan. The registry included 4,542 consecutive PCI-treated ACS patients between January 2009 and April 2013. The primary endpoint was the occurrence of major in-hospital complications. TA was performed in 1,715 patients (37.8%): 65.4% of ST-elevation myocardial infarction (STEMI), 31.1% of non-STEMI, and 11.3% of unstable angina (UA) patients. After multivariable analysis with propensity score adjustment, TA was not associated with improved primary outcomes (OR 1.279; 95% CI: 0.934-1.750). When each category of ACS was analysed individually, such a trend was observed in STEMI patients (OR 1.284; 95% CI: 0.836-1.972). In non-STEMI/UA patients, TA was associated with a higher risk of primary outcomes (OR 1.905; 95% CI: 1.199-3.025).

Conclusions: Despite its frequent usage in the contemporary Japanese PCI registry, TA does not appear to provide a clear clinical benefit in ACS-related PCI and may be harmful in patients presenting with non-STEMI/UA.

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Abbreviations

ACC	American College of Cardiology
ACS	acute coronary syndrome
CS	cardiogenic shock
HF	heart failure
IABP	intra-aortic balloon pump
JCD-KICS	Japanese Cardiovascular Database-Keio Interhospital Cardiovascular Studies
MI	myocardial infarction
NSTEMI/UA	non-STEMI/unstable angina
PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
TA	thrombus aspiration

Introduction

A reduction in coronary flow due to thrombus formation is observed in patients with acute coronary syndrome (ACS) as well as in those with ST-segment elevation myocardial infarction (STEMI) and non-STEMI/unstable angina (NSTEMI/UA). Various pharmacological and device-based strategies have been proposed for the direct intervention on this thrombus formation, among which is manual thrombus aspiration (TA)[1]. TA is considered to be a simple, safe, and effective procedure for preventing microvascular obstruction and improving short-term patient prognosis[2-4]. The clinically effective application of TA during primary percutaneous coronary intervention (PCI) in patients presenting with STEMI – while theoretically plausible – remains a controversial topic, despite a number of randomised clinical trials and meta-analyses published in the literature[2-7].

Thrombus formation is the prevailing cause of NSTEMI/UA and accounts for 50-60% of cases of patients presenting with ACS[8,9]. The risks associated with NSTEMI/UA are known to be similar to those of STEMI[10]. In the clinical setting, NSTEMI/UA patients frequently undergo TA to reduce the risk of distal embolisation, particularly when an angiographically proven intracoronary thrombus is present[11]. However, clinical studies investigating the application and effectiveness of TA in the context of NSTEMI/UA remain sparse[12,13].

The risks and benefits of TA must be carefully evaluated, as the procedure involves additional manual coronary manipulation and overall procedure time. We therefore sought to investigate the prognostic benefits of TA in patients presenting with STEMI and NSTEMI/UA. PCI patients registered with the Japanese multicentre PCI registry (Japanese Cardiovascular Database-Keio Interhospital Cardiovascular Studies [JCD-KICS]) were consecutively enrolled in the study between January 2009 and April 2013. Patients were treated at 13 different institutions in Japan where TA is performed relatively frequently. Thus, the present analysis provides insight into the conventional use of TA in the modern era of PCI treatment.

Methods

DATA SOURCE

The JCD-KICS is an ongoing, prospective multicentre registry designed to collect the clinical histories and outcome data of PCI patients[14]. Thirteen academic teaching hospitals within the Tokyo metropolitan area enrolled with the JCD-KICS, and all PCI procedures performed during the study period – including failure cases – were registered online using a web-based interface. Approximately 200 variables were collected for each patient, and clinical variables and in-hospital outcomes were defined in accordance with the National Cardiovascular Data Registry version 4.1. This registry, sponsored by the American College of Cardiology (ACC)[15,16], is the largest national clinical registry programme for diagnostic cardiac catheterisation and PCI, with more than 1,500 centres currently participating across the USA. Clinical research coordinators specifically trained in registering PCI procedures confirmed the correct notarisation of each patient and associated data. In addition, data reported online were monitored and investigators visited each hospital on a quarterly basis for the purpose of auditing the database for completeness and consistency.

STUDY POPULATION

We analysed data from consecutive ACS patients treated with PCI procedures at 13 hospitals in Japan from January 2009 to April 2013. The incidence of cardiogenic shock (CS) and out-of-hospital cardiac arrest was excluded from this study. To reduce patient selection bias, no other specific exclusion criteria were considered. Clinical, angiographic, and procedural complications entered into the JCD-KICS registry database were used. Thrombus aspiration was defined as any manual aspiration regardless of device (in our country several manual aspiration catheters were approved, but they all had a similar mechanism) **(Figure 1)**.

OUTCOME DEFINITION

Complications were defined as severe dissection or coronary perforation, myocardial infarction (MI) after PCI, CS or heart failure (HF), cerebral bleeding or stroke, and bleeding complications.

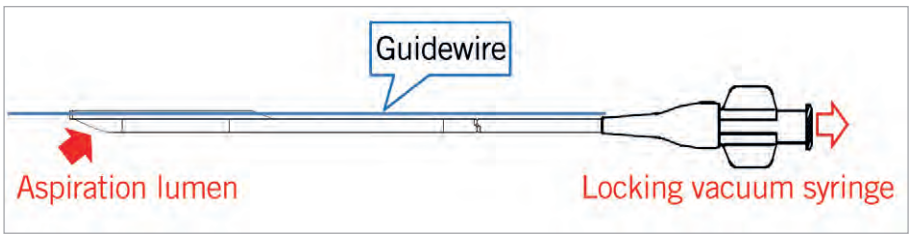

Figure 1. *Scheme of manual aspiration device that is frequently utilised in Japan.*

These definitions are in accordance with the NCDR CathPCI registry, and any additional data elements and definitions can be found at their website (https://www.ncdr.com/webncdr/cathpci/). Post-procedural myocardial infarction was defined as the new occurrence of a biomarker-positive myocardial infarction after PCI; only the patients with normal baseline cardiac biomarkers were included. The bleeding criteria used in this study are also consistent with Bleeding Academic Research Consortium grades 3A-C[17]. The primary endpoint of this study was defined as CS, HF, and in-hospital death.

STATISTICAL ANALYSIS

Continuous variables were expressed as means with standard deviation (SD) and comparisons were performed using the Student's t-test. Categorical variables were expressed as a percentage and the differences were examined using the chi-square test. Multivariate logistic regression analysis was performed to evaluate the relationship between the use of TA and in-hospital mortality, as well as other major in-hospital complications in STEMI and NSTEMI/UA patients. The variables used included baseline patient histories, ACS subtypes, and TA factors, which included the following: TA, age, sex, body mass index, history of old MI, HF, diabetes, cerebral vascular disease, peripheral arterial disease, chronic lung disease, chronic kidney disease, hypertension, smoking, history of PCI/CABG, and type of ACS. Due to the non-randomised nature of the study, a propensity score indicating the likelihood of receiving TA treatment was calculated using multivariate logistic regression analysis which included all significantly different variables between the TA and non-TA patient groups (age, body mass index, hypertension, history of CABG, diabetes, chronic kidney disease, emergency of PCI, left main disease, STEMI/NSTEMI, character of chest pain, and pre-procedural nuclear study). In our final analysis, this propensity score was included in the multivariate adjusted model. All statistical calculations and analyses were performed using the SPSS software package version 15 (SPSS, Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

PATIENT CHARACTERISTICS

Of the 4,542 ACS patients who underwent PCI during the study period, TA was performed in a total of 1,715 patients (37.8%). TA was performed in 1,281/1,960 (65.4%) patients presenting with STEMI, 223/717 (31.1%) patients presenting with NSTEMI and 200/1,774 (11.3%) patients with unstable angina (UA). Nine patients were counted in both UA and NSTEMI during the course of their hospitalisation. The use of TA was shown to decrease with increased patient age **(Table 1)**. TA was performed more frequently on male patients as opposed to female patients. In comparison with the TA patient group, patients who did not undergo TA presented more frequently with clinical syndromes such as hypertension, diabetes, previous MI, HF, aortic/peripheral arterial disease, chronic lung disease, chronic kidney disease including haemodialysis, and a history of prior PCI and CABG.

Table 1. Comparison of baseline characteristics in patients who underwent TA during PCI, and PCI without TA.

	non-TA, n=2,827	TA, n=1,715	*p*-value
Clinical variables			
Female, n (%)	667 (23.6)	334 (19.5)	0.001
Age, yrs	68.8±11.1	65.1±12.4	<0.001
Height, cm	161.3±9.0	163.4±9.1	<0.001
Weight, kg	62.3±12.6	64.9±13.5	<0.001
Body mass index, kg/m^2	23.9±3.6	24.2±3.7	0.002
Smoking, n (%)	993 (35.1)	778 (45.4)	<0.001
Family history of CAD	63 (2.2)	44 (2.6)	0.481
Acute coronary syndrome, n (%)			
STEMI, n (%)	679 (24)	1,281 (74.7)	<0.001
NSTEMI, n (%)	494 (17.5)	223 (13)	<0.001
Unstable angina, n (%)	1,574 (55.7)	200 (11.7)	<0.001
EF, %	57.3±13.6	53.3±12.4	<0.001
Emergent PCI, n (%)	855 (30.2)	1,186 (69.2)	<0.001
NYHA ≥III, n (%)	266 (9.4)	138 (8)	0.119
Previous medical history			
Hypertension, n (%)	2,085 (73.8)	1,089 (63.5)	<0.001
Hyperlipidaemia, n (%)	1,757 (62.2)	1,033 (60.2)	0.209
Diabetes, n (%)	1,101 (38.9)	552 (32.2)	<0.001
Old myocardial infarction, n (%)	532 (18.8)	173 (10.1)	<0.001
History of heart failure, n (%)	207 (7.3)	60 (3.5)	<0.001
Aortic disease and peripheral arterial disease, n (%)	194 (6.9)	58 (3.4)	<0.001
Chronic lung disease, n (%)	93 (3.3)	45 (2.6)	0.213
Haemodialysis, n (%)	146 (5.2)	21 (1.2)	<0.001
CKD stage 3 or 4, n (%)	232 (8.2)	54 (3.1)	<0.001
History of PCI, n (%)	742 (26.2)	191 (11.1)	<0.001
History of CABG, n (%)	162 (5.7)	19 (1.1)	<0.001
Angiographic variables			
Left main, n (%)	286 (10.1)	92 (5.4)	<0.001
2VD, n (%)	1,302 (46.1)	636 (37.1)	<0.001
3VD, n (%)	730 (25.8)	349 (20.3)	<0.001
Procedural variable			
Access site, n (%)			
Radial, n (%)	785 (27.8)	334 (19.5)	<0.001
Femoral, n (%)	1,983 (70.1)	1,353 (78.9)	<0.001
Use of pre-procedural IABP, n (%)	44 (1.6)	33 (1.9)	0.346
Fluoroscopy time, min	28.2±19.3	25.9±16.3	<0.001
Door to balloon time, min	111±76.3	99.8±53.2	0.001

2VD: two-vessel disease; 3VD: three-vessel disease; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CKD: chronic kidney disease; EF: ejection fraction; IABP: intra-aortic balloon pumping; NSTEMI, non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TA: thrombus aspiration

When compared angiographically with the TA groups, non-TA groups were more likely to have undergone PCI for complex lesions (10.1% vs. 5.4% for the left main trunk, 46.1% vs. 37.1% for 2-vessel disease, and 25.8% vs. 20.3% for 3-vessel disease,

respectively). There was no significant difference regarding the use of an intra-aortic balloon pump (IABP) between the two groups. Mean fluoroscopy time was recorded as 28.2±19.3 min for the non-TA group and 25.9±16.3 min for the TA group (p<0.001). Door-to-device time was also longer in the TA group compared to the non-TA group (111±76.3 min versus 99.8±53.2 min, p=0.001).

IN-HOSPITAL OUTCOMES

As seen in **Table 2**, higher complication rates were reported in the TA group (13.6% vs. 10.4%, p=0.001) with no difference observed in in-hospital mortality rates (2.5% vs. 1.8%, p=0.108). Composite outcome (death, HF, and CS) rates were shown to be higher in the TA group (7.6% vs. 4.4%, p<0.001). Post-procedural CS and HF occurred more frequently in the TA group (3.5% vs. 1.8%; p<0.001, 4.0% vs. 2.2%; p<0.001, respectively). No difference in overall bleeding complications was observed between the two groups within a 72-hour period. Multivariate analysis revealed TA was an independent predictor of primary outcomes in NSTEMI/UA patients (OR 1.905, 95% CI: 1.199-3.025) **(Table 3)**.

Multivariable analysis with propensity score adjustment showed that TA was not an independent predictor of primary outcomes (OR 1.279, 95% CI: 0.934-1.750), death (OR 1.341, 95% CI: 0.797-2.255), complications (OR 1.243, 95% CI: 0.991-1.560) or bleeding (OR 1.180, 95% CI: 0.763-1.824), as presented in **Figure 2**.

When each category of ACS was analysed individually, TA performance in patients presenting with STEMI was associated with primary outcomes (death, CS, and HF), complications and bleeding, but not significantly (OR [95% CI]: 1.28 [0.83-1.97], 1.29 [0.61-2.74], 1.16 [0.83-1.62], and 1.14 [0.59-2.19], respectively) **(Figure 3)**. Furthermore, TA in patients presenting with NSTEMI/UA was significantly associated with unfavourable outcomes including complications and primary outcomes (death, CS, and HF) (OR 1.62, 95% CI: 1.19-2.20, and OR 1.90, 95% CI: 1.10-3.02, respectively).

Table 2. In-hospital outcome of patients who underwent thrombus aspiration during PCI, and PCI without TA.

	non-TA, n=2,827	TA, n=1,715	*p*-value
Composite endpoint (death, heart failure, cardiogenic shock)	123 (4.4)	130 (7.6)	*p*<0.001
In-hospital mortality	51 (1.8)	43 (2.5)	0.108
Complications	294 (10.4)	234 (13.6)	0.001
Coronary dissection	32 (1.1)	22 (1.3)	0.673
Coronary perforation	23 (0.8)	12 (0.7)	0.729
Post-procedural myocardial infarction	65 (2.3)	29 (1.7)	0.197
Post-procedural cardiogenic shock	52 (1.8)	60 (3.5)	0.001
Heart failure	61 (2.2)	68 (4)	0.001
Cerebral infarction	15 (0.5)	6 (0.3)	0.500
Cardiac tamponade	7 (0.2)	10 (0.6)	0.083
Newly initiated haemodialysis	35 (1.2)	17 (1)	0.476
Bleeding complications within 72 hours	91 (3.2)	62 (3.6)	0.498
Access-site bleeding	31 (1.1)	15 (0.9)	0.542
Access-site haematoma	25 (0.9)	18 (1)	0.636
Retroperitoneal haemorrhage	2 (0.1)	2 (0.1)	0.636
Bleeding with transfusions or decrease of haemoglobin	78 (2.8)	52 (3)	0.583
Transfusions	76 (2.7)	46 (2.7)	1.000

All values are n (%). CK: creatinine kinase; TA: thrombus aspiration

Table 3. Risk predictors of primary endpoint (death, heart failure, cardiogenic shock).

	STEMI		NSTEMI/UA	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
TA	1.284 (0.836-1.972)	0.253	1.905 (1.199-3.025)	0.006
Age	1.049 (1.027-1.071)	<0.01	1.059 (1.034-1.084)	<0.01
Female	0.714 (0.429-1.188)	0.195	1.316 (0.823-2.102)	0.251
Old myocardial infarction	0.498 (0.181-1.372)	0.178	1.349 (0.738-2.463)	0.331
History of heart failure	2.944 (1.318-6.575)	0.008	2.083 (1.194-3.631)	0.01
Diabetes	0.938 (0.612-1.436)	0.768	1.163 (0.763-1.773)	0.482
Aortic disease and peripheral arterial disease	1.437 (0.623-3.317)	0.396	1.016 (0.517-1.996)	0.963
Chronic lung disease	2.797 (1.299-6.021)	0.009	1.105 (0.37-3.304)	0.858
Hypertension	0.774 (0.504-1.189)	0.242	0.548 (0.351-0.856)	0.008
Smoking	1.271 (0.82-1.971)	0.284	1.069 (0.667-1.712)	0.783
Family history of CAD	1.304 (0.44-3.866)	0.632	0.499 (0.066-3.779)	0.501
History of PCI	0.721 (0.282-1.846)	0.495	0.631 (0.35-1.137)	0.125
History of CABG	2.162 (0.588-7.945)	0.246	2.233 (1.116-4.469)	0.023
CKD stage 3 or 4	2.313 (0.977-5.474)	<0.01	3.416 (1.982-5.889)	<0.01
Body mass index, kg/m^2	1.023 (0.966-1.084)	0.431	0.993 (0.933-1.056)	0.814

CABG: coronary artery bypass grafting; CAD: coronary artery disease; CKD: chronic kidney disease; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; TA: thrombus aspiration; UA: unstable angina

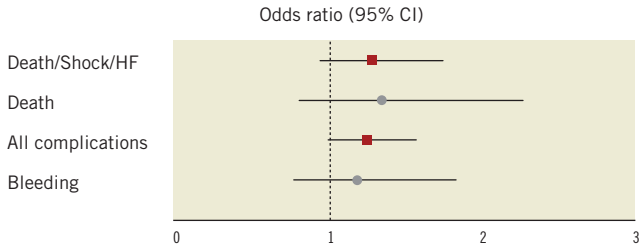

Figure 2. *Forest plot results of odds ratio of thrombus aspiration (TA) efficacy after propensity adjustment. Complications included severe dissection or coronary perforation, myocardial infarction after PCI, cardiac shock or HF, cerebral bleeding or stroke and bleeding complications. CI: confidence interval; HF: heart failure*

Discussion

The usefulness of TA in treating ACS has been a topic of debate for the last decade. Considering the pathophysiology of ACS, it is reasonable to consider carefully the effectiveness of TA in treating ACS patients. However, while previous studies have yielded conflicting results[4,18], in this study no association was shown between TA and improved outcomes in STEMI patients. Furthermore, the use of TA in NSTEMI/UA patients was shown to be associated with in-hospital complications.

TA IN STEMI PATIENTS

In comparison to previously published studies, TA was performed on a significantly higher number of patients in our registry. This accounted for 65.4% of all STEMI-related cases of PCI. During the same time period, TA was performed on just 18.9% of patients in the US national registry (CathPCI registry®)[18]. As previously mentioned, past studies – including meta-analyses – have shown inconsistent results regarding the clinical efficacy of TA[5,7,19]. It is of clinical significance that, despite extensive clinician experience and familiarity with the procedure, TA was once again not associated with improved clinical outcome in this study.

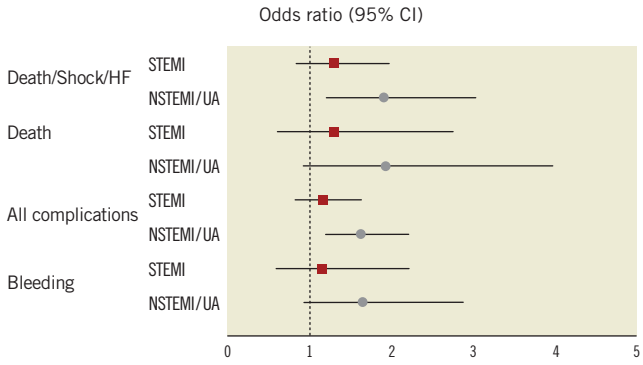

Figure 3. *Forest plot results of odds ratio of thrombus aspiration (TA) efficacy on each condition. Complications included severe dissection or coronary perforation, myocardial infarction after PCI, cardiac shock or heart failure, cerebral bleeding or stroke and bleeding complications. CI: confidence interval; HF: heart failure; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; UA: unstable angina*

Clinician familiarity with the procedure is further reflected by the shorter fluoroscopy time in the TA group compared to the non-TA group in the present study. It should be noted that shorter fluoroscopy time may also be indicative of less complex lesions in the TA group compared to the non-TA group. However, a similar periprocedural complication rate (coronary dissection and coronary perforation) was observed in both groups. Thus, it would seem that, even under these favourable circumstances, TA was not associated with a better prognosis[20].

TA IN NSTEMI/UA PATIENTS

At present, there are minimal data available for the assessment of the impact of TA in NSTEMI/UA patients. Although Vlaar et al demonstrated the safety and efficacy of TA in NSTEMI patients, their study was based on a small group of patients (n=70) with reduction shown only in "thrombus score" and TIMI flow[12]. To the best of our knowledge, there are no real-world data regarding the usage of TA in NSTEMI/UA patients, and relatively few patients usually undergo TA in these situations, as was the case in STEMI. In Japan, TA in NSTEMI/UA patients was frequently performed within our registry (31.1% in NSTEMI, 11.3% in UA), and this allowed us to compare the TA group to the non-TA group with adjustments made for confounding variables[18]. The reason behind this large number of patients being treated by TA was that its indication largely depended on the physician's subjective considerations rather than evidence-based suggestion, which is virtually non-existent[21]. Our study showed that TA in NSTEMI/UA patients was associated with unfavourable outcome, and this challenges the common belief of Japanese interventionalists.

In accordance with observations in STEMI patients, non-TA-treated NSTEMI/UA patients presented with a slightly higher BMI, less complex lesions and a shorter associated fluoroscopy time when compared to TA-treated patients. Despite these merits, the benefit of TA in the treatment of NSTEMI/UA remains debatable and may be potentially harmful to these patients when taking propensity score adjustment into account.

The reasons behind the unexpected and unfavourable outcomes of TA treatment presented here should be carefully considered. Pathologically, the thrombus burden in NSTEMI/UA is lower than that in STEMI, which could reduce the efficacy of TA in the prevention of distal embolism in NSTEMI/UA patients[22]. Patients with a higher visible thrombus volume might be more likely to benefit from the TA procedure; however, thrombus volume quantification remains a major clinical challenge[23]. Furthermore, according to the previous reports, 24% of patients had an occluded infarct artery, which was associated with a higher complication rate[24]. We might perform TA in an occluded infarct artery without any doubt, and we might not perform TA in a non-occluded artery, which might result in unfavourable patient selection for the TA group. In addition, challenges in the diagnosis of NSTEMI/UA and the subsequent determination of affected arteries may diminish the usefulness of TA treatment.

As the prevalence of NSTEMI increases, the lack of clear benefits and treatment options in this patient group should not be

overlooked[25]. TA does not appear to be a universally applicable strategy in the treatment of NSTEMI/UA patients as shown here and, despite favourable patient selection, an increased risk in procedure-related complications (including HF and CS) was observed.

Limitations

There are several limitations in the present study. First, this was the retrospective analysis of a registry database, and unknown variables such as ischaemic duration, post-angiographic and electrocardiographic data in NSTEMI/UA patients could thus not be excluded in the assessment of the efficacy of TA and patient outcomes. We included PCI patients over four years. Also, we might not have noticed the procedural improvement during this period simply by this registry database. Our study was too small to analyse the effect of time trend. Second, mechanical thrombectomy devices and newly available anticoagulant drugs such as a GP IIb/IIIa inhibitor are not used in Japan. The efficacy of mechanical thrombectomy is widely discussed in the literature and is known to impact on rates of complications and patient outcomes. However, we should not misunderstand that the concept of thrombus removal was not denied. If a more efficient thrombus aspiration device were to be developed, it might be related to a favourable outcome[26]. Thus, the results of this study must be considered within the context of the relevant clinical setting. The differences in outcomes across the different types of ACS in this study highlight the difficulty in selecting patients who would benefit from TA. Third, our data only revealed short-term outcome. Our registry did not contain long-term outcome. We need further investigation about the long-term efficacy of TA. Finally, we included PCI patients over four years. There might have been some procedural improvement during the study period, including implementation of transradial intervention[27]; however, the sample size of our study limited the sub-analysis on the effect of time trend.

Conclusion

Despite its frequent usage in ACS-related PCI, TA was not shown to be associated with improved outcomes in patients presenting with STEMI. TA was further associated with an increased risk of in-hospital complications in NSTEMI/UA patients.

Impact on daily practice

The appropriate use of thrombus aspiration remains a clinical challenge. In our analysis of a multicentre PCI registry, despite its frequent use, TA in STEMI patients was not associated with improved outcome. Furthermore, TA in non-STEMI/UA patients, who present with smaller culprit vessels with multiple comorbidities, may be harmful.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Second-generation everolimus-eluting stents demonstrate better vascular function, less thrombus formation, and less yellow intima than first-generation drug-eluting stents

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KEYWORDS

- angioscopy
- drug-eluting stent
- endothelial function

Abstract

Aims: We compared endothelial function and intra-stent condition after second-generation everolimus-eluting stent (EES) versus first-generation drug-eluting stent (DES) implantation.

Methods and results: We enrolled 117 patients with stable angina who were treated with EES (n=44), sirolimus-eluting stents (SES) (n=43), and paclitaxel-eluting stents (PES) (n=30). At nine-month follow-up, endothelial function was evaluated by intracoronary acetylcholine (Ach) infusion. Vascular responses to Ach were quantitatively measured. With angioscopy, cases were assessed for: 1) the degree of neointimal coverage (grade 0: no coverage, to 3: full coverage); 2) presence of in-stent thrombus; and 3) existence of yellow intima. Vasomotion to Ach distal to the EES was better preserved than to the SES and PES (vs. SES; $p<0.01$ and vs. PES; $p<0.01$), while vasomotions to Ach proximal to the stent were comparable among the three groups ($p=0.12$). From the angioscopic study, the incidences of in-stent thrombus and yellow intima in the EES group were significantly lower than in the SES and PES groups (thrombus - EES: 6.8%, SES: 27.9%, PES: 60.0%; $p<0.01$, yellow intima - EES: 11.4%, SES: 51.2%, PES: 36.7%, $p<0.01$), whereas the neointimal coverage was similar among the three groups ($p=0.44$).

Conclusions: EES demonstrated better endothelial function, less thrombus formation, and less yellow intima than first-generation DES at nine-month follow-up.

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Abbreviations

Ach	acetylcholine
BMS	bare metal stents
DES	drug-eluting stents
EES	everolimus-eluting stents
NTG	nitroglycerine
PCI	percutaneous coronary intervention
PES	paclitaxel-eluting stents
QCA	quantitative coronary angiography
SES	sirolimus-eluting stents
ST	stent thrombosis

Introduction

Drug-eluting stents (DES) have significantly reduced in-stent restenosis and target lesion revascularisation after percutaneous coronary intervention (PCI) as compared with bare metal stents (BMS)[1,2]. In spite of these benefits, concern over increased stent thrombosis (ST) still exists[3]. Although the incidences of ST are low, ST is an immediate life-threatening complication and may occur consistently up to at least five years after implantation of first-generation DES, sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES)[4,5]. Several pathophysiological factors could be associated with ST, such as delayed re-endothelialisation, incomplete stent strut coverage, prolonged inflammation, hypersensitivity reactions, late acquired malapposition, strut fractures, and neoatherosclerosis[6-10]. In particular, delayed re-endothelialisation and incomplete stent strut coverage have been considered as significant factors with regard to ST in human autopsy studies[7,8]. The use of durable polymer coating, the thickness of the stent struts, and the dose of the antiproliferative drug and its release kinetics in first-generation DES have been implicated as important contributory factors in these issues[11-13].

Meanwhile, second-generation DES, including everolimus-eluting stents (EES), have been developed with different drugs, more biocompatible polymers, improved drug release kinetics and thinner stent struts. Indeed, EES showed better outcomes including a lower risk of ST compared with first-generation DES in real-world patients[14-16]. This favourable clinical performance might be associated with better vascular response to EES. However, there have been few investigations on endothelial function and arterial healing in EES[17,18].

Coronary angioscopy is a unique imaging modality that allows inspection macroscopic pathology in living patients and direct visualisation of luminal structure such as atherosclerotic plaque, thrombus, stent struts, and proliferating neointima.

The aim of this study was to evaluate coronary endothelial function and intra-stent condition using angioscopy in patients at nine months after EES implantation, and to compare these data with first-generation DES results.

Methods

STUDY PROTOCOL

This single-centre, non-randomised study involves 48 patients implanted with EES (XIENCE™; Abbott Vascular, Santa Clara, CA, USA), included prospectively from January 2011 to January 2013, together with 46 patients implanted with SES (CYPHER™; Cordis Corporation, Miami Lakes, FL, USA) and 36 patients implanted with PES (TAXUS™; Boston Scientific Corporation, Natick, MA, USA), included prospectively from January 2009 to December 2011. Some of these study data regarding patients with SES (n=40) and PES (n=26) were included in our previous report[19]. Eligible subjects were diagnosed with stable effort angina and treated with a single DES for a *de novo* single lesion. All stents were implanted using standard PCI techniques. Follow-up coronary angiography, coronary endothelial function evaluation and coronary angioscopy were performed at nine months after PCI. Exclusion criteria for this study were: acute and old myocardial infarction, clinical or angiographic history of coronary vasospasm, previous coronary bypass graft surgery, left main coronary artery lesion, bifurcation lesion requiring two stents, chronic total occlusions, in-stent restenosis lesion, angiographic in-stent restenosis by follow-up angiography, symptomatic congestive heart failure, severe left ventricular dysfunction (ejection fraction <30%) and severe valvular heart disease. This study was approved by the ethics committee of our institution and all patients provided written informed consent.

MEDICATION REGIMEN

All patients received aspirin (100 mg/day) and clopidogrel (75 mg/day) during the follow-up period. Statins and renin-angiotensin system inhibitors including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were administered daily to all patients wherever possible, because these drugs may have salutary effects on coronary endothelial function[20-22].

EVALUATION OF CORONARY ENDOTHELIAL FUNCTION

Coronary endothelial function was estimated by measuring coronary vasomotion in response to acetylcholine (Ach) at nine-month follow-up. All vasoactive medications, including calcium channel blockers, long-acting nitrates, ACEI, ARB and β-blockers, were discontinued at least 24 hours before the test. After baseline angiography, endothelium-dependent vasomotor response was evaluated by using an intracoronary infusion of Ach in incremental doses at 10^{-7} and 10^{-6} mol/L for two minutes. At least three minutes were allowed between each infusion. If clinically needed, a temporary pacemaker was inserted through the femoral vein. Subsequently, endothelium-independent vasomotor response was tested after an intracoronary bolus infusion of nitroglycerine (NTG, 200 μg). Angiography was repeated every 30 seconds for two minutes after each drug infusion. The maximal vasomotor responses to Ach and NTG were determined by quantitative coronary angiography (QCA) with a CAAS II system (Pie Medical Imaging BV, Maastricht, The Netherlands). QCA measurements were performed by an independent blinded reviewer. Two segments, 5~25 mm proximal and distal to the stent, were analysed. Additionally, as a reference, an angiographically normal segment in another vessel was evaluated. If the stent was in the right coronary artery, an angiographically normal segment as far away as possible from the stent was analysed as the

reference. The same segments were identified by anatomical landmarks and assessed at each measurement. Changes in vessel diameter in response to Ach and NTG infusion were calculated as the percentage of changes versus the baseline coronary diameter.

ANGIOSCOPIC PROCEDURES AND EVALUATION

After assessment of endothelial function, coronary angioscopy was performed using a balloon occlusion type of angioscopy device (Vecmova NEO™; FiberTech Corporation, Tokyo, Japan). Details regarding the procedure and specifications for these devices have been described elsewhere[23]. Briefly, the angioscopic fibre was placed distal to the stent and was pulled back manually, from distal to proximal segment of the stent, under careful angioscopic and angiographic guidance. When the field of view was flushed clear of blood with Lactated Ringer's solution, inflation of the occlusion balloon was constantly maintained. Each angioscopic image acquisition took about 20 seconds, and all sequences were recorded for subsequent off-line analysis. Angioscopic images were evaluated with a focus on the following: 1) the dominant degree of neointimal coverage over the stent, 2) presence of thrombus inside the stent, and 3) existence of yellow intima over and underneath the stent **(Figure 1)**. The degree of neointimal coverage over the stent was classified into four grades as previously described[19,24-26]: grade 0, fully visible stent struts similar to immediately after stent implantation; grade 1, stent struts with very thin neointimal coverage, but protruded into the lumen and transparently visible; grade 2, stent struts embedded by neointima but seen translucently; and grade 3, stent struts fully embedded and not visible by angioscopy. If various grades were seen in the stent, the dominant pattern in the entire stent was used as the grade of the stent.

Statistical analysis

Statistical analysis was performed using the SPSS Version 22.0 (IBM Corp., Armonk, NY, USA). All continuous data are given as mean±standard deviation or median and interquartile range, according to their normal or non-normal distribution. One-way analysis of variance (ANOVA) with a Scheffe test for multiple comparisons was used in continuous variables. If data were skewed, Kruskal-Wallis was applied and followed by a Mann-Whitney test with Bonferroni correction for multiple comparisons. Categorical variables are presented as number (n) or percentage (%). The chi-square test with Bonferroni adjustment was used in categorical variables. The group differences on % changes in vessel diameter were tested by two-way ANOVA for repeated measurements with a Scheffe test for multiple comparisons. To identify factors that were independently associated with endothelial dysfunction, linear regression analyses were used. Including only variables with $p<0.05$ on simple linear regression test, forward stepwise multivariate regression analysis was performed. A two-tailed p-value less than 0.05 was considered statistically significant.

Results

Follow-up angiography was not performed in seven patients (three patients with EES, two patients with SES, and two patients with PES). Additionally, the segment proximal to the stent could not be

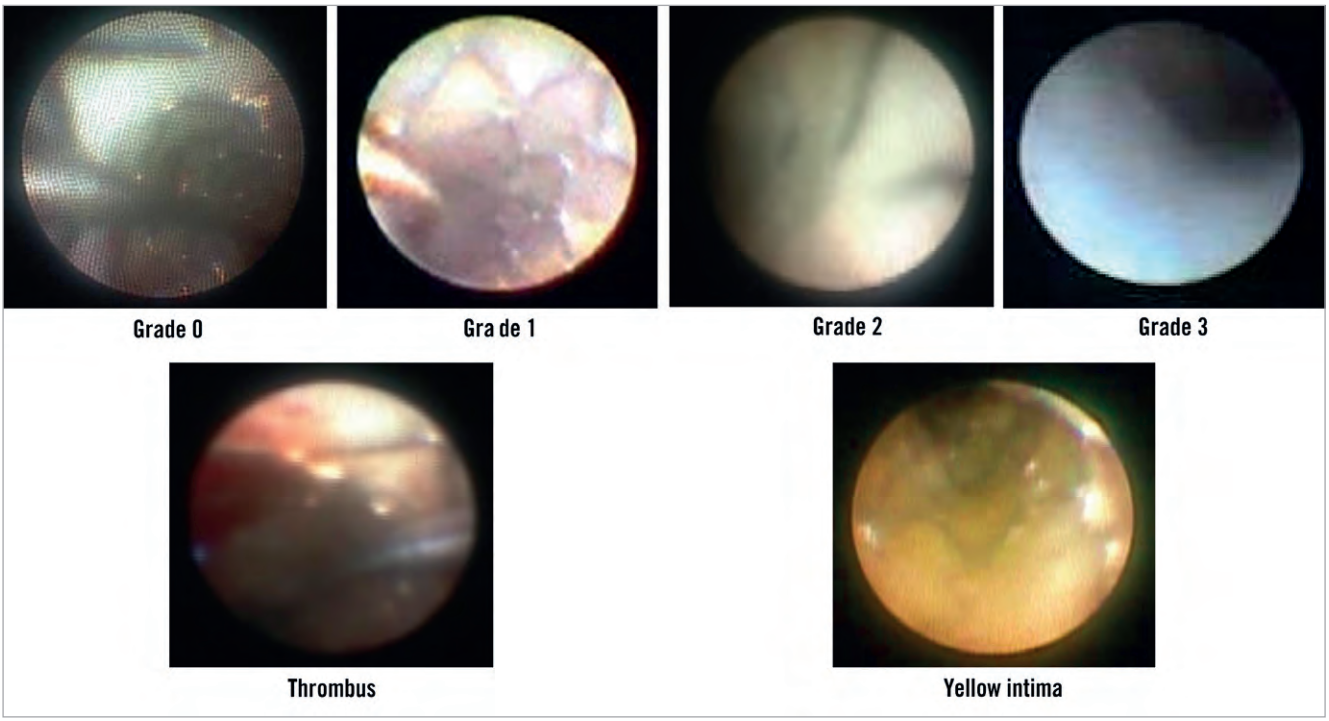

Figure 1. *Angioscopic images of neointimal coverage grade, thrombus and yellow intima. Grade 0: fully visible stent struts similar to immediately after stent implantation. Grade 1: stent struts with very thin neointima, but protruded into the lumen and transparently visible. Grade 2: stent struts embedded by neointima but seen translucently. Grade 3: stent struts fully embedded and not visible. Thrombus: red thrombus formation inside the stent; yellow intima: yellow intima over and underneath the stent.*

evaluated in four patients (one patient with EES and three patients with PES) due to ostial stent location, and clear angioscopic images could not be obtained in two patients (one patient with SES and one patient with PES).

As a result, a total of 117 patients (44 patients with EES, 43 patients with SES, and 30 patients with PES) were included in the analysis.

Baseline patient, lesion, and procedural characteristics are shown in **Table 1**. There were significant differences in the stent diameter and the stent deployment pressure among the three groups. Follow-up patient data are listed in **Table 2**. No significant differences were found in follow-up patient characteristics among the groups. At follow-up, late loss in the PES group was significantly greater than in the SES and EES groups **(Table 3)**. No adverse cardiac events occurred during the follow-up period and no patients showed in-stent restenosis on follow-up angiography in all three groups.

Table 1. Baseline patient, lesion, and procedural characteristics.

	EES (n=44)	SES (n=43)	PES (n=30)	*p*-value
Age	70.5±9.3	69.8±9.1	67.5±8.8	0.36
Men	32 (72.7%)	33 (76.7%)	21 (70.0%)	0.81
Hypertension	37 (84.1%)	32 (74.4%)	22 (73.3%)	0.44
Dyslipidaemia	28 (63.6%)	25 (58.1%)	13 (43.3%)	0.22
Diabetes mellitus	22 (50.0%)	26 (60.5%)	22 (73.3%)	0.13
Smoking	16 (36.4%)	19 (44.2%)	10 (33.3%)	0.60
LVEF (%)	64.3±8.9	63.7±11.8	66.0±7.2	0.59
Medications				
Statin	27 (61.4%)	24 (55.8%)	17 (56.7%)	0.86
ACEI or ARB	26 (59.1%)	22 (51.2%)	18 (60.0%)	0.68
Calcium channel blocker	21 (47.7%)	18 (41.9%)	16 (53.3%)	0.62
β-blocker	23 (52.3%)	16 (37.2%)	10 (33.3%)	0.20
Pre diameter stenosis (%)	81.9±12.3	77.7±12.6	77.4±11.7	0.18
Type B2 or C	29 (65.9%)	24 (55.8%)	16 (53.3%)	0.49
Stent diameter (mm)	3.0±0.4	2.9±0.4	3.2±0.3*	<0.01
Stent length (mm)	25.2±6.7	24.5±6.4	24.6±6.1	0.86
Stent deployment pressure (atm)	11.1±2.8	13.3±3.6¶	11.6±2.7	<0.01
Coronary artery lesion				0.41
LAD	22 (50.0%)	21 (48.8%)	19 (63.3%)	
LCX	14 (31.8%)	14 (32.6%)	4 (13.3%)	
RCA	8 (18.2%)	8 (18.6%)	7 (23.3%)	

Values are mean±standard deviation or number (%). *vs. SES, $p<0.01$; vs. EES, $p<0.05$. ¶vs EES, $p<0.01$. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; LAD: left anterior descending artery; LCX: left circumflex artery; LVEF: left ventricular ejection fraction; RCA: right coronary artery

Table 2. Patient characteristics at follow-up.

	EES (n=44)	SES (n= 43)	PES (n=30)	*p*-value
Follow-up period (months)	8.5±3.1	9.3±2.1	9.9±2.9	0.09
Medications				
Statin	39 (88.6%)	42 (97.7%)	30 (100%)	0.05
ACEI or ARB	42 (95.5%)	42 (97.7%)	30 (100%)	0.48
Calcium channel blocker	21 (47.7%)	18 (41.9%)	15 (50.0%)	0.76
β-blocker	23 (52.3%)	23 (53.5%)	11 (36.7%)	0.31
Aspirin + clopidogrel	44 (100%)	43 (100%)	30 (100%)	1.00

Values are mean±standard deviation or number (%). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 3. Angiographic and angioscopic findings at follow-up.

	EES (n=44)	SES (n=43)	PES (n=30)	*p*-value
In-stent late loss (mm)	0.05 (0.00-0.22)	0.01 (0.00-0.10)	0.46±0.35*	<0.01
Grade of strut coverage	1.45±0.82	1.37±1.00	1.67±1.12	0.44
In-stent thrombus	3 (6.8%)¶	12 (27.9%)	18 (60.0%)	<0.01
Yellow intima	5 (11.4%)‡	22 (51.2%)	11 (36.7%)	<0.01

Values are mean±standard deviation, median (interquartile range), or number (%). *vs. SES; $p<0.01$, vs. EES; $p<0.01$. ¶vs. SES; $p<0.05$, vs. PES; $p<0.01$. ‡vs. SES; $p<0.05$, vs. PES; $p<0.05$.

CORONARY ENDOTHELIAL FUNCTION

At the reference segments and segments proximal to the stent, coronary vasomotor responses to Ach and NTG were comparable among the three groups (p=0.46 and p=0.12, respectively) **(Figure 2)**. In contrast, vascular responses to Ach distal to the stent in the EES group were better preserved than in the SES and PES

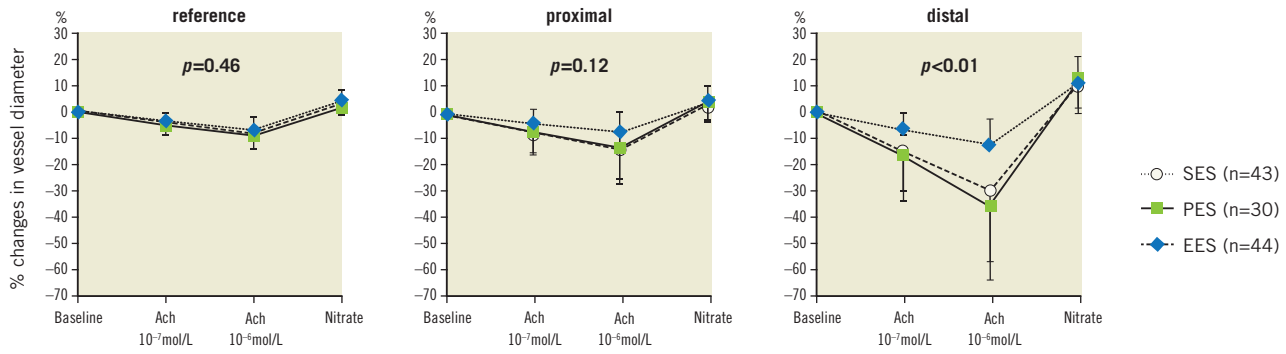

Figure 2. *Changes in vessel diameter in response to Ach and NTG infusion expressed as percentage of changes versus the baseline diameter. p-values indicate differences among the three groups. Ach: acetylcholine; NTG: nitroglycerine*

groups (p<0.01 in ANOVA; EES vs. SES, p<0.01; EES vs. PES, p<0.01; SES vs. PES, p=0.84) **(Figure 2)**.

ANGIOSCOPIC FINDINGS

Angioscopic data at follow-up are listed in **Table 3**. Incidences of in-stent thrombus and yellow intima in the EES were significantly lower than in the SES and PES groups (p<0.01 and p<0.01, respectively), while the average of dominant neointimal coverage grading was comparable among the three groups (p=0.44).

INDEPENDENT FACTORS OF ENDOTHELIAL DYSFUNCTION DISTAL TO THE STENT AFTER DES IMPLANTATION

A linear regression analysis was performed to determine the factors of vasomotor response to maximum dose of Ach (10^{-6} mol/L) distal to the stent. No patient or lesion variables were associated with the vasomotive reactions to Ach distal to the stent. The presence of yellow intima and the grade of neointimal coverage were significantly associated with vasoconstriction to Ach distal to the stent in a simple linear regression, but not in a stepwise multivariate regression. In a stepwise multivariate regression analysis, the presence of in-stent thrombus and the generation of DES (first/second) were determined to be the independent factors of endothelial dysfunction distal to the stent after DES implantation (p<0.001 and p<0.001, respectively) **(Table 4)**.

Table 4. Independent factors of endothelial dysfunction* after DES implantation.

	Stepwise multivariate regression		
	β coefficient	*p*-value	Adjusted R^2
Presence of in-stent thrombus	0.40	<0.01	0.31
First-generation/second-generation	0.29	<0.01	

*Vascular motion in response to acetylcholine (10^{-6} mol/L) at segment distal to DES.
DES: drug-eluting stent

Discussion

The main findings of the present study were the following. 1) Coronary vasomotions to Ach distal to the EES were better preserved than those of first-generation DES. 2) Incidences of in-stent thrombus formation and yellow intima with the EES were significantly lower than with the first-generation DES. 3) The presence of in-stent thrombus and the generation of DES were the independent factors of endothelial dysfunction distal to the DES.

Coronary endothelial dysfunction has been suggested to be an independent predictor of atherosclerotic disease progression and cardiovascular event rates[27]. Likewise, incomplete neointimal coverage and yellow intima could be related with an increased potential risk of future thrombotic events in DES[7,8,28-31]. In addition, the presence of in-stent thrombus would indicate lack of re-endothelialisation and/or endothelial dysfunction at the stented site.

There are numerous clinical data showing delayed arterial healing after first-generation DES implantation[19,24-26]. Components including durable polymers and thick stent struts in first-generation DES contributed to the delayed healing[11-13]. Moreover, several clinical studies of first-generation DES have revealed endothelial dysfunction at adjacent segments, especially in distal segments[19,32-34]. Although there is no definitive explanation for abnormal endothelial function adjacent to DES, there are several potential mechanisms to be considered. First, re-endothelialisation has been reported to be seriously delayed after first-generation DES implantation[7,8]. Accordingly, reduced nitric oxide production attributable to delayed re-endothelialisation at the stented site could be associated with endothelial dysfunction adjacent to the DES. Second, Sahler et al showed that antiproliferative drugs may have locally diffused through the vasa vasorum to the non-stented distal segments, leading to impaired endothelial function distal to the DES[35]. Third, Pendyala et al reported that polymer incompatibility and potentiation of superoxide activity may be a culprit of endothelial dysfunction with PES[36]. Fourth, as we have previously reported in the canine model of acute coronary syndromes, vasoactive substances released from thrombi, which are shed into the distal site and would impair distal endothelial function, may also play a critical role[37,38]. Furthermore, we have shown that endothelial dysfunction distal to first-generation DES was strongly associated with the existence of in-stent thrombus in the clinical setting[19]. Thus, thrombus at the stent site might aggravate endothelial function adjacent to the DES.

ARTERIAL HEALING AND ENDOTHELIAL FUNCTION AFTER EES IMPLANTATION

In the current study, the use of EES was associated with better-preserved endothelial function, less in-stent thrombus formation, and less yellow intima compared with first-generation DES, whereas EES did not show superiority in the grade of neointimal coverage.

EES consist of a thin strut platform coated with a durable fluoropolymer. Thin stent struts are associated with less arterial injury, less flow disturbance, more rapid endothelial cell coverage, and less thrombogenicity compared to thick stent struts[39-41]. Additionally, fluoropolymers of EES have also demonstrated thromboresistant properties with more rapid endothelialisation tendencies in several *ex vivo* and *in vivo* experiments[40,41]. Thus, better re-endothelialisation and less thrombus formation with EES may lead to better endothelial function than first-generation DES.

Yellow intima is considered as unstable plaque and could be related to future clinical events[28-31]. Previous angioscopic studies have revealed that yellow intima was more often observed after first-generation DES, especially SES implantation, compared with BMS[25,26]. Moreover, it has been reported that the yellow colour of plaque changes to a stable white colour during the six months after BMS implantation[42]. By contrast, in first-generation DES, incomplete neointimal coverage and chronic inflammation may be attributed to prolonged yellow intima exposure. EES treatment is associated with fewer inflammatory responses compared with first-generation DES[43]. Therefore, more stable healing processes might lead to a lower incidence of yellow intima in EES than in

first-generation DES, although neointima thickness in EES was comparable to first-generation DES.

Study limitations

Several important limitations of this study should be noted. First, this study was a non-randomised, non-consecutive enrolment and single-centre study with a relatively small number of patients. Additionally, patients were included in different time periods. However, stent selection bias was minimal and has probably not influenced the result, because stent selection was based only on stent availability over time. Indeed, there were no significant differences in baseline patient and lesion characteristics among the three groups. Second, only patients who were diagnosed with stable angina and treated with a single DES for a *de novo* single lesion were evaluated in this study. Therefore, our results may have a risk of patient selection bias and cannot be generalised to all patients in the real world. Third, because our study ended at nine months after DES implantation, our results refer to this specific point in time. Fourth, no baseline angioscopic data were available, although the frequency of yellow intima and thrombus at follow-up should be affected by conditions immediately after stent implantation. Presumably, however, the index frequency of yellow intima and thrombus was similar among the three groups as judged from the similarity of the baseline patient, lesion, and procedural characteristics. Fifth, the initial coronary endothelial function test was not performed. However, the initial endothelial function test could not be applied, because all patients had significant coronary lesions and the presence of significant stenosis would affect vasomotor response. To compensate for this limitation, we evaluated a reference segment as an internal, patient-specific control. Finally, the clinical outcome of our results in the long term remains unknown.

Conclusions

In this study, second-generation EES demonstrated better endothelial function, less thrombus formation, and less yellow intima than first-generation DES at nine months after stent implantation.

Impact on daily practice

It is very important to evaluate coronary endothelial function and intra-stent condition in patients treated with DES, because both endothelial dysfunction and delayed arterial healing could be associated with future cardiovascular event rates. The present study is the first report to reveal that second-generation EES produce better endothelial function and arterial healing than first-generation DES. Our results suggest second-generation EES treatment could provide superior clinical outcomes compared to first-generation DES.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Site-specific neoatherosclerosis assessed by optical coherence tomography in patients with in-stent restenosis

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KEYWORDS

- in-stent restenosis
- neoatherosclerosis
- optical coherence tomography

Abstract

Aims: To assess the pattern of site-specific neoatherosclerosis in patients with in-stent restenosis (ISR).

Methods and results: Optical coherence tomographic (OCT) data were analysed from 146 patients with ISR (39 bare metal and 107 drug-eluting stents). Sites of in-stent minimal lumen area (MLA) were (1) bifurcation (5 mm-long segment of the proximal main branch [MB], the confluence zone and a 5 mm-long segment of the distal MB), and (2) non-bifurcation, classified as marginal (MLA within a 5 mm-long segment adjacent to the stent margin) or body (MLA confined to the stent body) type. Median stent duration was 53.7 months. In-stent MLA sites located in bifurcation segments (vs. non-bifurcation) had a higher frequency of TCFA-containing neointima (48% [23/48] vs. 27% [26/98], p=0.015) and thrombi (63% [30/48] vs. 36% [35/98], p=0.003). When in-stent MLA was located in non-bifurcation segments, TCFA-containing neointima (43% vs. 14%, p=0.002) and intimal rupture (45% vs. 23%, p=0.029) were more common in marginal vs. body types. Post-procedural CK-MB was higher in lesions whose MLA was located at bifurcation vs. non-bifurcation sites (1.8 [1.2-4.2] vs. 1.4 [0.8-2.4] ng/ml, p=0.016) and in marginal vs. body type (2.1 [0.9-4.4] vs. 1.2 [0.7-1.8] ng/ml, p=0.015). In five lesions with stent fracture, 80% of the MLA sites showed either in-stent TCFA or intimal rupture.

Conclusions: In-stent neoatherosclerosis was more common when in-stent MLA was located at bifurcation (vs. non-bifurcation), near the stent margin (vs. body), and at the stent fracture site.

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Introduction

In-stent neoatherosclerosis is an important contributing mechanism of late stent failure, such as very late stent thrombosis and in-stent restenosis (ISR), after both bare metal stent and drug-eluting stent implantation[1-5]. However, the site-specific patterns of neointimal characteristics in ISR lesions still remain unclear. In native coronary artery disease, high-risk atherosclerotic plaques with a large necrotic core are prone to developing at bifurcation sites which are subject to abnormal conditions of endothelial shear stress[6-8]. Even though bifurcation stenting has been predisposed to stent thrombosis and ISR[9,10], the frequency and distribution of unstable neointima which develops after bifurcation stenting has not been known. The aims of this study were to use optical coherence tomography (OCT) to detect advanced neoatherosclerosis in patients with ISR and characterise the patterns of neoatherosclerosis at different sites, namely restenotic lesions located at bifurcation versus non-bifurcation sites and at stent edge versus non-edge segments.

Methods

From August 2008 to December 2013, 154 patients with ISR underwent pre-procedural OCT at the Asan Medical Center, Seoul, South Korea. Exclusion criteria were as follows: haemodynamic instability, inability of the OCT ImageWire (LightLab Imaging, Westford, MA, USA) or Dragonfly™ catheter (St. Jude Medical, St. Paul, MN, USA) to cross the lesion of restenosis into the distal vessel (owing to tight stenosis or severe vessel tortuosity), the presence of left main or saphenous vein graft lesions, acute myocardial infarction, or the presence of an angiographically visible thrombus. Before April 2011, OCT examination using the proximal occlusive technique could not be carried out in cases where the lesion was located near the ostium. OCT image analysis was performed at the Imaging Core Laboratory at Asan Medical Center. The following exclusions were made: one patient with a thrombotic coronary occlusion without significant neointima, four patients with dominant stent underexpansion and little neointima, and three patients with poor OCT images. In total, 146 patients with 146 lesions were finally included in the current analysis.

Serum creatine kinase-myocardial band (CK-MB) was measured before and after the procedure. All patients signed written, informed consent prior to the study.

The time-domain OCT procedure and its anatomical limitations for the occlusive technique in use prior to April 2011 have been previously reported[11,12]. OCT image acquisition was performed using a commercially available system for intracoronary imaging and a 0.019 inch ImageWire (LightLab Imaging). The artery was cleared of blood by continual flush delivery, as previously described. The flush consisted of Iodixanol 370 (Visipaque™; GE Healthcare, Cork, Ireland) applied at a flow rate of 3.0 ml/s. Since April 2011, OCT images have been acquired using a non-occlusive technique and the C7XR™ system (Dragonfly™ catheter and C7XR™; LightLab Imaging [now St. Jude Medical]).

Neointima was defined as tissue formed between the luminal border and the inner border of the struts. Calcific intima was defined as a well-delineated, signal-poor region with sharp borders. Lipidic intima was defined as a signal-poor region with diffuse borders[13]. In-stent thin-cap fibroatheroma (TCFA) was defined as a fibrous cap thickness at its thinnest part of ≤65 μm, and an angle of lipidic tissue of ≥120° inside the stent[14,15]. Intimal rupture was determined by OCT imaging as a break in the neointima's fibrous cap enabling communication of the lumen with the underlying ruptured cavity: this definition is analogous to that of plaque rupture seen in native atherosclerotic plaques, as reported previously[5,16]. Thrombi were defined as masses protruding into the vessel lumen, discontinuous from the surface of the vessel wall, and with a dimension ≥250 μm. Red thrombi were characterised by high-backscattering protrusions with signal-free shadowing, whereas white thrombi were characterised by signal-rich, low-backscattering projections into the lumen[17,18]. The axial locations of TCFA-containing intima and intimal rupture were assessed at the minimal lumen area (MLA) site (within 5 mm from the MLA frame)[4] and within a 5 mm segment proximal and distal to the MLA site.

Bifurcation segments of the main branch (MB) consisted of a distal MB segment (5 mm-long segment distal to the carina, defined as the frame immediately distal to the take-off of the side branch), a confluence zone (confluence of MB and side branch), and a proximal MB segment (a 5 mm-long segment just above the confluence zone)[19]. When the in-stent MLA was located within those bifurcation segments, TCFA-containing neointima and intimal rupture were assessed at the MLA site and each of the bifurcation segments. When the in-stent MLA was located within a non-bifurcation segment, the lesions were classified as marginal or body type according to location: 1) marginal type was defined when an in-stent MLA was located within a proximal or distal 5 mm-long segment adjacent to the stent margin, and 2) body type was defined when an in-stent MLA site was confined to the body of the stent **(Figure 1)**.

Stent strut coverage was assessed as previously described[20]. All OCT parameters reported required the agreement of two observers (SJ Kang, JM Ahn).

All values are expressed as the median value (interquartile range [IQR]) or as counts and percentages (categorical variables). Continuous variables were compared by the nonparametric Mann-Whitney test; categorical variables were compared with χ^2 statistics or Fisher's exact test. All p-values were two-sided, and p-values less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

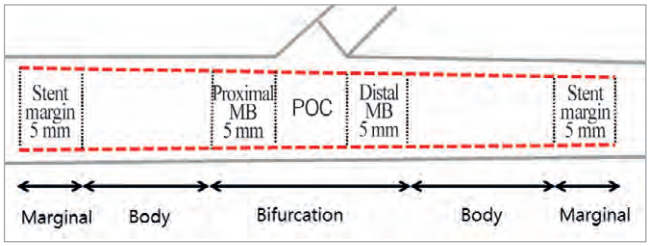

Figure 1. *Definition of in-stent restenosis site.*

Results

The clinical characteristics of the 146 study participants are summarised in **Table 1**. The median (IQR) follow-up time was 53.7 (18.7-87.4) months. The ISR lesions were associated with the following types of stent: 39 bare metal; 55 sirolimus-eluting (Cypher; Cordis, Johnson & Johnson, Miami Lakes, FL, USA); 23 paclitaxel-eluting (TAXUS; Boston Scientific Corp., Marlborough, MA, USA); four zotarolimus-eluting (Endeavor®; Medtronic Vascular, Santa Rosa, CA, USA); four Resolute zotarolimus-eluting (Endeavor Resolute; Medtronic Vascular); 17 everolimus-eluting (XIENCE V coronary stent system; Abbott Vascular, Santa Clara, CA, USA); two umirolimus (Biolimus) A9 (Nobori; Biosensors International, Singapore); and two Cilotax™ (Cardiotec Co. Ltd, Seoul, South Korea).

Overall, in the 146 ISR lesions, MLA was 1.5 mm^2 (0.9-1.9 mm^2). At the MLA site, TCFA-containing neointima and intimal rupture were seen in 49 (34%) lesions and 52 (36%) lesions, respectively. The MLA was located within a bifurcation segment in 48 (33%) lesions, while the remaining 98 (67%) lesions had the MLA located at a non-bifurcation segment. Overall, malapposition was observed in 23 (16%) lesions. The frequency of intraluminal thrombi was 81 (55%): red thrombi 10 (7%), white thrombi 55 (38%), and mixed thrombi 16 (11%).

In these 48 lesions, 71% of the in-stent MLA sites were located within the distal MB, 6% within the confluence zone, and 23% within the proximal MB **(Table 2, Figure 2)**. The frequency of TCFA-containing neointima was 52% at the distal MB, 38% at the confluence zone, and 58% at the proximal MB. The frequency of intimal rupture was 46% at the distal MB, 22% at the confluence zone and 38% at the proximal MB.

The MLA sites located within the bifurcation segments more frequently showed TCFA-containing neointima (48% [23/48] vs. 27% [26/98], p=0.015) and intraluminal thrombi (63% [30/48] vs. 36% [35/98], p=0.003) than in MLA sites located at non-bifurcation

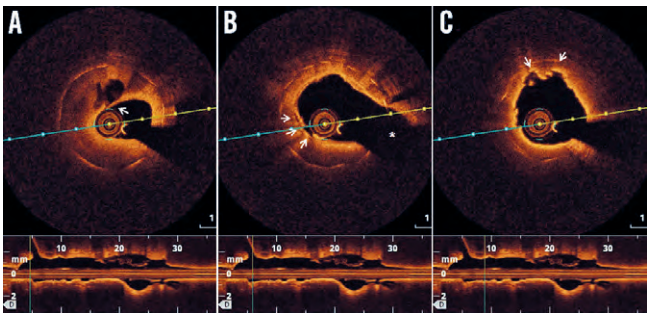

Figure 2. *OCT findings in the ISR lesions at bifurcation site. A) At the MLA site within distal main branch, ruptured cavity inside the stent, ruptured TCFA (arrow) were shown. B) In-stent TCFA with disruption (arrows) was demonstrated in the confluence zone with the diagonal branch (asterisk). C) At the proximal main branch, arrows indicate TCFA-containing neointima with disruption.*

Table 1. Baseline characteristics of the 146 patients and location of the in-stent minimal lumen area (MLA).

Variable	Total	Location of in-stent MLA		*p*-value
		Bifurcation	Non-bifurcation	
N	146	48	98	
Baseline clinical characteristics				
Age (years)	64.0 (56.0-69.0)	63.5 (57.2-69.0)	64 (56.0-69.0)	0.812
Male gender, n (%)	116 (80%)	39 (81%)	77 (79%)	0.829
Smoking, n (%)	76 (52%)	24 (50%)	52 (54%)	0.712
Hypertension, n (%)	97 (66%)	33 (69%)	64 (65%)	0.713
Hypercholesterolaemia, n (%)	125 (85%)	39 (81%)	86 (88%)	0.321
Diabetes mellitus, n (%)	56 (43%)	21 (44%)	35 (36%)	0.370
Previous myocardial infarction, n (%)	26 (18%)	11 (23%)	15 (15%)	0.261
Statin therapy at admission, n (%)	105 (72%)	36 (75%)	69 (71%)	0.624
Drug-eluting stent, n (%)	107 (73%)	30 (63%)	77 (79%)	0.047
Unstable angina at admission, n (%)	35 (24%)	12 (25%)	23 (24%)	0.839
High-sensitive C-reactive protein, mg/L	0.07 (0.03-0.18)	0.09 (0.04-0.22)	0.06 (0.03-0.17)	0.177
Types of vessel				
Left anterior descending, n (%)	91 (62%)	36 (75%)	55 (56%)	
Left circumflex, n (%)	9 (6%)	5 (10%)	4 (4%)	0.014
Right coronary, n (%)	45 (31%)	7 (15%)	38 (39%)	
Left main, n (%)	1 (1%)	0 (0%)	1 (1%)	
Total stent length, mm	28.0 (17.8-51.0)	30.0 (18.0-50.3)	28.0 (16.0-51.3)	0.741
Stent duration, months	53.7 (18.7-87.4)	74.9 (39.9-108.8)	48.8 (15.8-80.3)	0.012

Values are median (interquartile range) or n (%).

Table 2. OCT findings in the 48 lesions in which in-stent MLA was located within bifurcation segments.

At the MLA site	
Location of MLA	
Distal main branch, n (%)	34 (71%)
Confluence zone, n (%)	3 (6%)
Proximal main branch, n (%)	11 (23%)
MLA, mm^2	1.5 (1.0-1.9)
Lipid neointima, n (%)	45 (94%)
Intimal rupture, n (%)	20 (42%)
In-stent TCFA, n (%)	23 (48%)
5 mm-long segment proximal to the MLA	
Intimal rupture, n (%)	21 (44%)
In-stent TCFA, n (%)	33 (68%)
5 mm-long segment distal to the MLA	
Intimal rupture, n (%)	11 (23%)
In-stent TCFA, n (%)	19 (40%)
Thrombi within in-stent segment, n (%)	30 (63%)
Calcification within in-stent segment, n (%)	11 (23%)

Values are median (interquartile range) for continuous variables or n (%). MLA: minimal lumen area; OCT: optical coherence tomography; TCFA: thin-cap fibroatheroma

Table 3. OCT findings in the 98 lesions in which in-stent MLA was located at non-bifurcation segments.

N	Marginal type	Body type	*p*-value
	42	56	
In-stent thrombi, n (%)	21 (50%)	14 (25%)	0.018
In-stent calcification, n (%)	5 (12%)	5 (9%)	0.505
Lipid neointima, n (%)	39 (93%)	52 (93%)	1.000
At the MLA site			
MLA, mm^2	1.5 (0.9-1.8)	1.4 (0.9-1.9)	1.000
Intimal rupture, n (%)	19 (45%)	13 (23%)	0.029
In-stent TCFA, n (%)	18 (43%)	8 (14%)	0.002
5 mm in-stent segment adjacent to the stent margin			
Intimal rupture, n (%)	19 (45%)		
In-stent TCFA, n (%)	18 (43%)		
5 mm reference segment			
Plaque rupture, n (%)	6 (14%)		
TCFA, n (%)	8 (19%)		
5 mm in-stent segment proximal to the MLA			
Intimal rupture, n (%)		3 (5%)	
In-stent TCFA, n (%)		7 (13%)	
5 mm in-stent segment distal to the MLA			
Intimal rupture, n (%)		2 (4%)	
In-stent TCFA, n (%)		7 (13%)	

Values are median (interquartile range) or n (%). MLA: minimal lumen area; TCFA: thin-cap fibroatheroma

segments. Among the 23 lesions with TCFA at the MLA site, the TCFA was distributed at the flow divider in five (22%) lesions, at the lateral wall in nine (39%) lesions, and at both the flow divider and the lateral wall in nine (39%) lesions. TCFA-containing neointima (68% vs. 40%) and intimal rupture (44% vs. 23%) were more frequently observed in 5 mm-long segments proximal (vs. distal) to the MLA site (all $p<0.05$).

In the 98 lesions in which MLA was located at a non-bifurcation segment, 42 lesions were classified as marginal type and 56 lesions as body type **(Figure 3)**. At the MLA site, TCFA-containing neointima and intimal rupture were found more frequently in marginal vs. body type **(Table 3, Figure 4)**.

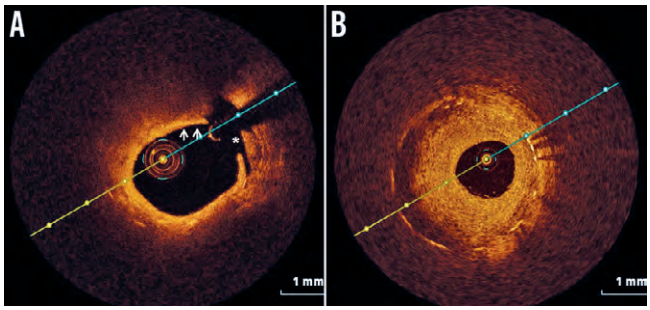

Figure 3. *OCT findings in the ISR lesions at non-bifurcation site. A) Marginal type (MLA site located within 5 mm in-stent segment adjacent to the proximal stent edge). Intimal rupture (asterisk) and TCFA (arrows) were shown. B) Body type (MLA site confined to the stent body portion).*

In five lesions, the MLA site was associated with stent fracture. All five affected stents were located in right coronary arteries, the specific fracture site being either stent body (n=4 lesions) or the proximal MB of the bifurcation segment (n=1 lesion). At the MLA site, four (80%) lesions showed in-stent TCFA (n=2) or intimal rupture (n=2). TCFA-containing neointima proximal to the MLA was seen in two (40%) lesions.

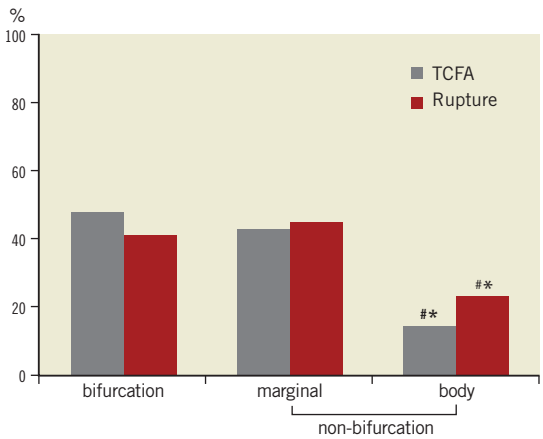

Figure 4. *Frequencies of in-stent TCFA and intimal rupture according to the location of in-stent MLA. (# p-value <0.05 vs. bifurcation, * p-value <0.05 vs. marginal type)*

All patients underwent repeat revascularisation for the treatment of their ISR lesions. Although pre-procedural peak CK-MB was similar (1.0 ng/ml [0.4-1.7 ng/ml] vs. 0.9 ng/ml [0.6-2.2 ng/ml], p=0.8), post-procedural CK-MB was significantly higher in ISR lesions whose MLA was located within a bifurcation segment as compared to a non-bifurcation segment (1.8 ng/ml [1.2-4.2 ng/ml] vs. 1.4 ng/ml [0.8-2.4 ng/ml], p=0.016). Among the lesions in which the MLA was located within a non-bifurcation, the post-procedural CK-MB was much higher in marginal-type ISR lesions compared with those in body type (2.1 ng/ml [0.9-4.4 ng/ml] vs. 1.2 ng/ml [0.7-1.8 ng/ml], p=0.015).

Post-procedure, TIMI <3 was shown in 11 lesions, which included five (45%) lesions with ISR at a bifurcation and three (27%) lesions with a marginal type of ISR. Seven (64%) of the 11 lesions showed in-stent TCFA or rupture.

Discussion

The major findings of this OCT study in patients with ISR are the following. 1) In-stent MLA sites were more likely to have TCFA-containing neointima and intraluminal thrombi when the MLA was located within bifurcation (vs. non-bifurcation). 2) When in-stent MLA was located within a non-bifurcation segment, TCFA-containing neointima and intimal rupture were more frequent in marginal-type (in-stent MLA within a 5 mm-long segment adjacent to the stent margin) compared to body-type (MLA site confined to the body) lesions. 3) Post-procedural CK-MB was significantly higher in the lesions whose MLA was located within bifurcation (vs. non-bifurcation) segments and also in those lesions classified as marginal (vs. body) type.

Previous studies showed that abnormal endothelial shear stress is associated with differential distribution of high-risk, rupture-prone plaques along the native coronary artery[6-8]. Bifurcations, inherently geometrically complex regions, generate disturbed laminar flow and abnormal wall shear stress patterns that have the potential to play a role in plaque accumulation and destabilisation[8,21,22]. Additionally, it has been suggested that atherosclerotic plaques at coronary artery bifurcations have a heterogeneous nature, depending on their anatomical location and the segment involved[23].

With constant exposure to turbulent blood flow and excessive shear stress, stents at bifurcations are predisposed to thrombus formation and ISR[9,10]. The degree of neointimal growth and vascular inflammation following stent implantation correlates inversely with wall shear stress[24-26]. In a recent computational simulation study, measurements of wall shear stress and blood stagnation (relative residence time) showed that wall regions were more prone to the risk of restenosis if they were located next to stent struts and to bifurcations[27]. Our current study demonstrated that neointimal growth has characteristics specific to the site of ISR. Advanced neoatherosclerosis, such as TCFA-containing neointima and intimal rupture, developed more frequently when the MLA of the ISR lesion was located at the bifurcation or adjacent to the stent margin. Pathological and *in vivo* imaging studies showed that in-stent neoatherosclerosis makes an important contribution to the failure of bare metal or drug-eluting stents by, for example, very late stent thrombosis or late ISR[1-5]. The site-specific progression of neoatherosclerosis may contribute to the particularly high risk of stent thrombosis and restenosis after bifurcation stenting. Stent duration was much longer when lesions with ISR were located at bifurcation vs. non-bifurcation sites (74.9 [39.9-108.8] vs. 48.8 [15.8-80.3] months, p=0.012). Neoatherosclerosis progresses over time, such that the development of vulnerable neointima and ISR at bifurcation points is likely to increase with time after stent implantation under continuous exposure to wall shear stress.

The mechanism of edge vascular response and edge restenosis has been considered multifactorial. Disruption of *de novo* atherosclerotic change in stented segments and reference segments may lead to edge restenosis as well as stent thrombosis[28]. Mechanical stress determined by angulation or calcification at the edge segment and biomechanical properties of the DES may cause chronic local inflammation, neointimal overgrowth and edge ISR[29]. The mechanism and impact of a higher rate of in-stent neoatherosclerosis at the stent margin needs to be clarified in further studies.

Ali et al reported that vulnerable neointima formation and post-procedural CK-MB elevation was greater in lesions associated with DES compared with bare metal stents, suggesting that neoatherosclerosis has an impact on distal embolisation and periprocedural MI[30]. In the current study, the high level of CK-MB post-stenting following treatment of ISR at bifurcation sites or near the stent margin may be partly explained by the presence of advanced neoatherosclerosis at those sites.

Nakazawa et al suggested that stent fracture was frequently associated with adverse pathological findings, such as restenosis and stent thrombosis[31]. In addition, Kashiwagi et al showed that intimal hyperplasia is enhanced at the fracture site. Loss of ability to scaffold the artery wall against mechanical stress and failure of local drug delivery may be related to excessive intimal growth at the fracture site[32].

Limitations

This study had several limitations. First, owing to its relatively small sample size, OCT characteristics of neointima were not compared within the various types of DES implanted. Second, clinical outcomes after treatment of ISR lesions were not reported. Third, attenuation caused by large amounts of red thrombus might have obscured the underlying neointima morphology, potentially leading to an underestimation of the frequencies of TCFA-containing neointima and intimal rupture. Although the side branch ostium is the most common site of ISR after bifurcation stenting, it was not assessed by side branch pullback OCT. Even though patients who required dilation prior to OCT imaging were systematically excluded, we cannot rule out the possibility that the OCT procedure may have contributed to some of the findings, such as neointimal disruption.

Conclusions

In-stent neoatherosclerosis was more common when in-stent MLA was located at the bifurcation (vs. non-bifurcation), near the stent margin (vs. body), and at the stent fracture site.

Impact on daily practice

Neoatherosclerosis has been one of the important mechanisms of late stent failure. In the current study, in-stent TCFA and intimal rupture were more common when in-stent restenosis was located at the bifurcation, stent margin and stent fracture sites. These findings may explain the higher rate of restenosis and stent thrombosis after stent implantation at those sites. Site-specific advanced neoatherosclerosis may contribute to the high risk of periprocedural myocardial infarction during target lesion revascularisation.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Fate and clinical significance of angiographically visible stent malapposition (peri-stent contrast staining) after drug-eluting stent implantation: a long-term clinical follow-up study

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KEYWORDS

- drug-eluting stent (DES)
- intravascular ultrasound (IVUS)
- stent fracture
- stent malapposition
- stent thrombosis

Abstract

Aims: Peri-stent contrast staining (PSS) is thought to represent angiographically visible incomplete stent apposition, and may be associated with adverse clinical sequelae. We investigated the prognostic significance of PSS in patients with sirolimus-eluting stents (SES).

Methods and results: Consecutive patients undergoing SES implantation with follow-up angiography (n=807, 644 male, mean age 66.0 years) at >6 months were studied. The primary endpoint was major adverse cardiac events (MACE), defined as a composite of death, myocardial infarction, stent thrombosis, and target lesion revascularisation. Twenty patients (2.48%) exhibited PSS at follow-up angiography. After a median of five years (3,744 patient-years) of follow-up, seven (35.0%) in the PSS group reached the primary endpoint versus 117 (14.9%) in the non-PSS group (p=0.013). Together with diabetes, renal failure, unstable angina, saphenous vein graft and longer total stent length, PSS independently predicted the primary endpoint (HR: 2.94, 95% confidence interval 1.36 to 6.35, p=0.006). PSS was also significantly associated with very late stent thrombosis (VLST), which occurred in three (15.0%) patients with PSS versus 13 (1.7%) patients without PSS (p=0.006).

Conclusions: PSS is an uncommon but significant angiographic finding in patients treated with SES implantation, which independently predicts MACE, and may contribute to an increased risk of VLST.

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Introduction

The initial success of drug-eluting stents in ameliorating restenosis has been tempered by the recognition of an apparently higher incidence of late stent-related complications relative to bare metal stents, including very late stent thrombosis (VLST)[1-10]. Amongst other factors, VLST has been linked to incomplete stent apposition as detected by intravascular ultrasound and/or optical coherence tomography[11-16]. However, these invasive imaging modalities are not in widespread routine clinical use, and the majority of coronary interventions remain guided by conventional x-ray angiography alone.

While Alfonso and co-workers reported that three patients suffered from VLST associated with angiographic coronary aneurysm, Imai et al described the phenomenon of peri-stent contrast staining (PSS), which they defined as contrast staining outside stent struts insufficient to fulfil the definition of a coronary artery aneurysm (localised dilatation of the lumen; >50% of the diameter of associated reference vessel segment) in a single-centre retrospective cohort study[17,18]. Imai and colleagues found an association between PSS within 12 months of sirolimus-eluting stent (SES) implantation and subsequent major adverse cardiac events (MACE), including target lesion revascularisation (TLR) and VLST[18]. The finding of PSS may therefore potentially identify patients at increased risk requiring prompt remedial intervention. However, their study was limited by low event rates and clinical follow-up was for up to only three years. Before the widespread recognition of PSS as a harbinger of increased risk, there is a need to confirm these findings in other centres. We sought to determine the longer-term clinical significance of PSS with follow-up up to five years, and to explore its relationship with stent strut fracture[19,20]. We further sought to determine the baseline clinical and procedural factors predisposing to PSS.

Editorial, see page 12

Methods

STUDY POPULATION, OUTCOME MEASURES AND FOLLOW-UP

We prospectively enrolled 939 consecutive patients undergoing percutaneous coronary intervention (PCI) with sirolimus-eluting stents to examine long-term angiographic and clinical outcome at the Fujita Health University Hospital, Toyoake, Japan, from June 2004 to August 2009. Patients with a target lesion in a native coronary artery undergoing elective stent implantation with agreement to follow-up coronary angiography were included in the study. Patients were excluded from the study if they had a contraindication to anticoagulation and antiplatelet therapy. Overall, 132 patients did not undergo follow-up angiography and were excluded from the study cohort, giving rise to a final study population of 807 patients **(Figure 1)**. Patients underwent routine follow-up angiography after a minimum of six months and were followed up clinically for a minimum of four years (median five years, interquartile range from four years to six years) with a total of 3,744 patient-years accrued and 100% clinical follow-up. The study was approved by our institutional ethics committee and was carried out in accordance with the guidelines set out in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Our primary endpoint was a composite of MACE, defined as subacute stent thrombosis (≤30 days after the procedure); late stent thrombosis (>30 days after the procedure); very late stent thrombosis (VLST, defined as stent thrombosis >1 year after the procedure); death, Q-wave and non-Q-wave myocardial infarction, and need for target lesion revascularisation (TLR).

All patients were followed up for the study endpoint by a combination of telephone interviews, review of medical records, and consultation with referring cardiologists and patients' primary care physicians. All events were adjudicated by an endpoint committee blinded to the angiographic data.

PERCUTANEOUS CORONARY INTERVENTION PROCEDURES

According to standard patient care, treatment with aspirin at a dose of 100-200 mg daily was started before the procedure and continued indefinitely. Treatment with a thienopyridine was begun before the procedure and continued for at least one year to avoid subacute and late stent thrombosis.

Sirolimus-eluting stent (CYPHER®; Cordis, Johnson & Johnson, Miami Lakes, FL, USA) implantation was performed according to standard clinical practice with radial or femoral approaches using

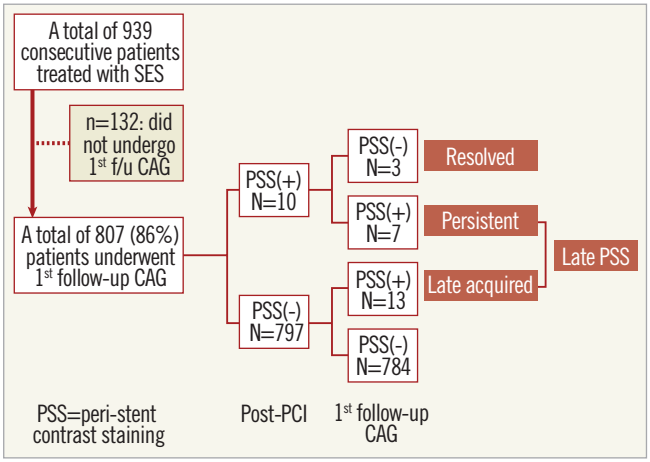

Figure 1. *Study flow chart illustrating study design. PSS: peri-stent contrast staining; SES: sirolimus-eluting stent*

guide catheters 6 Fr or greater in a size to facilitate subsequent quantitative coronary angiographic (QCA) analysis[21,22]. A bolus of 8,000-10,000 IU of heparin was administered during the procedure. To ensure full expansion of the stent, high-pressure intra-stent balloon inflation was performed. Stent and balloon sizes were determined using measurements of vessel dimension and plaque distribution made with IVUS, where technically possible. A total of 766 (95%) patients underwent IVUS-guided PCI. The IVUS criteria for optimal stenting were originally derived from the MUSIC study: (1) good stent apposition with symmetric stent expansion; (2) full stent expansion with sufficient lumen area (i.e., lumen area 80% or greater of the average reference lumen area pre-intervention); and (3) the absence of major dissection[23]. To fulfil these criteria, repeated high-pressure intra-stent balloon inflation or additional stenting was performed if necessary.

QCA analysis

QCA analyses were performed using the computer-based edge-detection Coronary Angiography Analysis System (CAAS II; Pie Medical Imaging, Maastricht, The Netherlands)[21,24]. Coronary angiograms were obtained in multiple views matched after intracoronary injection of nitrates. Interpolated reference vessel diameter, minimal lumen diameter (MLD) and percentage diameter stenosis were obtained at baseline (pre stenting), post-stenting, and at follow-up using the guiding catheter from the QCA system as a scaling device. QCA analyses were performed at the independent core laboratory of the Fujita Health University. QCA measurements of the target lesion were obtained in the "in-stent" (including only the stented segment) and in the 5 mm adjacent segments (the stent margins 5 mm proximal and distal to the stent). Late loss was defined as the change in MLD at follow-up (MLD post-stenting minus MLD at follow-up). Restenosis was defined as ≥50% diameter stenosis at follow-up by QCA.

PERI-STENT CONTRAST STAINING AND STENT FRACTURE DEFINITIONS

PSS was defined as contrast staining outside of the stent struts extending to >20% of the diameter of the corresponding reference vessel segments[18]. Stent fracture was defined as the significant disappearance of stent struts in the stent at follow-up angiography in comparison with the presence of stent struts immediately after stent implantation, or by newly developed fluoroscopic discontinuity of stent struts at follow-up[20]. The presence of PSS and stent fracture was determined in the core laboratory independently by two experienced observers blinded to all clinical data, with adjudication by a panel in cases of disagreement.

STATISTICAL ANALYSIS

All continuous variables are expressed as mean±SD for normally distributed variables or as medians and interquartile ranges for non-parametric data. Normality was assessed using the Kolmogorov-Smirnov test. The unpaired t-test or Mann-Whitney U test was used to assess differences in continuous variables between two groups as appropriate. Categorical data are presented as frequencies and percentages. Differences in categorical variables were assessed using the chi-square test or Fisher's exact test where appropriate. Cumulative event-free survival for MACE was assessed using the Kaplan-Meier method, and comparison between groups was performed using the log-rank test. Where appropriate, a multivariable Cox proportional hazards model was used to adjust for potentially confounding variables with $p<0.05$ on univariable analysis using a forward stepwise variable selection procedure. The validity of the proportionality of hazards assumption was appropriately checked. To evaluate the predictors of PSS, multivariable binary logistic regression analysis including variables with $p<0.05$ by univariable analysis was performed using a forward stepwise variable selection procedure. All data were analysed using SPSS Version 21 (IBM Corp., Armonk, NY, USA). Only a single culprit lesion was evaluated per patient to avoid the effects of intra-cluster correlation (ICC). Two-tailed values of $p<0.05$ were considered significant.

Results

Overall, there were 23 cases of PSS identified in the study cohort – 10 immediately after SES implantation and a further 13 cases identified at follow-up **(Figure 1)**. Of the 10 initial cases, three had resolved at pre-planned follow-up angiography. The final number of patients with PSS was therefore 20 (2.48%).

Table 1. Baseline demographic and clinical characteristics of the study cohort.

		Late PSS (n=20)	Non-PSS (n=787)	*p*-value
No. of lesions		20	787	–
Age (years)		64.8±8.8	66.3±9.4	0.771
Male (%)		16 (80.0)	626 (79.5)	0.962
Body mass index (kg/m^2)		23.6±2.4	24.0±3.1	0.645
Diabetes (%)		5 (25.0)	258 (32.8)	0.463
Hypertension (%)		11 (55.0)	490 (62.3)	0.509
Hypercholesterolaemia (%)		9 (45.0)	446 (56.7)	0.299
Renal insufficiency (%)		3 (15.0)	109 (13.9)	0.750
Current smoking (%)		11 (55.0)	251 (31.9)	0.029
Prior infarction (%)		9 (45.0)	305 (38.8)	0.572
Previous angioplasty (%)		13 (65.0)	379 (48.2)	0.137
Previous bypass surgery (%)		1 (5.0)	54 (6.9)	0.793
Clinical status (%)	Stable angina	15 (75.0)	571 (72.6)	0.809
	Unstable angina	1 (5.0)	105 (13.3)	0.499
	Acute myocardial infarction	3 (15.0)	86 (10.9)	0.476
	Recent myocardial infarction	1 (5.0)	25 (3.2)	0.485
Emergency PCI		5 (25.0)	153 (19.0)	0.567
Left ventricular ejection fraction (%)		59.4±10.7	57.6±12.5	0.492
Medical treatment (%)	Statins	12 (60.0)	470 (59.7)	0.979
	Beta-blockers	6 (30.0)	310 (39.3)	0.395

Values are expressed as mean±SD or n (%). PCI: percutaneous coronary intervention

Table 1 summarises the baseline demographic and clinical characteristics of the PSS and non-PSS groups. There was a significantly higher proportion of current smokers amongst the PSS patients but the two groups were otherwise comparable. With respect to vessel and lesion characteristics, patients in the PSS group exhibited greater vessel tortuosity **(Table 2)**. The procedural characteristics for the two groups were largely similar; however, the reference vessel diameter at baseline was greater in the PSS group **(Table 3)**. None of the patients had stent strut fracture at baseline. However, patients in the PSS group had a significantly higher incidence of stent strut fracture at follow-up relative to the non-PSS group (20.0% versus 5.7% respectively, p=0.008).

CLINICAL FOLLOW-UP

At the end of follow-up, of the 20 patients with PSS, seven (35%) reached the primary endpoint of MACE versus 117 (14.9%) in the non-PSS group (p=0.013) **(Figure 2A)**, a difference largely driven by myocardial infarction and the need for target lesion revascularisation **(Figure 2B, Figure 2C, Table 4)**. Overall, three patients (15.0%) in the PSS group experienced VLST versus 13 patients (1.7%) in the non-PSS group (p=0.006) **(Figure 2D, Table 4)**. After adjusting for the presence of stent fracture and other baseline clinical and angiographic differences, the presence of PSS remained a significant independent predictor of the primary outcome of MACE (hazard ratio [HR]: 2.94, 95% confidence interval [CI] 1.36 to 6.35, p=0.006) **(Figure 3, Table 5)**. The presence of diabetes, renal failure, unstable angina, saphenous vein graft and longer total stent length were also significant independent predictors of outcome.

Table 2. Baseline angiographic characteristics of the study cohort.

		Late PSS (n=20)	Non-PSS (n=787)	*p*-value
Location of target lesion (%)	Right coronary	6 (30.0)	232 (29.5)	0.960
	Left anterior descending	8 (40.0)	360 (45.7)	0.611
	Circumflex	5 (25.0)	172 (21.9)	0.784
	Left main	1 (5.0)	19 (2.4)	0.398
	Saphenous vein graft	0 (0.0)	7 (0.9)	0.675
In-stent restenosis (%)		3 (15.0)	81 (10.3)	0.454
De novo (%)		16 (80.0)	681 (86.5)	0.337
Eccentric (%)		18 (90.0)	574 (72.9)	0.122
Severe calcification (%)		4 (20.0)	118 (15.0)	0.552
Tortuosity (%)		8 (40.0)	154 (19.6)	0.024
Bifurcation (%)		13 (65.0)	367 (46.6)	0.104
Ostial location (%)		2 (10.0)	123 (15.6)	0.755
Chronic total occlusion (%)		1 (5.0)	25 (3.2)	0.485
Thrombosis (%)		2 (10.0)	84 (10.7)	0.924
Angle >60°		2 (10.0)	62 (7.9)	0.668
Multiple bending (%)		2 (10.0)	57 (7.2)	0.652
Type B2/C (%)		17 (85.0)	541 (68.7)	0.145

Values are expressed as n (%).

Table 3. Angiographic, procedural, and quantitative coronary angiography (QCA) data.

	Late PSS (n=20)	Non-PSS (n=787)	*p*-value
Procedural characteristics			
Stent size (mm)	3.1±0.3	3.0±0.4	0.488
Maximum inflation pressure (atm)	16.1±3.3	15.9±3.0	0.765
No. of stents per lesion	1.3±0.5	1.3±0.6	0.814
Total stent length (mm)	27.6±12.4	24.5±10.4	0.592
IVUS use (%)	19 (95.0)	747 (94.9)	0.998
Direct stenting (%)	6 (30.0)	310 (39.4)	0.396
Crush stenting (%)	1 (5.0)	29 (3.7)	0.536
Bifurcation stenting (%)	7 (35.0)	166 (21.1)	0.134
Kissing balloon technique (%)	1 (5.0)	34 (4.3)	0.592
Angle alteration			
Angle (°)	148.9±17.5	147.3±18.2	0.786
Post-angle (°)	162.5±13.2	160.1±12.6	0.626
Reduction angle (°)	13.6±11.0	12.8±12.2	0.563
Follow-up angle (°)	154.9±15.0	155.0±16.1	0.568
Increased angle (°)	7.6±6.8	5.3±9.4	0.047
Acute angiographic outcome			
Angiographic success (%)	19 (95.0)	776 (98.6)	0.262
TIMI 3 (%)	19 (95.0)	774 (98.3)	0.298
QCA			
Reference diameter at baseline (mm)	2.89±0.58	2.54±0.56	0.029
Lesion length (mm)	19.8±12.7	16.9±8.8	0.430
Minimal lumen diameter (mm)			
At baseline	1.06±0.64	0.89±0.45	0.360
After procedure	2.49±0.43	2.47±0.49	0.839
At follow-up	2.22±0.78	2.33±0.61	0.422
Acute gain (mm)	1.43±0.83	1.58±0.57	0.478
Late loss (mm)	0.27±0.60	0.14±0.53	0.529
Stent fracture at follow-up			
Stent fracture (%)	4 (20.0)	45 (5.7)	0.008
Complete fracture (%)	2 (10.0)	30 (3.8)	0.166
Partial fracture (%)	2 (10.0)	15 (1.9)	0.012

Values are expressed as mean±SD or n (%). IVUS: intravascular ultrasound; QCA: quantitative coronary angiography; TIMI: Thrombolysis In Myocardial Infarction

PREDICTORS OF PSS

Multivariable logistic regression analysis revealed that the presence of smoking, stent fracture and a larger reference diameter pre-procedure, all independently predict PSS **(Table 6)**. On pre-specified exploratory analysis, the presence of a circumflex lesion, in-stent restenosis, or chronic total occlusion did not predict subsequent late PSS.

Discussion

We found that PSS was an uncommon occurrence after SES implantation with a net incidence of 2.48% at follow-up angiography. However, it was nonetheless significantly associated with adverse

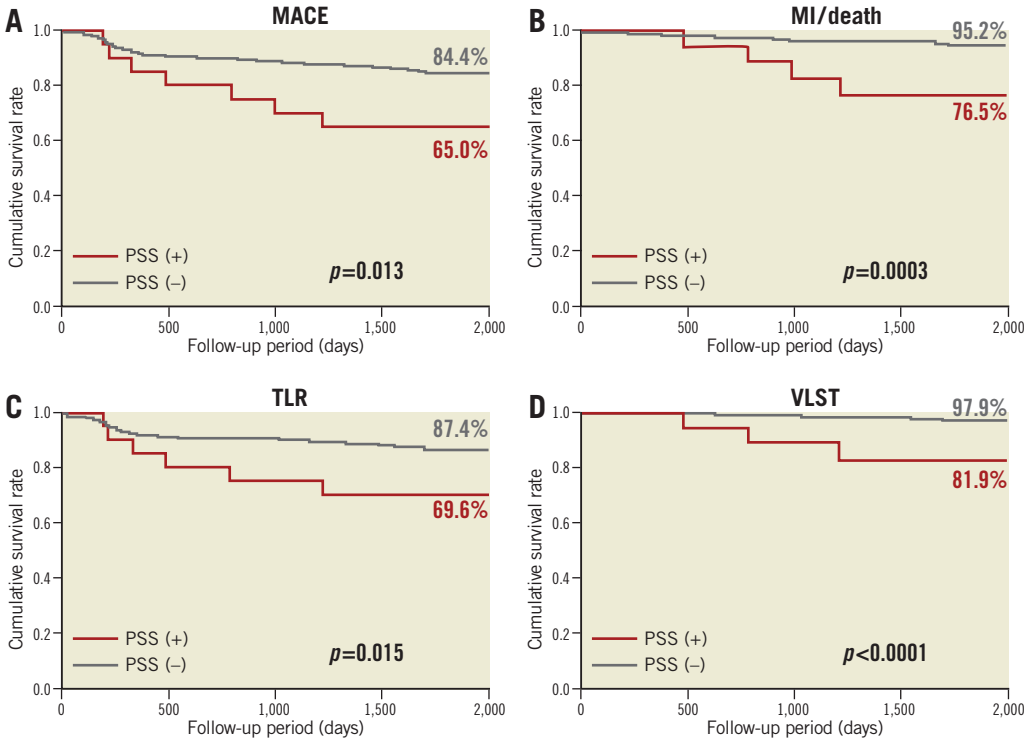

Figure 2. *Kaplan-Meier event-free survival rate for each clinical outcome. A) Kaplan-Meier estimates of event-free survival for the primary endpoint of major adverse cardiac events (MACE) stratified according to the presence or absence of peri-stent contrast staining (PSS). B) Kaplan-Meier estimates of event-free survival for myocardial infarction and death stratified according to the presence or absence of peri-stent contrast staining (PSS). C) Kaplan-Meier estimates of event-free survival from target lesion revascularisation (TLR) stratified according to the presence or absence of peri-stent contrast staining (PSS). D) Kaplan-Meier estimates of event-free survival for the secondary endpoint of very late stent thrombosis (VLST) stratified according to the presence or absence of peri-stent contrast staining (PSS).*

Table 4. Breakdown of study events stratified according to the presence or absence of peri-stent contrast staining (PSS).

	Late PSS (n=20)	Non-PSS (n=787)	*p*-value
In-stent restenosis, n (%)			
Focal	3 (15.0)	70 (8.9)	0.415
Diffuse	3 (15.0)	26 (3.3)	0.032
Overall	6 (30.0)	96 (12.2)	0.018
In-segment restenosis, n (%)			
Overall	7 (35.0)	127 (16.1)	0.025
Stent thrombosis, n (%)			
Definite	3 (15.0)	14 (1.8)	0.007
Probable	0 (0.0)	2 (0.3)	0.824
Possible	0 (0.0)	3 (0.4)	0.786
Definite/probable	3 (15.0)	16 (2.0)	0.010
All	3 (15.0)	19 (2.4)	0.015
Phase of stent thrombosis, n (%)			
Early	0 (0.0)	4 (0.5)	0.750
Late	0 (0.0)	2 (0.3)	0.823
Very late	3 (15.0)	13 (1.7)	0.006
Late/very late	3 (15.0)	15 (1.9)	0.008

Table 5. Summary of the results of univariable and multivariable analysis of the predictors of major adverse cardiac events (MACE) for the study cohort.

	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Late PSS	2.54 (1.18-5.44)	0.016	2.94 (1.36-6.35)	0.006
Body mass index	0.94 (0.89-0.99)	0.032		
Diabetes	2.00 (1.41-2.84)	0.001	1.98 (1.35-2.89)	0.001
Renal failure	2.84 (1.94-4.18)	<0.001	2.89 (1.91-4.35)	<0.001
Previous MI	1.55 (1.09-2.21)	0.013		
Prior CABG	2.34 (1.38-3.97)	0.002		
Unstable angina	1.68 (1.08-2.63)	0.021	1.90 (1.19-3.01)	0.004
LVEF	0.97 (0.96-0.99)	0.002		
Saphenous vein graft	6.28 (2.31-17.0)	0.001	5.13 (1.83-14.32)	0.002
Ostial location	1.58 (1.03-2.42)	0.035		
Stent fracture	2.08 (1.17-3.70)	0.012		
Number of stents	1.49 (1.17-1.90)	0.002		
Total stent length	1.02 (1.01-1.04)	0.003	1.27 (1.09-1.48)	0.003

Multivariable model included all baseline covariates with $p<0.05$ on univariable analysis, and was performed using a forward stepwise selection procedure. CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PSS: peri-stent contrast staining

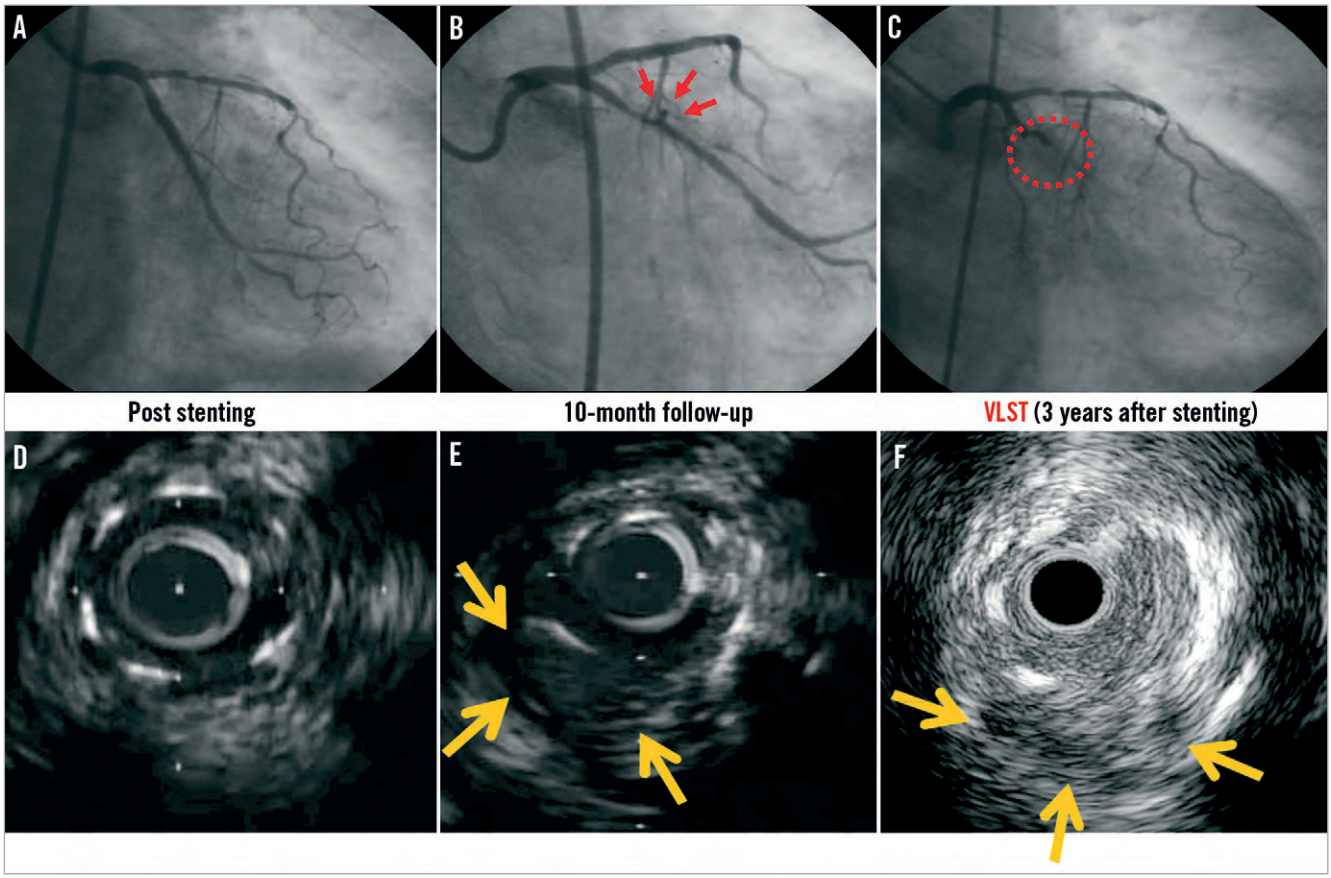

Figure 3. *Late acquired PSS and subsequent VLST. A 72-year-old female with stable angina underwent single stent implantation (3.0×18.0 mm) to the middle segment of the left circumflex coronary artery followed by high-pressure intra-stent balloon dilatation up to 14 atmospheres. Successful stent implantation was performed without significant residual stenosis by angiography (A). At 10-month follow-up, angiographically visible stent malapposition (i.e., peri-stent staining [PSS]) was observed without any significant clinical symptoms (B). At 1,416 days after initial stent implantation, she suddenly developed chest pain and hypotension. Emergent coronary angiography revealed thrombotic occlusion in the stented segment, representing very late stent thrombosis (C). Corresponding IVUS images are shown in the lower panels. These demonstrate a widely patent lumen without stent strut collapse immediately after the stent implantation (D). At 10-month follow-up, IVUS reveals that the external elastic membrane (EEM) is markedly increased and is associated with an incompletely apposed stent strut. This phenomenon produced significant lumen behind the stent strut from 6 o'clock to 9 o'clock (arrows in E). Follow-up IVUS demonstrates that thrombus occupies the lumen both inside the stent as well as behind the stent strut from 5 o'clock to 8 o'clock (arrows in F).*

Table 6. Results of logistic regression analysis of the predictors of peri-stent contrast staining (PSS).

	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Current smoking	2.61 (1.07-6.38)	0.035	2.51 (1.01-6.21)	0.047
Tortuosity	2.74 (1.10-6.82)	0.030		
Stent fracture	4.12 (1.32-12.84)	0.014	3.64 (1.13-11.79)	0.031
Reference diameter	2.32 (1.12-4.85)	0.024	2.42 (1.13-5.18)	0.023

Multivariable model included all baseline covariates with $p<0.05$ by univariable analysis, and was performed using a forward stepwise selection procedure.

clinical sequelae. For the first time, we were able to demonstrate that PSS is a significant independent predictor of MACE after adjusting for potential confounding variables, including stent fracture.

Imai et al first described the phenomenon of PSS and suggested an association between this finding and adverse outcomes, including TLR and VLST[18]. The incidence of PSS in the present study mirrors that reported by Imai et al. However, despite the fact that they studied 3,081 lesions in total from 1,998 patients, their median follow-up was only three years, and therefore their overall event rate was too low to allow meaningful statistical analysis of their principal study outcomes (TLR after one year and VLST), leaving uncertainty about the long-term clinical significance of this finding. In contrast, the median of five years (3,744 patient-years) of follow-up achieved in the present study, together with our broader but clinically relevant endpoint of MACE, allowed us to evaluate the independent prognostic significance of PSS whilst adjusting for potential confounders, including stent fracture. Furthermore, by studying

only one lesion per patient, we avoided the potential problem of intra-cluster correlation between lesions within patients, which limits the previous work by Imai et al.

Our findings are discordant with those of Yakushiji et al who examined the significance of late PSS in a subgroup of patients from the HORIZONS-AMI study[25]. They found a similar incidence of PSS at follow-up (2.1%) to the present study; however, in contrast to the present study, none of these patients experienced stent thrombosis. There are a number of potential explanations for this discrepancy. Firstly, the patients studied were treated with a mixture of bare metal and paclitaxel-eluting stents, whereas, in the present study, only patients undergoing SES implantation were studied. Secondly, patients with PSS had a higher rate of thienopyridine use at three years compared with those without PSS (50% versus 27%, respectively, p=0.016) with 21/22 (96%) also receiving aspirin. This prolonged use of dual antiplatelet therapy may have abrogated any thrombotic risk associated with PSS in their cohort. Thirdly, their median follow-up duration was three years from enrolment versus five years in the present study. This significantly shorter duration of follow-up will have reduced their power to detect any difference in event rates between those with and without PSS.

We found that current smoking, stent fracture and a larger reference vessel diameter were significantly associated with the development of PSS. These findings are discordant with those of Imai et al who identified chronic total occlusions, circumflex lesions, and in-stent restenosis as predictors of PSS. However, the latter associations should be treated with caution, as multiple lesions were analysed within patients without adjustment for intra-cluster correlation, resulting in potential overestimation of the significance of these associations.

Our analysis revealed that active smoking was one of the most important predictors for the occurrence of PSS. We speculate that the endothelial dysfunction engendered by smoking could predispose to the appearance of PSS in long-term follow-up; however, further work is required to elucidate the exact mechanisms responsible.

The phenomenon of PSS is likely to be an angiographic correlate of incomplete stent apposition. Its association with stent strut fracture is in keeping with this. However, stent malapposition is likely to be multifactorial in aetiology, and our finding that stent fracture was not an independent predictor of outcome is supportive of this. We have previously shown that, amongst other mechanisms, incomplete stent strut apposition can occur as a result of failure of neointimal hyperplasia as well as lesion remodelling[15]. Our present work confirms that, whilst PSS and stent fracture are associated, only PSS is of independent prognostic value for the outcome of MACE.

The significant association between PSS and thrombotic sequelae identified in the present study is in accord with the work of Cook et al, who, using IVUS, identified a high prevalence of incomplete stent apposition in patients with drug-eluting stents presenting with VLST[13]. More recently, we reported that incomplete stent apposition without neointimal hyperplasia by OCT was significantly associated with the presence of OCT-detected thrombus at follow-up, and may constitute a potent substrate for late stent thrombosis[15]. Although OCT and IVUS are likely to be significantly more sensitive at detecting incomplete stent apposition, the majority of patients undergoing PCI are not evaluated with these intracoronary imaging techniques[26]. Thus, the ability potentially to identify significant PSS with the more widely available conventional angiography alone affords the opportunity for remedial intervention.

In our cohort, we observed a VLST rate of ~2% after five years (0.4% per annum), implying a need for continued vigilance in patients treated with drug-eluting stents.

Although rare, this complication can be potentially devastating. We speculate that the presence of PSS may identify a subgroup of patients at higher risk who may benefit from prolonged or lifelong dual antiplatelet therapy; however, this hypothesis requires formal evaluation. The finding by Yakushiji et al that patients with PSS do not experience a greater rate of VLST in a setting where a significant number of these patients were on dual antiplatelet therapy is circumstantially supportive of such a strategy[25].

Study limitations

As PSS is a recently described phenomenon, our study is by necessity retrospective in nature. It was also conducted at a high-volume tertiary referral centre incurring the possibility of selection bias. Additionally, our study was not carried out in multicentre randomised fashion. Nevertheless, this also allowed us to standardise patient assessment and achieve a high rate of follow-up angiography (86%), and 100% clinical follow-up.

Our primary endpoint was a composite of MACE. Despite our large sample size and long minimum follow-up duration, we were underpowered to address specifically the independent prognostic significance of PSS for VLST with adjustment for potential confounders. However, given the rarity of the latter, this is only likely to be possible in the setting of a large multicentre international registry study.

Furthermore, while our primary endpoint was MACE defined as various stages of stent thrombosis, death, myocardial infarction, and need for target lesion revascularisation (TLR), some investigators might prefer to use only death and myocardial infarction. However, we feel that even VLST and TLR would also have significant impact on patients' clinical course because lesions with PSS may be associated with in-stent or in-segment restenosis requiring revascularisation due to abnormal vessel healing response following the SES implantation.

Although our study only evaluated patients undergoing SES implantation, peri-stent staining has also been described with more contemporary stents such as everolimus-eluting devices[27]. However, given the large number of patients who have received first-generation SES and the widespread current use of second-generation products, which have also been afflicted with this complication, we feel our data retain continuing relevance for current clinical practice. Indeed, given the long-term nature of the risk associated with peri-stent contrast staining, we feel it is important to alert the interventional cardiology community to this finding, which may be

present but apparently clinically silent amongst patients undergoing repeat angiography or intervention.

Conclusions

PSS is an uncommon but significant angiographic finding in patients treated with SES which independently predicts MACE, and may contribute to the increased risk of VLST in these patients. Further work is required to clarify the optimum management of patients with angiographically visible incomplete stent apposition and to investigate the mechanisms responsible for it.

Impact on daily practice

While peri-stent contrast staining (PSS) is thought to represent angiographically-visible incomplete stent apposition, previous IVUS/OCT studies revealed that incomplete stent apposition plays a role in thrombus formation following drug-eluting stent implantation[13-15]. However, previous studies have provided conflicting circumstantial evidence concerning the role of PSS in very late stent thrombosis[1,25]. Our study clearly and statistically demonstrated for the first time that PSS independently predicted major adverse cardiac events including death, MI, stent thrombosis and target lesion revascularisation, together with diabetes, renal failure, unstable angina, saphenous vein graft and longer total stent length. Furthermore, PSS was also significantly associated with very late stent thrombosis. Given that millions of patients around the world have been treated with the first generation sirolimus-eluting CYPHER® stent, PSS is a serious concern and should be recognised as a potential risk-marker for very late drug-eluting stent failure.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Short-term effects of Nano+™ polymer-free sirolimus-eluting stents on native coronary vessels: an optical coherence tomography imaging study

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KEYWORDS

- drug-eluting stent
- neointimal hyperplasia
- optical coherence tomography
- polymer-free stent

Abstract

Aims: Newly developed drug-eluting stents (DES) aim to promote early endothelialisation and prevent stent thrombosis. We sought to evaluate the extent of neointima growth by optical coherence tomography (OCT) three months after implantation of a polymer-free stent with a nano-sized-pore surface eluting sirolimus.

Methods and results: In this prospective, multicentre, open-label study, patients were enrolled with documented stable angina or silent ischaemia and planned intervention for up to two *de novo* coronary lesions (in different vessels), with lesion length of ≤18 mm. The primary OCT endpoint was the percentage of in-stent neointimal volume obstruction at three months. The secondary endpoints included binary restenosis, stent thrombosis and device-oriented composite endpoints: a composite of cardiac death, myocardial infarction (MI) non-attributable to non-target vessel and clinically indicated target lesion revascularisation at three months. A total of 45 patients with 47 lesions were enrolled from four European sites. Eventually, 43 patients with 45 lesions underwent OCT examination at three months (one case was excluded for poor image quality and one case due to catheter dysfunction). The median and interquartile range of in-stent neointimal volume obstruction was 8.2% (4.7-10.7), of strut coverage was 93.0% (83.2-96.5) and of incomplete apposed struts was 0% (0.0-0.9), respectively. At three months, the mean angiographic in-stent late lumen loss was 0.17±0.27 mm. No case of stent thrombosis, cardiac death or clinically indicated target lesion revascularisation was reported at three months.

Conclusions: Polymer-free sirolimus-eluting stents with a nano-sized-pore surface are effective in inhibiting neointimal tissue proliferation and promoting early vascular healing with high strut coverage at three-month follow-up. (ClinicalTrials.gov number: NCT01925027).

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Introduction

Bare metal stents (BMS) have practically been replaced by drug-eluting stents (DES), as previous trials have shown a reduction of in-stent-restenosis and repeat revascularisation[1-4]. To prevent the formation of neointimal hyperplasia, current DES are coated with a thin polymer film which regulates the amount of drug that is eluted into the treated vessel. Accumulating evidence shows that permanent polymer could trigger a chronic inflammatory response, which is characterised by a delayed re-endothelialisation, resulting in incomplete strut coverage and the potential for late stent thrombosis (LST)[5-7]. Based on these considerations, newer generations of DES have focused on the safety profile, changing from durable polymer to biodegradable polymer and ultimately to polymer-free stents in order to diminish vascular inflammation further. The assessment of vascular repair (i.e., to quantify strut coverage) after stent implantation by using optical coherence tomography (OCT) has shown that strut coverage is higher in biodegradable polymer stents than in permanent polymer stents[8,9]. So far, there have been only a few studies assessing strut coverage at a very short-term time point (three months). Also, there have been only two OCT studies[10,11] which examined the patterns of strut coverage in polymer-free stents. In the present study, the polymer-free stent with a nano-sized-pore surface has been considered as an alternative modality of local drug delivery. We hypothesised that polymer-free stents have an early arterial healing, thereby reducing the risk of late stent thrombosis, and a controlled growth of neointima, which may reduce the likelihood of restenosis. In our present study, we sought to evaluate the extent of three-month neointimal coverage after the implantation of polymer-free nano-sized-pore surface sirolimus-eluting stents (SES) (Nano+™, Lepu Medical, Beijing, China).

Methods

TRIAL DESIGN

We performed a prospective, multicentre, single-arm, open-label study in coronary artery disease patients enrolled in four European investigational sites between August 2013 and June 2014. Selection criteria included: 1) patients who had documented stable angina or silent ischaemia demonstrated by positive functional study with a *de novo* target lesion of >50% diameter stenosis; 2) planned intervention on up to two *de novo* lesions in different epicardial vessels; 3) lesion length of less than 18 mm; 4) native coronary artery of 2.5-4.0 mm diameter; and 5) patient and physician agreement to follow-up visits including angiographic and OCT assessment at three months. Major clinical exclusion criteria included: 1) evidence of ongoing acute myocardial infarction in ECG prior to procedure; 2) left ventricular ejection fraction <30%; and 3) known hypersensitivity or contraindication to medication or material in the study. Angiographic exclusion criteria included: severe tortuous, calcified or angulated coronary anatomy of the study vessel which in the opinion of the investigator would result in suboptimal imaging or excessive risk of complication from placement of an OCT catheter; target lesion in left main stem; target lesion involving a side branch >2.0 mm in diameter; aorto-ostial lesion (within 3 mm of the aorta junction); total occlusion or TIMI flow 0 prior to wire crossing; target vessel containing visible thrombus; restenotic lesion; arterial or saphenous vein graft lesions or lesions distal to a diseased arterial or saphenous vein graft.

All major adverse cardiac events were adjudicated by an independent clinical events committee, and a data safety monitoring board monitored patient safety. The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent.

STUDY DEVICE

The Nano+™ is a drug-coated stent which consists of a stainless steel platform crimped onto a delivery system which includes a high-pressure, semi-compliant balloon incorporated into the distal tip of a rapid exchange delivery catheter system. The strut thickness is 91 μm. The two ends of the stent present a sinusoidal curve shape while the middle parts have a special cyclic structure, all aligning in a helix shape (**Figure 1A** and **Figure 1B**). A large number of pores are present on the adluminal stent surface (**Figure 1C** and **Figure 1D**). The pore diameter is 400 nm and occupies only 1/800 of the stent thickness. The delivery system has a crossing profile of 0.93 mm with two radiopaque markers at the ends of the balloon to facilitate proper stent placement. For this trial, the Nano+ stent was available in five nominal stent diameters (2.5-4.0 mm), and eight lengths (9-36 mm). In summary, the stent releases the antiproliferative agent from the pores directly into the vessel wall without the use of any drug-eluting polymer as coating. Nano+ has a sirolimus dose of 2.2 μg/mm^2 and 85% of the drug is released within 30 days.

CORONARY STENT PROCEDURE

All patients received dual antiplatelet therapy before the procedure (oral aspirin 160-300 mg per day and clopidogrel or prasugrel or ticagrelor). Intraprocedural anticoagulation was achieved with unfractionated heparin as per standard practice. After the procedure, all patients were required to receive aspirin 75-100 mg per day indefinitely and a once daily dose of clopidogrel 75 mg or prasugrel 10 mg or ticagrelor 90 mg bid for the whole length of the study. Three types of biomarker (creatinine kinase, creatinine kinase-MB and troponin T or I) were sampled at least 24 hours prior to PCI and determined pre-discharge or within 48 hours, whichever came first. The highest value per reference was taken into consideration for adjudication of myocardial infarction. Patients will have clinical follow-up at six months and one year.

QUANTITATIVE CORONARY ANALYSIS

Two-dimensional quantitative coronary analysis (QCA) was performed at an independent core lab (Cardialysis BV, Rotterdam, The Netherlands) with the CAAS system (CAAS 5.9; Pie Medical BV, Maastricht, The Netherlands). The region of interest was the stented segment and the peri-stent segment, defined as 5 mm proximal and distal to the stent edge. The following parameters for QCA were computed: minimal luminal diameter (MLD), percentage of diameter stenosis (%DS) and reference vessel diameter (RVD). Binary

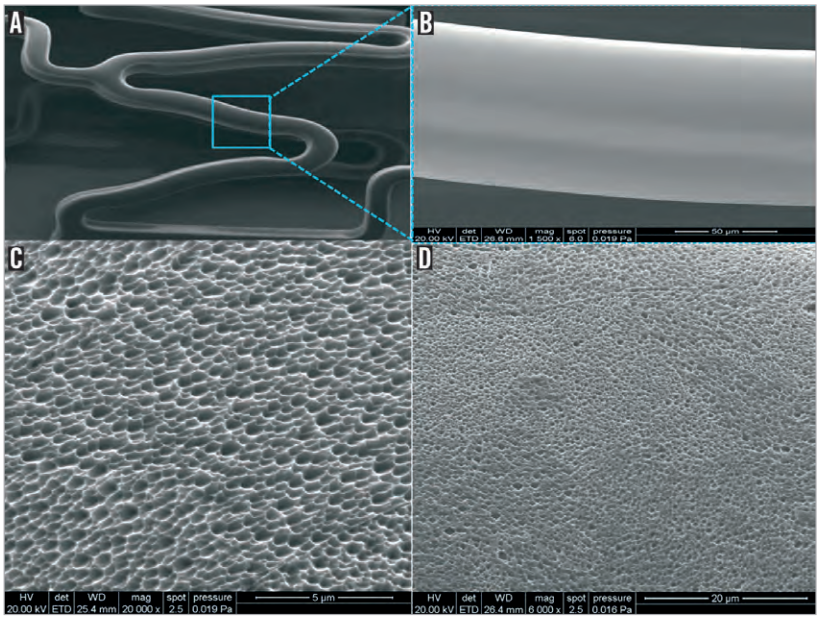

Figure 1. *Stent design. Strut design after expansion (A). The strut thickness is 91 µm (B), and a large number of sirolimus-filled pores are present on the adluminal stent surface. Electron microscopy shows the size of the nano pores at a magnification of 20,000x (C) and 6,000x (D).*

restenosis was defined as a diameter stenosis of 50% or more in any of the studied segments (stent and peri-stent segments) at follow-up. Late loss was defined as the difference between post-procedure MLD and follow-up MLD.

OCT IMAGING AND ANALYSIS

At three-month follow-up, OCT was performed using the three different frequency-domain OCT systems (C8 ILUMIEN OPTIS PCI Optimization System and Dragonfly II™ OCT catheter; C7-XR™ OCT Intravascular Imaging System and Dragonfly™ catheter; both consoles and catheters are from St. Jude Medical, St. Paul, MN, USA; LUNAWAVE OFDI System and FastView™ OFDI Imaging Catheter; Terumo, Tokyo, Japan). The intravascular imaging catheter was placed distal to the region of interest. OCT imaging commenced at a pullback speed of 18 mm/sec which retrieved images at 180 frames per second by Dragonfly II™ catheter, 20 mm/sec, 100 frames per second by Dragonfly™ catheter, and 20 mm/sec, 158 frames per second by FastView™ catheter.

All OCT images were analysed at an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) by analysts who were blinded to patient and procedural information. QIvus 2.2 software (Medis, Leiden, The Netherlands) was used. Cross-sectional OCT images were analysed at 1 mm intervals. Stent and luminal cross-sectional areas (CSA) were measured, and the neointimal cross-sectional area was calculated as the stent CSA minus the luminal CSA. The stent volume (SV), lumen volume (LV) and neointimal volume (NV=SV- LV) were also computed. Percentage of in-stent neointimal volume obstruction (%NVO) was calculated as NV/SV x 100%. Neointimal thickness was defined as the distance between the endoluminal surface of the neointima and the luminal surface of the strut reflection at the mid-point of the strut and on a line perpendicular to the neointima and strut. A covered strut was defined as having neointimal thickness more than 0 µm[12]. The percentage of covered struts was calculated as the number of covered struts ×100 divided by the number of total struts which were analysable. Incomplete strut apposition was defined as a clear separation between strut and vessel wall with a distance greater than the thickness of the strut (91 µm). The spread-out sheets of each individual stent were created displaying struts using colour codes for coverage status. The graphics were obtained by correlating the longitudinal distance of each strut from the distal edge of the scaffold with the angle defining its circumferential position with respect to the centre of gravity of the vessel in each OCT pullback, taking as reference 0° the position at 3 o'clock[13-17].

In addition, the healing index to quantify the degree of vessel healing was calculated[18,19]. This score combines the following parameters: a) presence of intraluminal defect (%ILD; ILD area both free from the wall and attached to lumen/stent area) is assigned a weighting factor of "4"; b) presence of both malapposed and uncovered struts (%MU) is assigned a weighting factor of "3"; c) presence of uncovered struts alone (%U) is assigned a weighting factor of "2"; d) presence of malapposition alone (%M) is assigned a weighting factor of "1"; and finally e) presence of neointimal volume obstruction of more than 30% will be calculated by %NVO minus 30 then assigned a weighting factor of "1" (if neointimal volume was less than 30% , this factor was omitted). The parameters used to compute the healing index are shown in **Figure 2**.

STUDY ENDPOINTS

The primary endpoint was the percentage of in-stent neointimal volume obstruction at three-month follow-up. The secondary endpoints were angiographic, OCT and clinical endpoints.

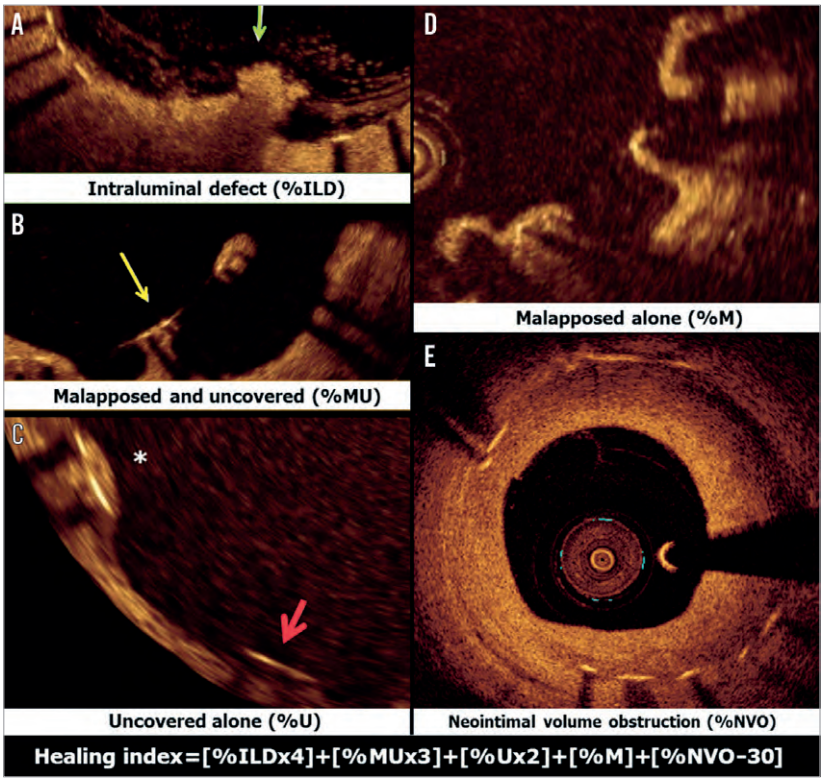

Figure 2. *Example of five parameters used for healing index calculation. The healing index was weighted according to OCT findings. The score was calculated from the presence of: (i) intraluminal defect area (A, green arrow); (ii) malapposed and uncovered struts (B, yellow arrow); (iii) uncovered struts alone (C, red arrow, as opposed to struts labelled with an asterisk which were covered struts); (iv) malapposition alone (D, all four struts were malapposed with good neointimal coverage); and (v) neointimal volume obstruction more than 30% (E). This parameter will be omitted if neointimal volume obstruction less than 30%. ILD: intraluminal defect; M: malapposition; MU: malapposed and uncovered; NVO: neointimal volume obstruction; U: uncovered*

The angiographic endpoints were binary restenosis, late lumen loss, MLD and percentage of diameter stenosis (%DS) post-procedure and at three months. The OCT endpoints were neointimal area and volume, mean stent area and volume, mean lumen area and volume, minimal stent area and volume, minimal lumen area and volume, neointimal thickness of the strut coverage, percentage of covered struts, and incomplete strut apposition area at three months. The clinical endpoints of this study were: 1) device-oriented composite endpoints (DOCE) and their individual components; 2) acute success; 3) stent thrombosis (ST) according to the definitions of the Academic Research Consortium[20].

Definitions of clinical endpoints

The device-oriented composite endpoints (DOCE) were defined as cardiac death, myocardial infarction not clearly attributable to a non-intervention vessel, and clinically indicated target lesion revascularisation. The definition of cardiac death included any death with immediate cardiac cause (e.g., MI, low-output failure, fatal arrhythmia); deaths related to the procedure, including those related to concomitant therapy; unwitnessed death; and death of unknown cause. In this study, the per protocol definition for MI was the World Health Organization (WHO) MI definition[21], i.e., the development of new pathological Q-waves or creatinine kinase rise of two or more times the upper limit of normal (ULN) accompanied by a creatinine kinase-MB rise. Other definitions were equally assessed in enzymatic terms as follow: 1) the third universal definition of myocardial infarction (TUD)[22] is defined by an elevation of cardiac troponin values >5x the upper reference limit in patients with normal baseline value; 2) the SCAI definition[23] is defined by an elevation of CK-MB >10x ULN or, in the absence of CK-MB measurements, elevation of cardiac troponin (cTn T or I) >70x ULN. Some of these criteria require additional criteria, such as symptoms, new ischaemic ECG changes or new LBBB, angiographic loss of patency of a major coronary artery or side branch or persistent slow- or no-flow or embolisation, or imaging demonstrating new loss of viable myocardium or regional wall motion abnormality.

Target lesion revascularisation is defined according to the definition of the Academic Research Consortium[20]. Acute success was a composite of: 1) device success defined as successful implantation of the study device with less than 30% residual stenosis by visual assessment; 2) procedural success is considered successful if there is post-procedure in-stent diameter stenosis <30% by visual assessment and TIMI 3 at post-procedure or TIMI 2 at pre-and post-procedure and no occurrence of in-hospital DOCE.

SAMPLE SIZE AND STATISTICAL METHODS

For the Nano+ OCT study, no formal sample size calculation was performed as there were no previous data concerning the expected magnitude of the effect. The endpoint analyses presented in this report were performed on an intention-to-treat basis. Categorical variables were summarised with frequencies and percentages. Continuous variables were reported as mean and standard deviation (SD) or median and interquartile ranges depending on the distribution of the data. The Student's t-test or non-parametric test was used to compare continuous variables. The statistical software used in this study was SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

ROLE OF THE FUNDING SOURCE

The investigators designed the study. Data collection and data analysis were performed at an independent central research organisation (Cardialysis BV, Rotterdam, Netherland). The sponsor had no role in data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

PATIENT AND PROCEDURAL CHARACTERISTIC

A total of 45 patients were enrolled in the study (details of recruitment are provided in the Appendix). **Table 1** shows baseline clinical characteristics, risk factors and current medication. The mean age of patients was 64.0±9.8 years with male predominance. The lesion characteristics are shown in **Table 2**. The right coronary artery was the most frequently treated vessel and half of the patients had a B2 lesion classification. The number of study stents implanted was 1.1 per lesion, with overlapping stents in four lesions. Procedural success was achieved in 44 patients; one patient did not meet the criteria of procedural success since this patient had sustained a periprocedural MI.

ANGIOGRAPHIC RESULTS

The QCA data at pre-procedure, post-procedure and at three months in all 47 lesions are shown in **Table 3**. The %DS was 60.9±10.8 before the intervention, 9.9±5.5 after the intervention, and 12.9±8.6 after three months. The procedure-induced acute lumen gain was 1.50±0.38 mm. At three-month follow-up, late lumen loss was 0.17±0.27 mm, and there was no evidence of binary restenosis (%DS >50%).

OPTICAL COHERENCE TOMOGRAPHY ANALYSIS

OCT was performed in 43 patients (two patients were excluded from the analysis due to poor OCT image quality [n=1] and OCT catheter dysfunction [n=1]). **Table 4** presents the results of OCT analysis of the primary endpoint. A total of 45 lesions containing 7,005 struts were included in the analysis, with a mean of 155.7±53.2 struts being analysed per lesion. Neointima volume obstruction was 8.2% (IQR 4.74-10.72). The median percentage of covered struts was 93.0% (IQR 83.2-96.5). **Figure 3A** shows the cumulative frequency of the percentage of covered struts: approximately two thirds of patients had more than 90% strut coverage after three months. Median neointimal

Table 1. Baseline characteristics of patients.

		N=45 patients
Age (years), mean±SD		64.0±9.8
Men, n (%)		33 (73.3)
Current smokers, n (%)		6 (13.3)
Diabetes, n (%)		5 (11.1)
Hypertension, n (%)		24 (53.3)
Hyperlipidaemia, n (%)		6 (13.3)
Family history of CAD, n (%)		19 (42.2)
Previous CABG, n (%)		1(2.2)
Previous PCI, n (%)		10 (22.2)
Previous myocardial infarction, n (%)		10 (22.2)
Stable angina, n (%)		30 (66.7)
Silent ischaemia, n (%)		6 (13.3)
Current cardiac medication before index procedure	Aspirin, n (%)	39 (86.7)
	Clopidogrel, n (%)	12 (26.7)
	Beta-blocker, n (%)	30 (66.7)
	Statin, n (%)	32 (71.1)
Antiplatelet regimens in the first three months	Aspirin, n (%)	45 (100.0)
	Clopidogrel, n (%)	40 (88.9)
	Prasugrel, n (%)	1 (2.2)
	Ticagrelor, n (%)	4 (8.9)

Data are mean±standard deviation or number (%). CABG: coronary artery bypass graft; CAD: coronary artery disease; PCI: percutaneous coronary intervention

Table 2. Baseline target lesions and procedural characteristics.

	N=45 patients/ 47 lesions
Target vessel	
Left anterior descending, n (%)	6 (12.8)
Left circumflex artery, n (%)	14 (29.8)
Right coronary artery, n (%)	27 (57.4)
AHA/ACC lesion classification	
B1, n (%)	20 (42.6)
B2, n (%)	25 (53.2)
C, n (%)	2 (4.3)
Moderate to heavy calcification, n (%)	8 (17.0)
Diameter stenosis (%)	60.9±10.8
Obstruction length (mm)	12.7±4.4
Total nominal length of implanted stents per lesion (mm)	20.0±9.2
Overlapping stents, n (%)	4 (8.5)
Reference vessel diameter (mm)	2.83±0.46
Minimal lumen diameter (mm)	1.10±0.35
Mean lumen diameter (mm)	2.51±0.39
Acute success	
Device success (lesion level), n (%)	47/47 (100.0)
Procedure success (patient level), n (%)	44/45 (97.8)

Data are mean±standard deviation or number (%). AHA/ACC: American Heart Association/American College of Cardiology

Table 3. Quantitative coronary angiographic follow-up results (intention to treat, N=47).

Variable		Pre-procedure	Post-procedure	3-month follow-up
Reference vessel diameter (mm)	In-stent	2.83±0.46	2.89±0.42	2.79±0.41
	In-segment		2.81±0.46	2.73±0.43
Diameter stenosis (%)	In-stent	60.9±10.7	9.9±5.49	12.9±8.6
	In-segment		18.1±7.6	18.2±8.2
Minimal lumen diameter (mm)	In-stent	1.10±0.35	2.59±0.34	2.43±0.40
	In-segment		2.29±0.41	2.23±0.41
Mean lumen diameter (mm)	In-stent	2.51±0.39	2.98±0.39	2.86±0.40
	In-segment		2.92±0.40	2.82±0.39
Stent length (mm)	In-stent		17.61±7.78	17.51±7.66
	In-segment		26.56±7.76	26.44±7.62
Acute gain (mm)	In-stent		1.50±0.38	
	In-segment		1.20±0.41	
Late loss (mm)	In-stent			0.17±0.27
	In-segment			0.06±0.19
Binary restenosis	In-stent			0 (0.0)
	In-segment			0 (0.0)

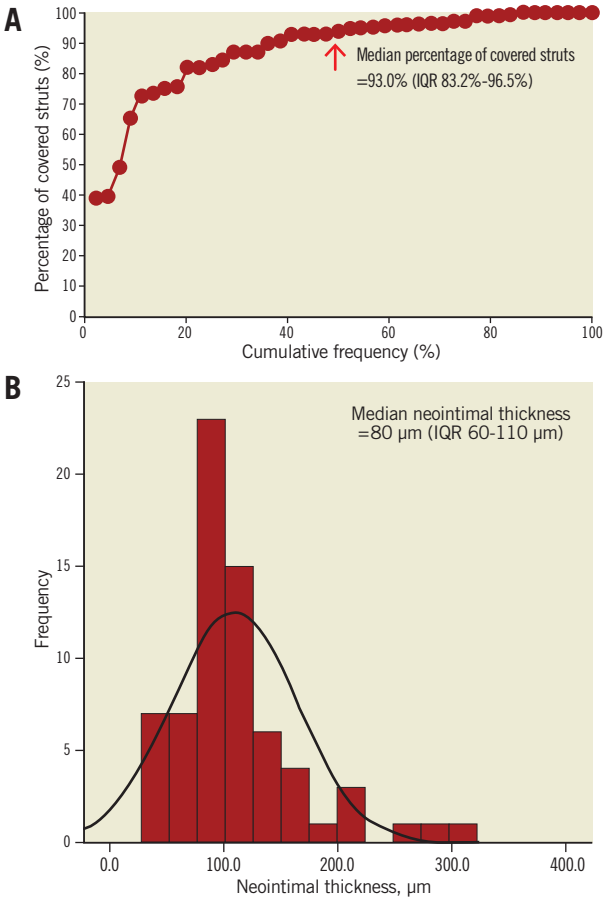

Figure 3. *Cumulative frequency curve of percentage of covered struts (A) and histogram of neointimal thickness (B).*

thickness at three months was 80 (IQR 60-100) µm and maximum neointimal thickness was 300 (IQR 220-350) µm. **Figure 3B** presents the distribution of neointimal thickness in all lesions. A total of 51 out of 7,005 struts were malapposed; the median percentage of ISA was 0% (IQR 0.0-0.86). Among malapposed lesions, a mean area of ISA >2 mm^2 was present in only two lesions. There was no thrombus area larger than 300 µm^2. **Figure 4** shows an example of a vessel treated with the Nano+ stent at three-month follow-up. **Figure 5** demonstrates spread-out vessel charts in an individual case, including the healing score and percentage of strut coverage from all 45 OCT pullbacks. The median healing index was 16.2 (IQR 7.5-33.6): the lowest score was 0 and the highest score was 177.7.

CLINICAL ENDPOINTS AND OUTCOMES

The three-month device-oriented composite endpoint (DOCE) rate was 2.2% (one patient), which resulted from a single periprocedural MI according to the per protocol definition (WHO MI definition) **(Table 5)**. The cause of the periprocedural MI was a coronary dissection (type F) after stent post-dilation, resulting in the need for bail-out implantation of overlapping stents. In **Table 6**, all cardiac biomarkers are tabulated according to the current MI definitions. All three types of cardiac biomarker were available in 97.8% of patients (44/45), while in one patient (2.2%) only creatinine kinase-MB and troponin were available. Overall, creatinine kinase and creatinine kinase-MB ratios were normal, while the troponin ratio was 9.04±35.67 times greater than ULN from the excessive increase of troponin in the case with periprocedural MI. When we subcategorised periprocedural myocardial infarction according to all current enzymatic criteria, there was a wide range of values exceeding the ULN (from 2.3% to 24.4%) depending on the definition. There was no stent thrombosis up to three months.

Discussion

The Nano+ study has assessed new criteria of coronary arterial healing three months after implantation of polymer-free SES. In this study, at three months the Nano+ stent showed: i) a low

Table 4. Optical coherence tomography results (intention to treat).

Overall (N=45 lesions)	Median (IQR 25-75)
Strut level analysis	
Total analysed struts, n	7,005
Mean number of struts per cross-section, n	143 (128.0-169.0)
Percentage of covered struts‡	93.0 (83.2-96.5)
Neointimal thickness, µm	80 (60-110)
Number of malapposed struts, n*	51
Percentage of malapposed struts¶‡	0.00 (0.00-0.86)
Percentage of strut presence of both malapposed and uncovered‡	0.00 (0.00-0.57)
Cross-section-level analysis	
Total analysed cross-sections, n	1,406
Minimum lumen area, mm^2	5.73 (4.21-6.47)
Lumen area, mm^2	7.02 (5.72-8.42)
Stent eccentricity index	0.90 (0.88-0.92)
Minimum stent area, mm^2	6.57 (5.86-7.45)
Stent area, mm^2	7.58 (6.69-9.04)
Neointimal area, mm^2	0.62 (0.36-0.90)
Mean ISA area, mm^2	0.00 (0.00-0.03)
Lesion-level analysis	
Total analysed lesion, n	45
Mean area of ISA >2 mm^2, n (%)	2 (4.4)
Thrombus area >300 $µm^2$, n (%)	0
Neointima volume, mm^3	10.13 (6.05-16.21)
Stent volume, mm^3	138.67 (96.14-173.59)
Lumen volume, mm^3	129.92 (86.61-159.00)
Total malapposition volume, mm^3	0.00 (0.00-0.39)
Percentage of neointima volume obstruction	8.20 (4.74-10.72)
Healing index (no unit)	16.2 (7.5-33.6)

*sum of all ISA struts, ¶based on crude analysis, ‡parameter used in healing index calculation. ISA: incomplete stent apposition

Table 5. Clinical outcomes at 3-month follow-up (intention to treat).

Clinical outcome	In-hospital (N=45/45)	3 months (N=45/45)
Cardiac death	0	0
Myocardial infarction	1 (2.2)	0
Periprocedural MI according to the WHO MI definition	1 (2.2)	0
Spontaneous MI	0	0
Clinically indicated target lesion revascularisation	0	0
Device-oriented composite endpoint (DOCE)		
CD, MI not clearly attributable to a non-intervention vessel, and CI-TLR	1 (2.2)	0
Definite/probable ST	0	0

CD: cardiac death; CI-TLR: clinically indicated target lesion revascularisation; DOCE: device-oriented clinical events; MI: myocardial infarction; ST: stent thrombosis; WHO: World Health Organization

percentage of neointimal volume obstruction; ii) a high percentage of covered struts; iii) a low number of malapposed struts comparable to other DES platforms; and iv) an acceptable neointimal thickness when compared to DES which have been investigated at the same time point **(Table 7)**. Quantitative coronary angiographic analysis showed standard acute lumen gain, low late lumen loss and no (binary) restenosis and, at three-month follow-up, there was no stent thrombosis and there were no major adverse cardiac events other than a single periprocedural MI.

The Nano+ stent is one of the polymer-free drug-eluting stents which have been tested recently[24]. This particular stent is made of 91 µm-thick 316L stainless steel struts and utilises nano-sized pores on its adluminal surface as a reservoir for drug elution. This stent has a similar efficacy and safety profile when compared to the durable polymer sirolimus-eluting stent in the treatment of stable CAD patients[24]. However, it has not yet been investigated whether this novel concept (polymer-free drug-eluting stent with a nano-sized-pore

Table 6. Cardiac biomarkers <48 hrs after index procedure.

	Total CK 44/45 (97.8%)	CK-MB 45/45 (100%)	Troponin (T and I) 45/45 (100%)
Mean ratio of enzyme vs. ULN	0.69±0.40	0.83±1.13	9.04±35.67 (range 0.11-280)
	n (%)	n (%)	n (%)
>1x ULN	3 (6.8)	9 (20.0)	21 (46.7)
>2x ULN	1 (2.3)¶ (WHO)	5 (11.1)	13 (28.9)
>3x ULN	0 (0)	3 (6.7) (Ext-H in the absence of CK)	11 (24.4)
>5x ULN	0 (0)	0 (0) (SCAI for CK-MB plus additional criteria)	8 (17.8) (TUD)
>10x ULN	0 (0)	0 (0) (SCAI for CK-MB)	7 (15.6)
>35x ULN	0 (0)	0 (0)	1 (2.2) (SCAI for cTn plus additional criteria)
>70x ULN	0 (0)	0 (0)	1 (2.2)¶ (SCAI for cTn)

¶Patients with protocolar periprocedural MI (WHO definition). The enzymatic criteria of periprocedural MI are provided as follow: 1) WHO[21] CK >2x ULN accompanied by CK-MB rise; 2) Ext-H[51] CK >2x ULN accompanied by CK-MB rise, if no CK was measured, elevation of the CK-MB >3x UNL, if CK and CK-MB were not measured, elevation of cTn >3x UNL; 3) TUD[22] cTn >5x ULN; 4) SCAI[23] CK-MB >10x ULN, or in the absence of CK-MB measurements, elevation of cTn >70x ULN. CK: creatinine kinase; CK-MB: creatinine kinase-MB; cTn: cardiac troponin; Ext-H: extended historical myocardial infarction definition; SCAI: Society for Cardiovascular Angiography and Interventions; TUD: third universal definition of myocardial infarction; ULN: upper limit normal

Table 7. Comparison of degree of vascular healing assessed by OCT in different type of DES (first-generation, polymer-free, biodegradable polymer and second-generation DES) at 3 months±1 month.

Author/year	Time point	Study stent, n (strut thickness)	% covered	% uncovered	%ISA	Neointimal thickness, µm	%NVO	Acute gain (mm)	Late loss (mm)
First-generation DES									
Takano et al[12] 2006	3 mo	CYPHER=21 (STh: 140 µm)	NA	15% (range 0-27)	16% (range 1-33)	29 (range 0-510)	NA	NA	NA
Polymer-free DES									
Moore et al[10] 2009	3 mo	CYPHER=12 (STh: 140 µm) Yukon=12 (STh: 87 µm)	88.3 (11.8) vs. 97.2 (6.1)¶	NA	2.2 (2.1) vs. 1.2 (1.1)¶	77.2 (25.6) vs. 191.2 (86.7)	NA	NA	0.06 (0.29) vs. 0.16 (0.33)
BICARE FIM[11] 2014	4 mo	SES + probucol N=25 (STh: 91 µm)	98.93	1.07¶	0.22¶	NA	NA	1.83 (0.44)	0.14 (0.19) with 1 binary stenosis
DEMONSTRATE[52] 2014	3 mo 1 mo	Cre8 DES=19 (STh: 80 µm) Multilink8=19 (STh: 81 µm)	NA	1.59 (2.10) vs. 0.86 (1.38)	4.18 (5.09) vs. 1.21 (1.72)	70 (40) vs. 160 (120)	NA	NA	0.10 (0.33) vs. 0.43 (0.36)
Nano+	3 mo	SES=45 (STh: 91 µm)	93.0 (83.2-96.5)¶	NA	0.00 (0.00-0.86)	80 (60-110)	8.2 (4.7-10.7)	1.50 (0.38)	0.16 (0.27)
Biodegradable polymer DES									
Kim BK et al[9] 2013	3 mo	BES=30 (STh: 112 µm) SES=30 (STh: 140 µm)	NA	14.7 (0-23.4) vs. 8.6 (0.7-21.5)¶G	0.1 (0.0-1.0) vs. 0.1 (0.0-1.0)¶	30 (20) vs. 40 (30)	NA	1.9 (0.5) vs. 1.9 (0.5)	0.1 (0.2) vs. 0.2 (0.4)
BuMA-OCT[29] 2014	3 mo	BuMA=33 (STh: 100 µm) EXCEL=36 (STh: 120 µm)	94.2% vs. 90.0%¶	NA	1.28% vs. 1.80%¶	70 (30) vs. 60 (20)	5.7 (5.0-7.6) vs. 5.3 (4.1-6.4)	1.61 (0.59) vs. 1.51 (0.49)	0.06 (0.09) vs. 0.07 (011)
DESSOLVE I 2013 Attizzani GF et al[30]	4 mo	MiStent*=10 (STh: 64 µm)	NA	14.34 (15.35)¶	3.74 (7.35) ¶	71.73 (39.78)	8.01 (6.21)	NA	NA
DESSOLVE I 2013 Ormiston J et al[31]	4 mo	MiStent*= 10 (STh: 64 µm)	NA	7.3 (range 0.4-46.3)	0.4 (range 0-22.7)	2.6 (range 0.6-24.6)	7.0 (range 2.3-22.9)	NA	0.03 (range -0.22-0.21)
Second-generation DES									
Endeavor OCT[42] 2009	3 mo	Endeavor=31 (STh: 91 µm)	99.9 (0.4) (ACS & SIHD)	NA	0.2	NA	NA	1.7 (0.6)	0.5 (0.3)
Kim SJ et al[39] 2013	3 mo	EES=36 (STh: 81 µm) ZES=24 (STh: 91 µm)	77.1 vs. 81.5	NA	2.3 vs. 1.4	58.7 (47.0) vs. 126.1 (131.5)	NA	1.92 (0.59) vs. 1.98 (0.41)	0.06 (0.10) vs. 0.22 (0.31)
Kim S et al[41] 2013	3 mo	ZES=20 (STh: 91 µm) EES=20 (STh: 81 µm)	NA	6.2 (6.9) vs. 4.7 (5.1)¶	0.7 (2.2) vs. 0.7 (1.7)¶	74 (41) vs. 75 (35)	NA	1.54 (0.44) vs. 1.43 (0.53)	0.13 (0.24) vs. 0.10 (0.15)
Nishinari et al[40] 2013	2,4,6, 8,10 weeks	Endeavor=4 (STh: 91µm) at 10 weeks	NA	19.2 (5.6)	0.0	146.2 (49.9)	NA	NA	NA
Hashikata et al[43] 2014	3 mo	R-ZES=20 (STh: 91 µm)	93.6 (3.5)*	NA	3.1 (2.2)*	54.1 (5.9)	NA	NA	NA

Data are reported as mean (SD) or median (IQR 1st–3rd) or median (range). ¶ Data analysed per strut level. *The report did not provide the level of statistical analysis. BES: biolimus-eluting stent; DES: drug-eluting stent; EES: everolimus-eluting stent; G: generalised estimating equation model (GEE); ISA: incomplete stent apposition; NA: not available; NVO: neointimal volume obstruction; R-ZES: Resolute zotarolimus-eluting stent; SES: sirolimus-eluting stent; STh: strut thickness; ZES: zotarolimus-eluting stent

surface) accelerates the tissue coverage (and possibly re-endothelialisation) while still preserving the ability to inhibit excessive neointimal formation.

The new generation of the OCT system provides an axial image resolution of 10-20 µm that allows precise assessment of neointimal proliferation, especially the lack of tissue coverage and the presence of residual thrombi; both parameters have been associated with an increased risk of stent thrombosis[5,25,26].

SHORT-TERM OCT STUDIES IN POLYMER-FREE DRUG-ELUTING STENTS

Amongst the other DES, there are three coating-free stent platforms similar to the Nano+ stent **(Table 7)**: 1) the Yukon® Choice stent[10,27] (Translumina GmbH, Hechingen, Germany) which is made of 316L stainless steel with an 87 µm strut thickness, eluting drug from a modified microporous surface; 2) the BioFreedom™[27,28] (Biosensors Europe SA, Morges, Switzerland) is a 316L stainless steel stent with

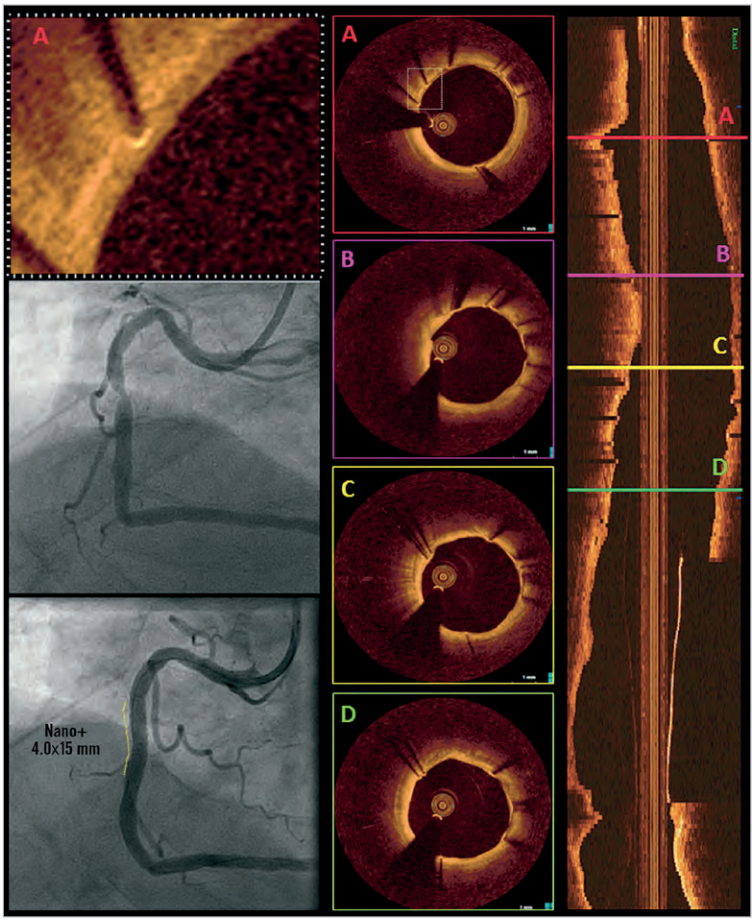

Figure 4. *Example of optical coherence tomography findings. Left middle and lower panels demonstrate pre- and post-procedure coronary angiography of right coronary artery, respectively. A Nano+ stent 4.0×15 mm was implanted into the right coronary artery. A three-month follow-up OCT image shows the longitudinal view (right panel) with corresponding cross-section sampling from four different in-stent segments (A to D, middle panels). A zoom-in image in white dotted frame (A, left upper panel) shows that the stent struts are covered with bright, homogeneous tissue and smooth luminal surface with neointimal thickness of 85.3 μm; percentage of covered struts is 95.1 with a healing index of 9.7.*

119 μm strut thickness, which has adluminal microabrasion allowing retention and elution of antiproliferative drugs; 3) the BICARE™[11] (Lepu Medical) has a platform identical to the present device but with a dual drug elution of sirolimus and probucol. The drug concentrations are 1.6 μg/mm^2 for sirolimus and 0.8 μg/mm^2 for probucol. The published data on these two devices (Yukon and BICARE) demonstrated the safety of these devices, and at three-month follow-up they showed similar tissue coverage (on OCT) and late lumen loss (on QCA) to the Nano+ stent in this present study.

SHORT-TERM OCT STUDIES IN BIODEGRADABLE POLYMER DRUG-ELUTING STENTS

There are two biodegradable polymer stent trials in which OCT data are available at short-term follow-up, the BuMA-OCT trial and the DESSOLVE I trial. In the BuMA-OCT trial[29], stent strut coverages were compared between a PLGA polymer with electro-grafting base layer sirolimus-eluting stent (SES) (BuMA™; SINOMED, Tianjin, China) and a PLA polymer SES (EXCEL; JW Medical Systems, Weihai, China); the data showed that both the BuMA and the EXCEL stent had low percentages of neointimal volume obstruction (5.3% and 5.7%) which are similar to the Nano+ stent, but the BuMa and EXCEL stents had a relatively higher percentage of malapposed struts. In the DESSOLVE I trial[30,31], the device used was the MiStent® sirolimus-eluting stent (cobalt-chromium stent with a 64 micron strut thickness coated with polylactide-coglycolic acid and sirolimus; Micell Technologies, Inc., Durham, NC, USA), and the vascular reaction after implantation at four, six and eight months was investigated by OCT[30,31]. The Nano+ stent in our present study seems to have rates of covered struts and malapposition which are comparable to those of the MiStent in the DESSOLVE I trial.

SHORT-TERM OCT STUDIES IN SECOND-GENERATION DRUG-ELUTING STENTS

The second-generation DES with thinner cobalt-chromium struts, improved crossability, trackability and biocompatibility, have been globally adopted in daily practice. Second-generation DES showed

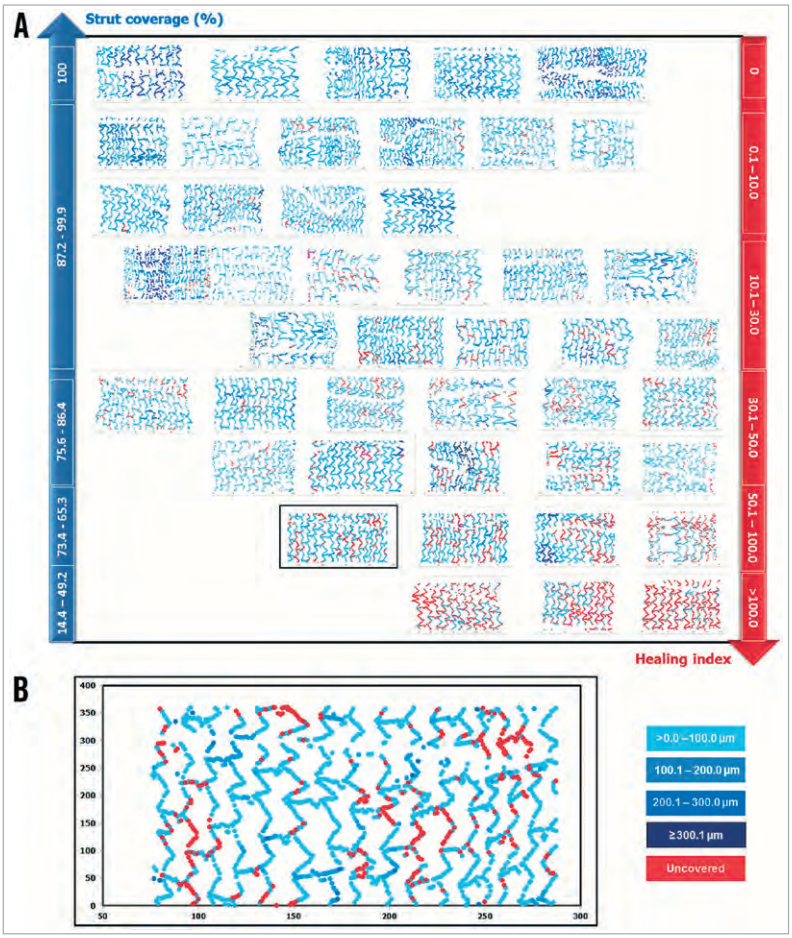

Figure 5. *Spread-out vessel chart of all stents. A) Percentage of covered struts and healing index. The blue vertical axis on the left-hand side shows the percentage of covered struts, while the red vertical axis on the right-hand side shows the healing index. Struts are colour-coded according to covered and uncovered status. Covered struts are depicted in blue: light blue indicates a neointimal thickness more than 0 µm to 100.0 µm, blue indicates a neointimal thickness 100.1-200.0 µm, navy blue indicates a neointimal thickness 200.1-300.0 µm, dark blue indicates a neointimal thickness more than 300.1 µm, and red indicates uncovered struts. B) Zoom-in spread-out vessel chart in which all struts are colour-coded according to coverage status: percentage of covered struts is 73.5 with a healing index of 54.*

a lower number of malapposed struts[32], a lower revascularisation rate[33,34], and a lower MACE[34,35] rate at long-term follow-up than first-generation DES.

The vascular healing after implantation of such new-generation devices replacing first-generation DES has also been assessed at medium-term follow-up (between nine and 12 months or later). The OCT data showed that new-generation DES have more complete neointimal coverage and lower strut malapposition rates than the first-generation DES[36-38]. The short-term OCT assessment of second-generation DES has been investigated in two devices, the XIENCE V® everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, CA, USA) and the Resolute® zotarolimus-eluting stent (R-ZES) (Medtronic CardioVascular, Santa Rosa, CA, USA). These studies showed a wide range of strut coverage (77.1-99.9%) and malapposed struts (0-3.1%)[39-43]. The plausible explanation for the heterogeneity of results might be the difference in analytic approach in calculating the percentage of covered struts or malapposed struts. Räber et al have reported the impact of various statistical analyses in OCT trial interpretation: the crude and the GEE-based percentages are clearly higher than the percentage from aggregated and multilevel analysis methods[44]. In addition, the wide variation in the percentage of covered struts might be the consequence of: 1) the generation of OCT systems, for instance the quality of the images of the recent OFDI system is by far superior to the earlier generation of OCT (M2/M3); 2) the criteria used to define strut coverage. The thickness criteria can vary from an absolute threshold of 0 µm to a minimum threshold of 10 µm (or more); or coverage may simply be defined by the presence of any covering tissue layer detectable on visual inspection. In the present study, the Nano+ stent showed coverage and malapposition rates which were comparable to the rates in second-generation DES.

APPLICATION OF HEALING INDEX FOR ASSESSING CORONARY ARTERIAL HEALING

The healing index was first reported in the TROFI study[18,19]. Vascular healing depends upon multiple factors (coverage, malapposition, exuberant neointimal proliferation and intraluminal defect). The benefit of the healing index methodology is that it standardises the assessment of the speed and degree of "healing" in patients treated

with different types of stent, assessed at different time points. The healing indices provided in **Table 8** were studied in the LEADERS trial[8] (Biolimus A9 BioMatrix Coroflex stent vs. Sirolimus-eluting Cypher stent), RESOLUTE trial[16] (zotarolimus-eluting Resolute stent vs. everolimus-eluting Xience metallic stents), ABSORB trial[45] (everolimus-eluting BVS) and TROFI trial (Biolimus A9 in a STEMI population). The healing index of the Nano+ stent can be compared with the healing indexes of other stents **(Table 8)**. The most influential factors of the healing index are the percentage of uncovered struts and number of ISA: both are low in the present study. Therefore, the Nano+ stent showed a low score of the healing index that can be appreciated at three months in comparison with other stents also investigated at the same time point.

CLINICAL IMPORTANCE OF STRUT COVERAGE ASSESSED BY OCT

It has been hypothesised that the ongoing inflammation process, triggered by durable polymer coating, may cause unfavourable clinical outcomes[46,47]: polymer-free stents have the potential to decrease this issue, resulting in a lower number of uncovered struts, malapposition or evagination[48] which are attributed to durable polymer-coated DES. In the literature, the OCT study criteria for lack of coverage (e.g., Ratio of Uncovered to Total Stent Struts Per Cross Section: RUTTS) are mainly derived from histopathological studies[5,49]. These studies have demonstrated that the lack of neointimal coverage after implantation is an important factor for late and very late stent thrombosis, since healthy endothelial tissue plays a key role in preventing thrombus formation. These observations have triggered extensive clinical research on the relevance of early tissue coverage (as assessed by OCT) for long-term outcomes of new DES. The OCT approach has shown its accuracy in detecting uncovered stent struts when compared to light and electron microscopy in a porcine model[50]. However, to date OCT has not been able to provide information on the type of tissue coverage, an observation which could become more relevant for the long-term clinical outcome.

Limitations

The present study is limited by the absence of post-procedural OCT images for comparison with the OCT images during follow-up. Post-procedural OCT data would have enabled us to understand the progression or regression of strut malapposition during the follow-up period. In addition, this study was a small single-arm trial without the use of a comparator.

Conclusions

Polymer-free sirolimus-eluting stents with a surface of nano-sized pores are effective in inhibiting neointimal tissue proliferation and promoting early vascular healing with high strut coverage at three-month follow-up.

Impact on daily practice

The novel concept of local drug delivery from metallic DES has been modified to decrease sequelae from chronic exposure to permanent polymer and to promote endothelisation. The Nano+ stent is a polymer-free sirolimus eluting stent utilising nano-sized pores on its adluminal surface as a reservoir for drug elution. At three months, the Nano+ stent showed a rapid strut coverage process although the level of actual strut coverage is similar to other current stent technologies in daily practice. Strut coverage has been shown to be a significant factor in the reduction of stent thrombosis; this current study reports promising data from the use of this platform.

Appendix

LIST OF THE INVESTIGATORS WHO CONTRIBUTED TO CASES ENROLLED IN THE NANO+ TRIAL

Principal investigators and recruiting sites: Belgium: Dr Edouard Benit, Hasselt Heart Centre, Jessa Ziekenhuis, Hasselt, Belgium, total enrolment=24 patients; Dr Olivier Gach, CHU de Liege, Liege, Belgium,

Table 8. Comparison of healing index among different stent types with period of evaluation and patient setting.

Patient status	n	time point	mean±SD	median (range)
In stable patients				
Sirolimus-eluting durable polymer	29	9 months	43.3±36.2	26.1 (4.6-127.4)
Biolimus A9-eluting biodegradable polymer	22	9 months	35.2±25.0	36.7 (1.1-79.6)
Sirolimus polymer-free stent Nano+™	45	3 months	30.3±38.9	16.2 (0.0-177.7)
Zotarolimus-eluting biocompatible durable polymer	17	13 months	18.7±20.4	15.2 (0.0-79.0)
Everolimus-eluting biocompatible durable polymer	15	13 months	10.8±15.3	3.4 (0.0-47.7)
Everolimus-eluting fully biodegradable BVS	28	6 months	9.4±13.3	3.1 (0.0-53.7)
In STEMI patients				
Biolimus A9-eluting biodegradable polymer	25	post-PCI	202.8±41.5	198.1 (67.9-344.3)
Biolimus A9-eluting biodegradable polymer	25	6 months	13.4±19.6	9.0 (0.0-97.2)
Biolimus A9-eluting biodegradable polymer+thrombectomy	26	post-PCI	206.3±38.7	200.6 (101.9-358.7)
Biolimus A9-eluting biodegradable polymer+thrombectomy	26	6 months	20.1±22.2	15.1 (0.0- 96.9)

BVS: bioresorbable vascular scaffold; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction. The STEMI patients have been published in the TROFI study[18,19]. All data of the patients in the stable group have been reported (LEADERS: Biolimus A9 vs. sirolimus-eluting durable polymer; RESOLUTE: zotarolimus and everolimus metallic stents; ABSORB: everolimus BVS).

total enrolment=15 patients; Dr Clemens von Birgelen, Thoraxcentrum Twente, University of Twente, Enschede, The Netherlands, total enrolment=4 patients; Dr Sjoerd H. Hofma, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands, total enrolment=2 patients.

Conflict of interest statement

C. von Birgelen has been a consultant to Boston Scientific and Medtronic and has received lecture fees from MSD and AstraZeneca; the research department of the Thoraxcentrum, Twente has received institutional research grants from Biotronik, Boston Scientific, and Medtronic. All of the other authors have no conflicts of interest to declare.

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Importance of confirmation by instant stent-accentuated three-dimensional optical coherence tomography during bifurcation stenting: far distal rewiring of iSA3D-OCT

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Description

An 83-year-old man with effort angina was admitted for percutaneous coronary intervention due to a stenosis in the ostial left anterior descending artery (LAD). After predilatation, the left main LAD was stented with a 3.5×24 mm 2-link biolimus-eluting stent (Nobori™; Terumo, Tokyo, Japan). After proximal optimisation technique and rewiring to the left circumflex artery, the distal rewiring was confirmed by two-dimensional modalities **(Figure 1A)**. Instant stent-accentuated three-dimensional optical coherence tomography (iSA3D-OCT) was reconstructed in about 30 s from OCT (Dragonfly™ JP; St. Jude Medical, St. Paul, MN, USA) by ImageJ v1.47 (National Institutes of Health, Bethesda, MD, USA) with self-made macro programs. According to intraprocedural iSA3D-OCT, the recrossed wire passed through the far distal cell limited the expansion by the link **(Figure 1B, Moving image 1)**. Kissing balloon dilatation was performed by simultaneously inflating 3.5×15 mm balloons. Final iSA3D-OCT showed floating struts and struts covering sparsely **(Moving image 2)**. A large centre cell rewiring might have been better, even if a metallic carina was made.

Distal rewiring confirmed by two-dimensional modalities may not lead to favourable results in some cases. Confirmation of a rewiring cell by intraprocedural iSA3D-OCT is important to find such cases.

Conflict of interest statement

The author has no conflicts of interest to declare.

Online data supplement

Moving image 1. iSA3D-OCT after rewiring.
Moving image 2. iSA3D-OCT after kissing balloon dilation.

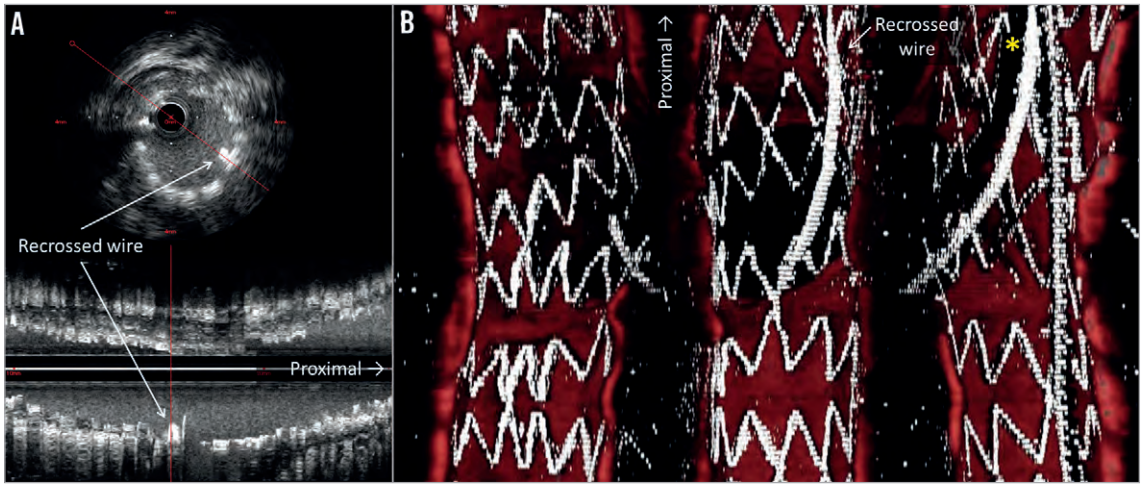

Figure 1. *Intravascular ultrasonography showing distal rewiring (A) and iSA3D-OCT showing rewiring through far distal cell limited expansion by link (B). Asterisk (in top right corner) indicates guidewire shadow artefact.*

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Long-term clinical outcomes of mechanical versus bioprosthetic aortic valve replacement in older patients

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KEYWORDS

- aortic valve replacement
- bioprosthetic valve
- mechanical valve

Abstract

Aims: To compare the long-term outcomes of mechanical valves as opposed to bioprosthetic valves in order to inform valve selection.

Methods and results: From January 1996 to December 2010, 561 patients aged 60 to 75 years undergoing AVR for the first time were evaluated (mechanical valve: N=251; bioprosthetic valve: N=310). The primary outcome was all-cause death, and secondary outcomes were reoperation, bleeding events, thromboembolism, endocarditis and major adverse prosthesis-related events (MAPE). MAPE were the composite of reoperation, bleeding, thromboembolism and endocarditis. Long-term outcomes were compared with the use of propensity scores to adjust for selection bias. After risk adjustment, both groups of patients showed a similar risk of death at 10 years (hazard ratio [HR] 1.25, 95% confidence interval [CI]: 0.85-1.85, p=0.26), reoperation (HR 2.94, 95% CI: 0.79-11.11, p=0.11) and thromboembolism (HR 0.38, 95% CI: 0.10-1.40, p=0.15). Compared with the patients given mechanical valves, those who received bioprosthetic valves were at a higher risk of endocarditis (HR 7.65, 95% CI: 1.74-33.52, p=0.007), but were, however, at a lower risk of bleeding (HR 0.25, 95% CI: 0.12-0.52, p<0.0001) and MAPE (HR 0.61, 95% CI: 0.39-0.96, p<0.033).

Conclusions: Compared with mechanical AVR, bioprosthetic AVR showed a similar long-term survival rate and favourable MAPE event rate.

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Abbreviations

AF	atrial fibrillation
AVR	aortic valve replacement
CABG	coronary artery bypass graft
CI	confidence interval
HR	hazard ratio
MAPE	major adverse prosthesis-related events
MI	myocardial infarction
NYHA	New York Heart Association
TAVR	transcatheter aortic valve replacement

Introduction

The current American Heart Association guidelines recommend mechanical valves for aortic valve replacement (AVR) in patients younger than 60 years, and bioprosthetic valves in patients older than 70 years. Either a bioprosthetic or a mechanical valve is recommended between 60 and 70 years[1]. This grey zone reflects the current trend towards increasing use of bioprostheses in progressively younger patients[2], and also the complexities and trade-offs of selecting an aortic valve prosthesis in older patients. Patients with mechanical valves require lifelong anticoagulation, and risk of bleeding events increases with advancing age. In contrast, risk of reoperation in patients with bioprosthetic valves increases with time and decreases with advancing age.

Two historic randomised clinical trials compared outcomes after valve replacement with first-generation bioprosthetic and mechanical valves[3,4]. Although these trials are notable for their prospective, randomised design, their major limitations are that comparisons were made between first-generation valves, and most of the study population in these trials was under 60 years of age. Furthermore, recent innovation in transcatheter aortic valve replacement (TAVR) is applicable to replace deteriorated biological prostheses, which may affect the strategy in case of reoperation for octogenarians and their late survival[5,6]. To address the limitations of the earlier randomised trials, a new randomised trial demonstrated a similar survival rate between bioprosthetic and mechanical valves but a higher incidence of bleeding events in mechanical valves and more frequent reoperation in bioprosthetic valves[7]. Recently, large registry data gave support to this with a similar result[2,8]. However, it is not clear whether this finding is applicable to other populations, including an Asian population. Thus, we conducted a long-term observational study to compare outcomes of mechanical and bioprosthetic valve replacement for patients aged more than 60 years in an Asian population.

Methods

STUDY DESIGN

Patients who underwent valve surgery at our institution were prospectively registered using a standard case-reporting form. Case report forms, including patient demographics, clinical presentation, echocardiographic data, and procedural data were stored in an electronic database. Clinical follow-up data of study patients were prospectively collected via clinical visits or telephone, and entered into the database at one month and six months after operation, and subsequently on an annual basis. From January 1996 to December 2010, a total of 773 patients undergoing AVR with a mechanical or bioprosthetic valve were consecutively enrolled in the present study. The criteria for exclusion from the study were defined as patients undergoing urgent surgery, or non-coronary artery bypass graft cardiac surgical procedures, those with a prior history of any valve replacement and who had received AVR for infective endocarditis **(Figure 1A)**. All patients provided informed consent, and the study was approved by the institutional review board.

CHOICE OF PROSTHESIS AND SURGICAL PROCEDURES

The selection of a mechanical or a bioprosthetic valve was made following a detailed preoperative discussion among the surgeon, the patient, and family members. The pros and cons of mechanical or bioprosthetic valves were described, including the need for anticoagulation after mechanical valve replacement or the possible need for reoperation after bioprosthetic valve replacement. The decision on mechanical or bioprosthesis selection was left entirely to the individual patient and his/her carers. The operation was conducted in the standard manner. Briefly, all patients underwent AVR through a median sternotomy. A standard cannulation was performed in the routine fashion. After having clamped the aorta and arrested the heart with antegrade/retrograde cold blood, or cold crystalloid cardioplegia added to topical cooling, the ascending aorta was opened and the valve was replaced, either by a bioprosthetic or a mechanical valve fixed to the aortic annulus.

ANTICOAGULATION

During the postoperative period, anticoagulated patients initially received unfractionated heparin until the international normalised ratio (INR) was within therapeutic range. Patients with mechanical prostheses were anticoagulated with warfarin according to our protocol to a target of INR 2.5 (range, 2.0 to 3.0). In patients who underwent bioprosthetic valve replacement, warfarin anticoagulation was used at the discretion of the surgeon for a period of three months after the operation. Warfarin was subsequently discontinued if sinus rhythm was maintained and no other indication for anticoagulation was present. Non-anticoagulated patients with bioprosthetic valves were kept on 100 mg of aspirin daily unless contraindicated.

OUTCOMES

The primary endpoint was the rate of death from any cause over the duration of follow-up. Secondary endpoints were aortic valve reoperation, bleeding events, thromboembolism and endocarditis. Major adverse prosthesis-related events (MAPE) were the composite of reoperation, bleeding events, thromboembolism and endocarditis. These complications were defined according to the guidelines for reporting mortality and morbidity after cardiac valve intervention[9]. Briefly, a bleeding event is any episode of major internal or external bleeding that causes death, hospitalisation, or

permanent injury, or necessitates transfusion. Thrombosis is any thrombus not caused by infection attached to or near an operated valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Embolism is any embolic event that occurs in the absence of infection after the immediate period.

STATISTICAL ANALYSIS

Continuous variables are presented as the mean±standard deviation, and they were compared using the Student's t-test. Categorical variables are presented as counts or percentages, and they were compared using the chi-square test. A log-rank test was used to compare mortality and event rates between mechanical and bioprosthetic valves. A nonparametric Kaplan-Meier estimate was used to estimate the survival curve. To adjust for the difference in baseline characteristics between mechanical and bioprosthetic valves, the propensity score was estimated using the twang package in the R version 3.0.1 based on age, gender, body surface area, diabetes mellitus, hypertension, smoking status, previous myocardial infarction, previous stroke, New York Heart Association functional state, atrial fibrillation, chronic renal failure, left ventricular ejection fraction, and coronary artery bypass grafting. The propensity score matching was performed by matching between mechanical and bioprosthetic valve groups on the logit of the propensity score using a calliper of 0.2 SD of the logit of the propensity score[10]. Patients were censored at the time of their last follow-up visit or at the time of death if the outcome of interest had not occurred, and censoring was assumed to be independent of predictors and outcomes. Unadjusted hazard ratios and adjusted hazard ratios were derived from a Cox proportional hazards model with propensity score matching. Statistical significance was defined as p-value <0.05. Data were analysed using SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) and R version 3.0.1 (the R Foundation for Statistical Computing, Vienna, Austria).

Results

PATIENT CHARACTERISTICS

A total of 561 patients (mechanical valve, N=251; bioprosthetic valve, N=310) were analysed in this study, and 531 patients (95.4%) completed follow-up. Patient age was 67.5±4.5 years (range, 60 to 75 years) at the time of surgery **(Table 1)**. There were 319 (56.9%) male and 242 (43.1%) female patients. A total of 159 (28.3%) patients were in New York Heart Association (NYHA) functional Class III or IV. The total follow-up for the entire cohort was 3,167 patient-years, with a mean duration of 5.6 years (interquartile range: 2.2 to 8.3 years; maximum 15.6 years). The distribution of mechanical and bioprosthetic valves was constant across the age range **(Figure 1B)**. Compared with patients who received mechanical valves, those who received bioprosthetic valves had lower body surface area and ejection fraction, but a similar age and prevalence of most other comorbidities. It was noted that patients with bioprosthetic valves were more likely to undergo concomitant coronary artery bypass graft surgery (28.1% versus 21.1%) but the difference did not reach statistical significance. The dominant underlying lesion was either isolated aortic stenosis (252 patients; 44.9%) or mixed aortic stenosis and regurgitation (182 patients; 32.4%). Intraoperative characteristics were similar for patients with bioprosthetic versus mechanical valves, with a similar mean time on cardiopulmonary bypass and aorta cross clamp time **(Table 2)**.

Table 1. Baseline characteristics of the study population.

Variables	Overall				Propensity score-matched			
	Mechanical (N=251)	Bioprosthetic (N=310)	*p*-value	SD of mean	Mechanical (N=238)	Bioprosthetic (N=238)	*p*-value	SD of mean
Age (mean), years	67.4±4.6	67.6±4.3	0.57	4.5%	67.3±4.5	67.1±4.6	0.58	4.4%
Female, n (%)	101 (40.2%)	141 (45.5%)	0.21	10.7%	96 (40.3%)	85 (35.7%)	0.25	9.5%
Body mass index, kg/m^2	24.0±2.7	24.8±14.7	0.24	29.6%	24.1±2.8	24.4±3.0	0.34	10.3%
Body surface area, m^2	1.64±0.15	1.61±0.17	0.019	18.7%	1.65±0.15	1.67±0.14	0.11	13.8%
Smoking, n (%)	103 (41.0%)	106 (34.2%)	0.096	14.1%	99 (41.6%)	107 (45.0%)	0.40	6.9%
NYHA III/IV, n (%)	68 (27.1%)	91 (29.4%)	0.55	5.1%	67 (28.2%)	71 (29.8%)	0.68	3.5%
Hypertension, n (%)	103 (41.0%)	138 (44.5%)	0.41	7.1%	99 (41.6%)	100 (42.0%)	0.91	0.8%
Diabetes, n (%)	48 (19.1%)	70 (22.6%)	0.32	8.6%	44 (18.5%)	29 (12.2%)	0.06	17.5%
Previous MI, n (%)	3 (1.2%)	10 (3.2%)	0.11	13.7%	3 (1.3%)	2 (0.8%)	0.48	4.9%
Previous stroke, n (%)	9 (3.6%)	16 (5.2%)	0.37	7.8%	8 (3.4%)	12 (5.0%)	0.30	8.0%
Chronic AF, n (%)	20 (8.0%)	31 (10.0%)	0.41	7.0%	19 (8.0%)	14 (5.9%)	0.39	8.3%
Chronic renal failure, n (%)	6 (2.4%)	2 (0.6%)	0.15	14.8%	6 (2.5%)	2 (0.8%)	0.16	13.4%
Concurrent CABG, n (%)	53 (21.1%)	87 (28.1%)	0.054	16.3%	51 (21.4%)	42 (17.6%)	0.25	9.6%
Ejection fraction, %	53.2±12.2	51.1±13.6	0.08	16.3%	53.0±12.2	53.3±11.0	0.81	2.6%

AF: atrial fibrillation; CABG: coronary artery bypass graft; MI: myocardial infarction; NYHA: New York Heart Association functional class

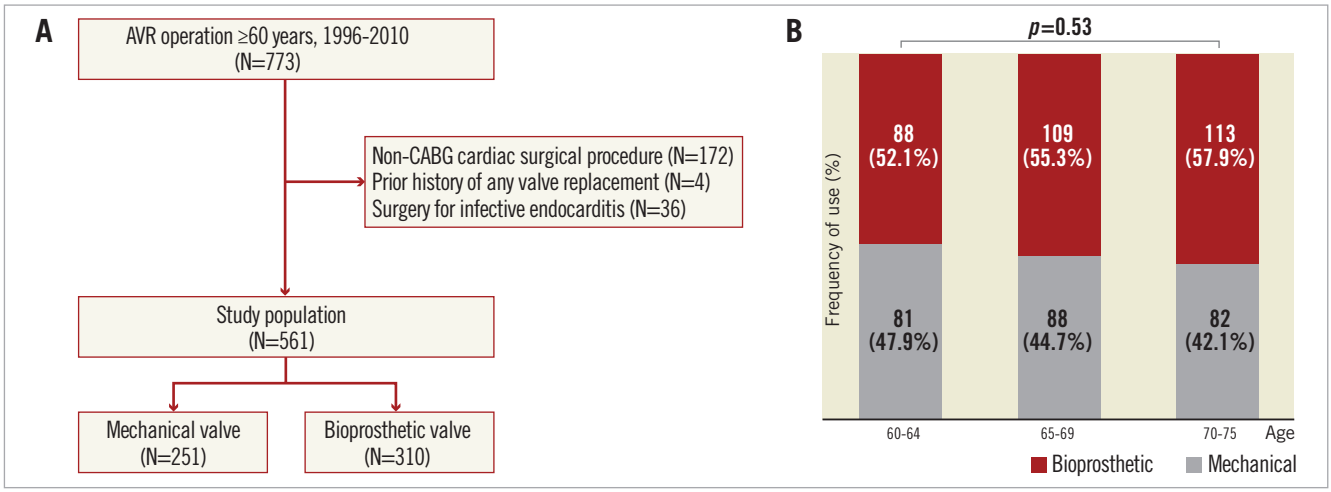

Figure 1. *Flow diagram detailing patient selection. AVR: aortic valve replacement; CABG: coronary artery bypass grafting*

CLINICAL OUTCOMES

There were no differences in early outcomes between mechanical and bioprosthetic valves **(Table 3)**. Four patients died after the index procedure in the mechanical group (1.6%), and eight patients died in the bioprosthetic group (2.6%, p=0.42).

In this registry, the 10-year cumulative mortality rate after AVR was 28.3% for patients who received mechanical valves and 31.6% for those who received bioprosthetic valves (unadjusted hazard ratio [HR] 1.30, 95% confidence interval [CI]: 0.91-1.86, p=0.15) **(Figure 2A, Table 4)**. After risk adjustment, patients who received bioprosthetic valves experienced a similar long-term survival rate to those who received mechanical valves (adjusted HR 1.25, 95% CI: 0.85-1.85, p=0.26) **(Figure 2B, Table 5)**.

The 10-year cumulative reoperation rates were 1.3% for patients who received mechanical valves and 5.8% for those who received bioprosthetic valves **(Table 4)**. The incidence of aortic valve reoperation was higher among patients who received bioprosthetic valves than among those who received mechanical valves although the difference did not reach statistical significance (unadjusted HR 2.70, 95% CI: 0.73-10.00; p=0.14). The result from the propensity score-matched cohort was similar (adjusted HR 2.94, 95% CI: 0.79-11.11, p=0.11) **(Figure 3A, Table 5)**.

The 10-year incidence of bleeding events was 24.5% for patients given mechanical valves and 6.9% for those given bioprosthetic valves as shown in (unadjusted HR 0.30, 95% CI: 0.16-0.54, p<0.0001) **(Table 4)**. After risk adjustment, patients who received bioprosthetic valves had a lower risk of bleeding (adjusted HR 0.25, 95% CI: 0.12-0.52, p<0.0001) **(Figure 3B)**. Among bleeding events, cerebral haemorrhage was lower in patients who received bioprosthetic valves (unadjusted HR 0.12, 95% CI: 0.01-0.97, p=0.046), but this statistically significant difference diminished after risk adjustment (adjusted HR 0.15, 95% CI: 0.02-1.22, p=0.08). Among

Table 3. Early outcomes.

Variables	Mechanical (N=251)	Bioprosthetic (N=310)	*p*-value
Death, n (%)	4 (1.6)	8 (2.6)	0.42
Thromboembolism, n (%)	0 (0.0)	0 (0.0)	>0.99
Pacemaker insertion, n (%)	1 (0.4)	2 (0.6)	0.69
Wound infection, n (%)	1 (0.4)	3 (1.0)	0.63
Pneumonia, n (%)	0 (0.0)	1 (0.3)	>0.99
Low cardiac output syndrome, n (%)	3 (1.2)	1 (0.3)	0.33
Length of stay, days	10.5±7.1	10.7±7.2	0.85

Table 2. Operative characteristics.

Variables	Mechanical (N=251)	Bioprosthetic (N=310)	*p*-value
Type of valve disease			
Aortic stenosis, n (%)	105 (41.8%)	147 (47.4%)	
Aortic regurgitation, n (%)	59 (23.5%)	68 (21.9%)	0.47
Mixed aortic stenosis and regurgitation, n (%)	87 (34.7%)	95 (30.6%)	
Cardiopulmonary bypass time, min	129±62	123±51	0.28
Aorta cross clamp time, min	80±37	80±32	0.97
Mechanical valves			
Carbomedics		54 (21.5%)	
Edwards MIRA		15 (6.0%)	
St. Jude Medical		143 (57.0%)	
Sorin Bicarbon		26 (10.4%)	
Others		13 (5.2%)	
Bioprosthetic valves			
St. Jude Medical Biocor		31 (10.0%)	
Carpentier Edwards		197 (63.5%)	
Medtronic Hancock®		63 (20.3%)	
Others		19 (6.1%)	

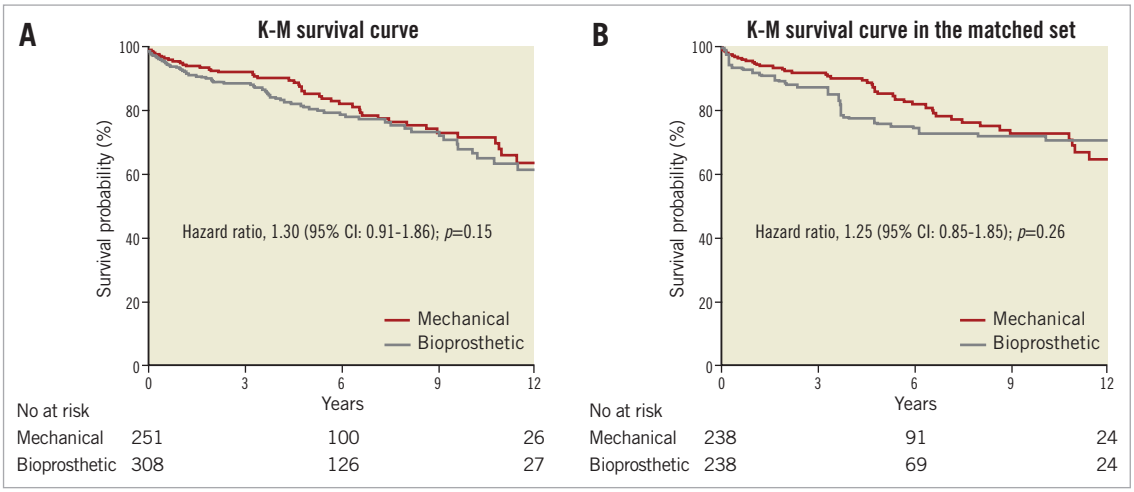

Figure 2. *Kaplan-Meier curves showing the unadjusted survival rate (A) and adjusted survival rate (B) according to valve type.*

51 patients who experienced bleeding events, 30 patients required hospitalisation (mechanical valve, n=22; bioprosthetic valve, n=8). There was a significant difference in the cumulative incidence of subsequent hospitalisation between the two groups (14.4% vs. 4.5%, p=0.009). Overall in-hospital duration was 12.0±19.7 days (mechanical valve, 14.2±23.4 days; bioprosthetic valve, 7.1±5.2 days, p=0.35). Among those who experienced bleeding events, 26 patients received a transfusion (mechanical valve, n=21; bioprosthetic valve, n=5). There was a significant difference in the cumulative incidence of receiving a transfusion (14.3% vs. 2.3%, p<0.001). There were no differences between the two groups in terms of units of transfused red blood cells, (3.3±1.8 units vs. 4.3±2.1 units, p=0.47), nor with fresh frozen plasma (3.5±1.8 units vs. 4.0±2.7 units, p=0.67). In line with total bleeding events, patients given a mechanical valve had a higher risk of hospitalisation due to a bleeding event (unadjusted HR 0.38, 95% CI: 0.18-0.81, p=0.012), as well as receiving a transfusion (unadjusted HR 0.23, 95% CI: 0.09-0.55, p=0.001).

The 10-year incidence of thromboembolism was similar between patients receiving mechanical and bioprosthetic valves (5.1% versus 6.5%; unadjusted HR, 1.03; 95% CI, 0.45 to 2.38; p=0.94) **(Table 4)**. There were no significant differences in the thromboembolism rate after risk adjustment (adjusted HR 0.38, 95% CI: 0.10-1.40, p=0.15) **(Figure 3C)**. In contrast, patients with bioprosthetic valves showed a trend towards more frequent endocarditis compared to those with mechanical valves (unadjusted HR 4.14, 95% CI: 0.91-18.87, p=0.067). This trend became evident after risk adjustment (adjusted HR 7.65, 95% CI: 1.74-33.52, p=0.007) **(Figure 3D)**.

By 12 years, MAPE had occurred in 29.6% of patients with mechanical valves and in 16.8% of patients with bioprosthetic valves (unadjusted HR 0.61, 95% CI: 0.40-0.92, p=0.017) **(Figure 3E)**. After risk adjustment, patients who received bioprosthetic valves had a lower risk of MAPE (adjusted HR 0.61, 95% CI: 0.39-0.96, p=0.033) **(Figure 3F)**.

SUBGROUP ANALYSIS OF LONG-TERM MORTALITY

Long-term mortality in the mechanical and bioprosthetic groups was compared by patient subgroup **(Figure 4)**. The risk of mortality

Table 4. Long-term outcomes.

Outcome	Mechanical valve (N=251)		Bioprosthetic valve (N=310)		*p*-value*
	Number of events	Incidence rate	Number of events	Incidence rate	
Death	44	28.3	64	31.6	0.15
Reoperation	3	2.4	7	5.8	0.12
Bleeding	38	24.5	13	6.9	<0.0001
Cerebral haemorrhage	6	4.8	1	1.4	0.017
Thromboembolisation	6	5.1	9	6.5	0.94
Thrombosis	0	0	0	0	>0.99
Embolism	6	5.1	9	6.5	0.94
Endocarditis	2	2.0	8	3.6	0.047
MAPE	52	29.6	40	16.8	0.016

**p*-value was estimated by log-rank test. MAPE: major adverse prosthesis-related events

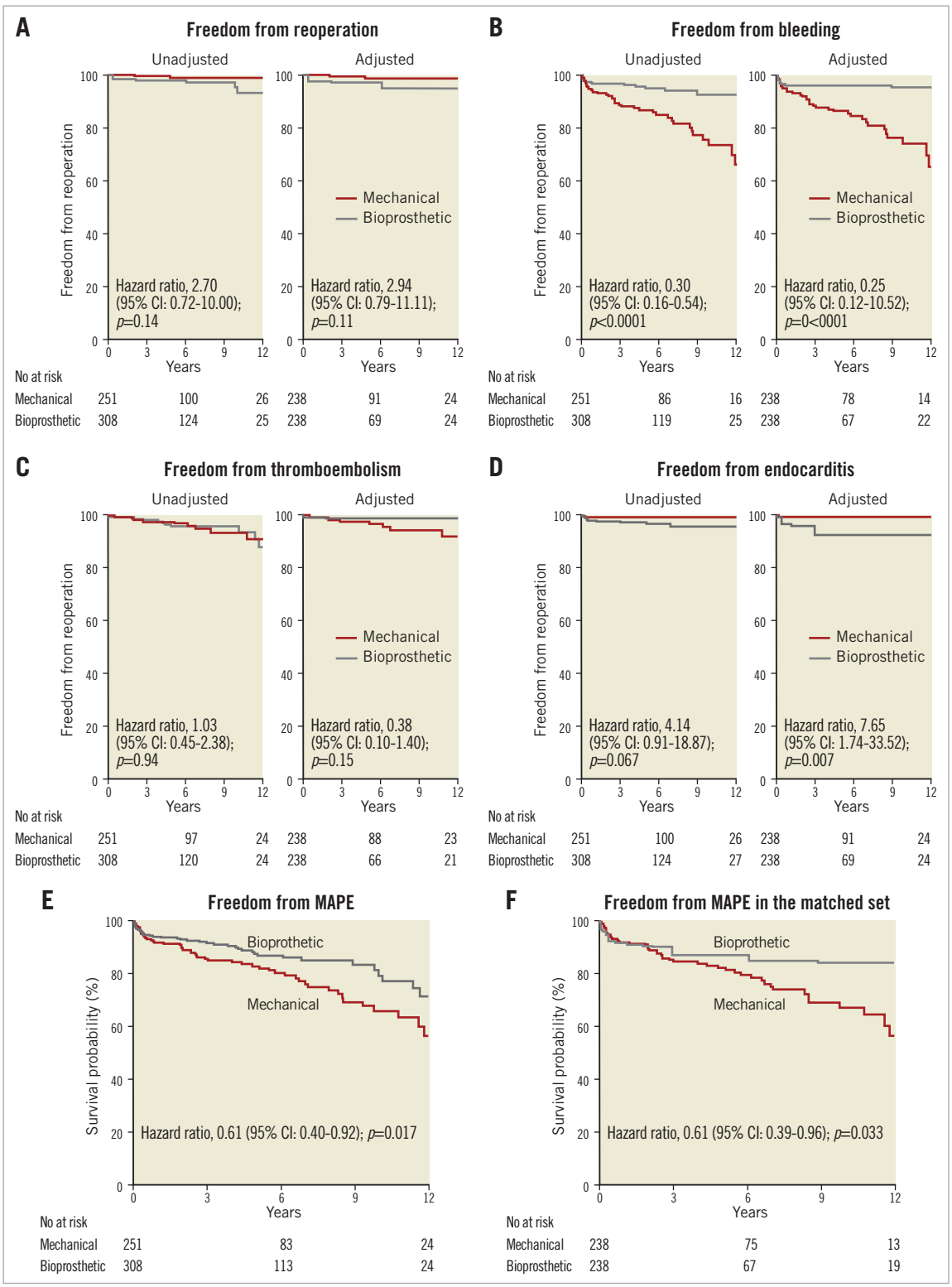

Figure 3. *Kaplan-Meier curves showing the unadjusted and adjusted rates of reoperation (A), bleeding (B), thromboembolism (C), and endocarditis (D), according to valve type. Unadjusted (E) and adjusted (F) MAPE rates. MAPE: major adverse prosthesis-related events (including reoperation, bleeding, thromboembolism or endocarditis)*

varied across patient characteristics. In general, the long-term mortality of patients who received bioprosthetic valves was similar to that of those who received mechanical valves. However, the long-term mortality of patients treated with bioprosthetic valves was higher in female and NYHA Class III/IV subgroups compared to those with mechanical valves.

Table 5. Adjusted hazard ratio between mechanical and bioprosthetic valve replacement.

	Unadjusted HR		Adjusted HR	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Death	1.30 (0.91-1.86)	0.15	1.25 (0.85-1.85)	0.26
Reoperation	2.70 (0.72-10.00)	0.14	2.94 (0.79-11.11)	0.11
Bleeding	0.30 (0.16-0.54)	<0.0001	0.25 (0.12-0.52)	<0.0001
Cerebral haemorrhage	0.12 (0.01-0.97)	0.046	0.15 (0.02-1.22)	0.08
Thromboembolisation	1.03 (0.45-2.38)	0.94	0.38 (0.10-1.40)	0.15
Endocarditis	4.14 (0.9-18.87)	0.067	7.65 (1.74-33.52)	0.007
MAPE	0.61 (0.40-0.92)	0.017	0.61 (0.39-0.96)	0.033

MAPE: major adverse prosthesis-related events

Discussion

This observational study of 561 patients between 60 and 75 years of age who underwent AVR with mechanical valves and bioprosthetic valves demonstrates that: 1) overall mortality was similar for patients with mechanical and bioprosthetic valves; 2) bleeding events were more common in patients with mechanical valves but endocarditis was more frequent in those with bioprosthetic valves; 3) reoperation tended to occur more frequently in patients with bioprosthetic valves; and 4) overall composite events were more frequent in patients given mechanical valves.

In the Veterans Administration Study, patients who underwent AVR with mechanical valves had a significantly higher 15-year survival rate than those with bioprosthetic valves[3]. Brown et al, in a one-to-one study, matched patients aged 50 to 70 years undergoing AVR and found a 10-year survival of 68% in the mechanical valve group and 50% in the bioprosthetic valve group[11]. However, other studies demonstrated similar long-term survival. In the Edinburgh Heart Valve Trial, at 12 years there was a survival advantage in the mechanical valve group compared with the bioprosthetic valve group, but this advantage disappeared at 20 years[4]. Brennan et al compared outcomes of the Medicare-linked cohort study and found patients given a bioprosthesis had a similar adjusted risk for death[2]. Lung and Bland in a meta-analysis with regression analyses did not find significant differences in the survival rate between mechanical and bioprosthetic valves after correcting for age[12]. Our data was consistent with these previous studies. In the present study, 10-year mortality was 35.7% in patients with mechanical valves and 38.0% in those with bioprosthetic valves (p=0.15). Adjusted outcomes showed no difference in 10-year mortality between the two groups.

Previously, the advantages and disadvantages of mechanical or bioprosthetic valves have been well documented. The advantageous durability of mechanical valves is offset by the risk of thromboembolism and the need for long-term anticoagulation and its associated risk of bleeding. In contrast, bioprosthetic valves do not require long-term anticoagulation yet carry the risk of structural failure and reoperation. In our study, bleeding events were more common in patients with mechanical valves, but endocarditis was more frequent in those with bioprosthetic valves. Reoperation tended to occur more frequently in patients with bioprosthetic valves; however, thromboembolism did not show a difference between the two groups. Due to the large number of bleeding events, overall MAPE rates were higher for patients with mechanical valves. Although treating reoperation and bleeding events equally is controversial,

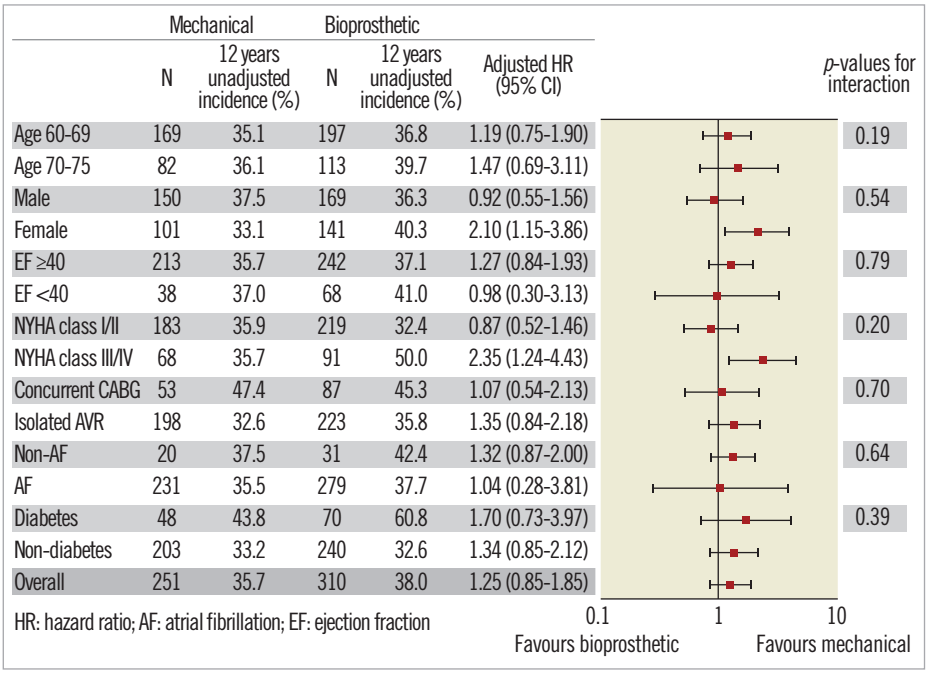

Figure 4. *Comparison of long-term mortality in mechanical and bioprosthetic groups by patient subgroup. AF: atrial fibrillation; EF: ejection fraction; HR: hazard ratio*

promising less invasive treatment for degenerated bioprostheses ("valve-in-valve" TAVR)[5,6] would allow us to consider the composite MAPE as non-negligible. In addition, the superior durability of current bioprostheses favours the selection of a bioprosthetic valve[13].

Bleeding, where the event rate ranges from 13.7% at 10 years to 24.4% at 15 years, is the Achilles heel of the mechanical valve[2,11]. In addition to the risk of bleeding, warfarin requires restrictions on food, alcohol and drugs, and lifelong coagulation monitoring. To overcome this complication of mechanical valves, new oral anticoagulation was applied in a randomised trial, but failed because of an excess of thromboembolic and bleeding events[14]. Thus, a quality of life study needs to be instigated on the choice of prosthesis.

There is a paucity of Asian data on the long-term outcomes of aortic valve replacement with mechanical and bioprosthetic valves. The risk of bleeding and thromboembolism has been shown to be different according to race, as was the chance of bioprosthetic valve degeneration. Therefore, our data will provide important information for the selection of prosthetic valves for AVR in an Asian population.

The physicians involved in the decision-making process should be very aware of patient outcomes with the use of different prostheses. An increasing risk of major adverse effects and lifestyle alteration, i.e., lifelong anticoagulation with warfarin after mechanical valve replacement, improved durability of new technologies but still relatively higher risk of reoperation after bioprosthetic valve replacement, the potential option of minimally invasive procedures in case of reoperation and, finally, the individual patient's preference should be fully discussed with the patient.

Study limitations

Our study has several important limitations. First, it was a single-centre observational study and may be subject to selection bias and confounding by unmeasured severity of illness which may be correlated with the use of different valves. Second, the number of patients and follow-up time duration were limited, and it is likely that reoperation after bioprosthetic valve replacement will increase. Finally, we could not reliably ascertain other important endpoints, such as cardiovascular symptoms, functional status or decrements in quality of life associated with the use of anticoagulation therapy for mechanical valves and the monitoring of anticoagulant dosages. Despite these limitations, the current analysis demonstrates clear findings in agreement with reported data, and provides important information to guide valve type selection for older patients in current daily practice.

Conclusions

The following observations should be made: 1) overall mortality was similar for patients with mechanical and bioprosthetic valves; 2) bleeding events were more common in patients with mechanical valves but endocarditis was more frequent in those with bioprosthetic valves; 3) overall composite events were more frequent in patients given mechanical valves.

Impact on daily practice

The trend in current practice seems to be more use of bioprosthetic AVR with the possibility to use TAVR if prosthetic valve stenosis or regurgitation occurs. Although this strategy needs further investigation, our study provides important information about the choice of prosthesis in older patients.

Funding

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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How should I treat progression of disease of the jailed left anterior descending ostium after bioresorbable vascular scaffold implantation in the left circumflex?

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CASE SUMMARY

BACKGROUND: A 60-year-old male with recurrent angina (CCS class II) and equivocal exercise treadmill tests presented for elective coronary angiography. He had bioresorbable stent implantation for stable angina 12 months previously in the ostial to mid circumflex, which jailed the ostium of the left anterior descending (LAD) artery.

INVESTIGATION: Coronary angiogram, fractional flow reserve, intravascular ultrasound, optical coherence tomography.

DIAGNOSIS: Moderate distal left main disease, angiographically significant but functionally not significant LAD disease and moderate ostial circumflex disease.

MANAGEMENT: Medical therapy.

KEYWORDS: bioresorbable stent, bioresorbable vascular scaffold (BVS), fractional flow reserve (FFR), intravascular ultrasound (IVUS), scaffold

PRESENTATION OF THE CASE

A 60-year-old male re-presented with stable angina (CCS class II) and equivocal exercise treadmill test 12 months after undergoing previous elective percutaneous coronary intervention (PCI) with implantation of a bioresorbable vascular scaffold (BVS) for ostial and proximal left circumflex (LCx) lesions. Other past medical history of note included diabetes mellitus, chronic kidney disease (CKD) stage 4 and hypertension.

With regard to his index procedure, he had undergone elective PCI for CCS III stable angina with implantation of a 3.0×28 mm Absorb (Abbott Vascular, Santa Clara, CA, USA) BVS for an ostial and proximal left circumflex (LCx) lesion **(Figure 1A, Figure 1B)** with final left main stem bifurcation kissing balloon inflation (KBI). According to optical coherence tomography (OCT) findings, prior to KBI, the left anterior descending artery (LAD) orifice was jailed by BVS struts **(Figure 1C, Figure 1D)**. Hence, KBI with a 3.0×20 mm non-compliant (NC) (left main coronary artery [LMCA]-LCx) and a 2.5×20 mm NC balloon (LMCA-intermediate) was performed. Though repeat OCT imaging post-KBI was not obtained due to background CKD, the final angiogram indicated an excellent result **(Figure 2A, Figure 2B, Moving image 1, Moving image 2)**.

A coronary angiogram on his current admission (12 months after index procedure) showed moderate stenosis of the distal LMCA, severe stenosis of the ostial LAD and intermediate stenosis of the ostial intermediate branch **(Figure 2C, Figure 2D, Moving image 3, Moving**

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image 4), whereas the BVS in the proximal LCx was free from significant stenoses. We decided to assess the haemodynamic significance of all the aforementioned lesions and measure the minimal lumen area of the ostial LAD stenosis using fractional flow reserve (FFR) and intravascular ultrasound (IVUS), respectively. After hyperaemia, induced by intravenous administration of adenosine, FFR was measured at 0.87 in the LAD, 0.87 in the intermediate and 0.97 in the LCx. IVUS confirmed the jailed LAD ostium from BVS struts with a minimum lumen area of 5.73 mm² **(Figure 3)**.

In this specific patient, who was not asymptomatic, some people may suggest intervening according to the results of the coronary angiogram. However, we might be able to wait for the absorption of the BVS struts, which would theoretically lead to an increased SB ostium strut-free area. How should this patient be treated?

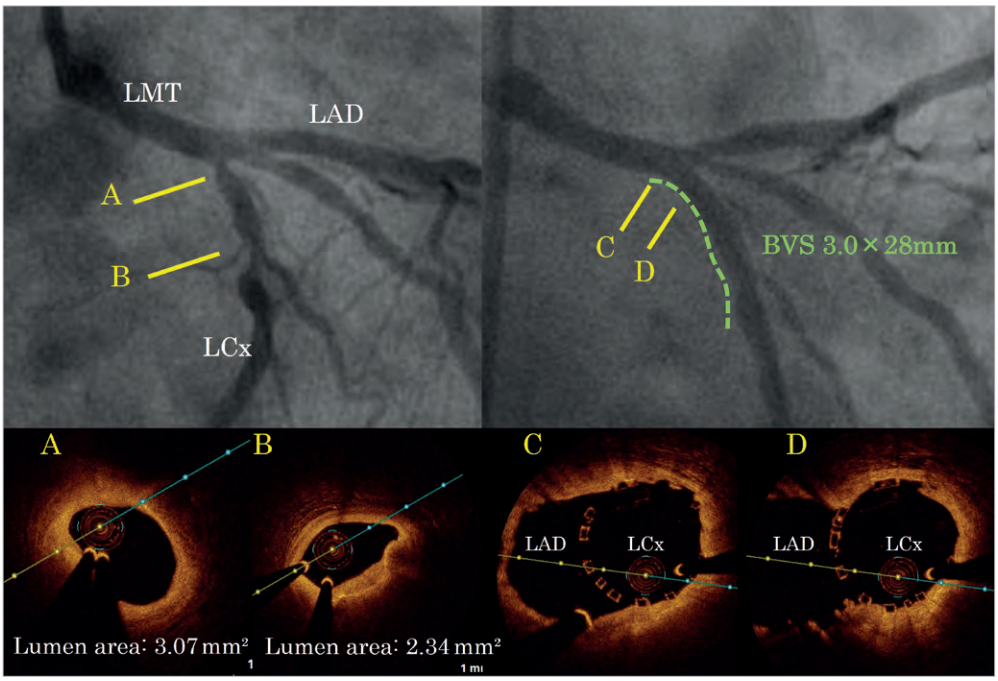

Figure 1. *Index procedure angiographic and optical coherence tomography (OCT) images before and after bioresorbable vascular scaffold (BVS) implantation. Pre-procedural angiogram (left), and angiogram after BVS implantation (right). OCT demonstrated lumen area of 3.07 mm² in the ostial LCx (A) and a minimum lumen area of 2.34 mm² in the mid LCx site (B). The left anterior descending artery (LAD) orifice was jailed by the BVS struts (C, D).*

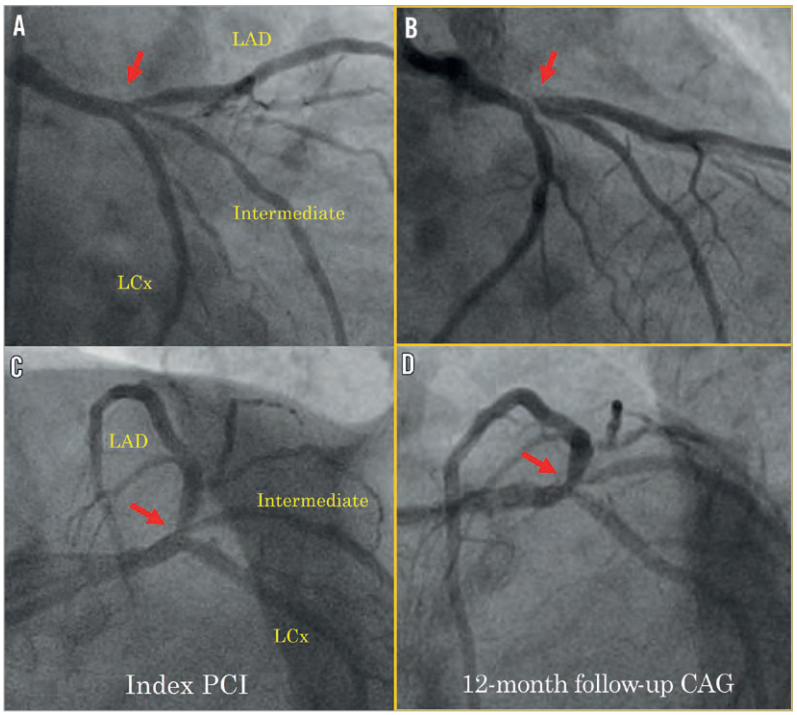

Figure 2. *Comparison between index PCI post-procedural and 12-month follow-up coronary angiogram. Red arrows indicate the left anterior descending artery (LAD) lesion site. (A & C: right anterior oblique caudal view; B & D: left anterior oblique caudal view).*

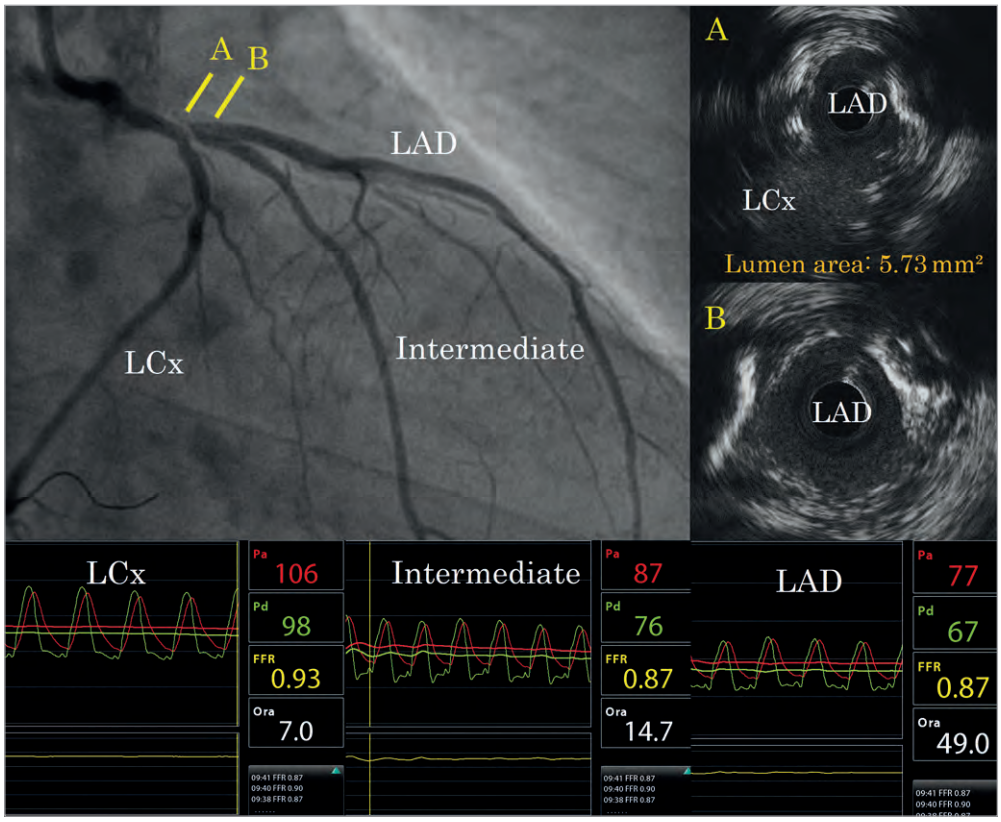

Figure 3. *The results of FFR and IVUS measurements. FFR value was 0.87 in the left anterior descending (LAD) and intermediate arteries and 0.97 in the left circumflex. IVUS revealed jailed BVS struts with a minimum lumen area of 5.73 mm² at the carina site (A) and lumen area of 5.96 mm² distal to the carina site (B). BVS: bioresorbable vascular scaffold; FFR: fractional flow reserve; IVUS: intravascular ultrasound*

How would I treat?

THE INVITED EXPERTS' OPINION

Ashok Seth*, FRCP, FACC, FESC, DSc; Gaurav Mohan, MD, DM; Vijay Kumar, MD, DNB

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This interesting case from Sato et al demonstrates the occurrence of an angiographically severe stenosis at the LAD ostium 12 months post-implantation of a BVS to treat an ostial proximal Cx stenosis when the BVS struts jailed the LAD ostium. The patient has some chest pain but no convincing objective evidence of ischaemia on non-invasive evaluation treadmill test (TMT).

It is well recognised that angiography is deceptive. In fact, the ostium of a jailed side branch can "look" dramatically worse due to impaired visualisation contributed to by incomplete blood/contrast mixing and image filtering/edge enhancement mismatch of digital angiography[1]. Furthermore, at 12 months, the thick struts of BVS lying across the LAD ostium may develop neointimal tissue bridges[2], which could also worsen the angiographic appearance at the LAD ostium. As an OCT examination was not performed at the 12-month follow-up, this "real possibility" remains speculative. Thus, for us, the key to decision making is based on the intravascular physiology (FFR) and imaging (IVUS) data.

The FFR of 0.87 in the LAD and intermedius with intravenous adenosine hyperaemia clearly demonstrates good flow down both vessels. FFR >0.8 has been well proven to be associated with extremely favourable outcomes at follow-up on optimal medical therapy alone when compared to PCI[3]. While IVUS has only a moderate correlation for physiological significance and prognosis in non-left main coronary lesions, an MLA >4.0 mm^2 (this patient's LAD ostium was measured at 5.73 mm^2) identifies with reasonable accuracy non-significant lesions in which PCI can be safely deferred[3]. As 12 months have already elapsed since the index procedure, any further progression of ostial LAD and intermedius lesions from here on is unlikely. Furthermore, as the BVS resorbs by two to three years, there would be resolution of neointimal bridges, unjailing of the LAD ostia and positive remodelling of the vessels, all of which could lead to significant improvement of angiographic appearances at follow-up.

We would thus follow up this patient on optimal medical therapy. Keeping in mind the uncovered struts of BVS protruding in the left main, we would prefer to continue dual antiplatelet therapy till the BVS resorbs. We would perhaps perform non-invasive radionucleide perfusion imaging at two years post-index procedure and perform angiography, FFR and OCT at three years post-index procedure, by which time we would expect the BVS to be totally resorbed. We would "wait and watch" with keenness as "fresh knowledge and understanding" will come forth through such cases.

Conflict of interest statement

A. Seth is a member and consultant of the Absorb Global Clinical Advisory Board, Abbott Vascular, Santa Clara, CA, USA. The other authors have no conflicts of interest to declare.

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How would I treat?

THE INVITED EXPERTS' OPINION

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Sato et al present a very interesting and challenging case of progression of disease in the "jailed" ostium of a LAD after successful treatment of an ostial LCx lesion with an Absorb BVS one year earlier.

According to their description, the patient returned with mild to moderate symptoms of exertional angina (CCS II) and an inconclusive treadmill test, being referred for a repeat cinecoronariography, which showed patency of the Absorb BVS in the ostium and proximal LCx and a "severe"(?) lesion in the origin of the LAD and intermediate arteries. Functional invasive assessment (FFR) was performed which ruled out the presence of ischaemia both in the LCx and in the LAD or intermediate coronary arteries. Additional assessment with an invasive imaging modality (IVUS) showed an ostium of the LAD "jailed" by the scaffold but with a minimum lumen area of 5.73 mm^2. Based on the clinical history and angiographic, FFR and IVUS findings, the authors question how they should manage this case.

The presence of ischaemia still represents the "key element" in the decision-making process of patients with stable coronary disease. Studies with both non-invasive and invasive assessment of ischaemia have repeatedly demonstrated that patients with moderate to severe ischaemic burden usually have worse outcomes (death and non-fatal myocardial infarction) as compared to those individuals with none or mild ischaemia despite the angiographic findings[3-6]. In the present case, all three coronaries showed FFR values above 0.80, which rules out the presence of significant ischaemia and is a consistent predictor of favourable outcomes, at least in the midterm journey[7,8].

Of note, a discrepancy between visual lesion estimation and the presence of ischaemic obstructions is relatively frequent. In the FAME trial, a significant number of angiographically significant stenoses were reclassified after FFR assessment. In this particular case, the presence of a trifurcated left main trunk makes the visual assessment even more challenging. By the still pictures provided by the authors at follow-up **(Figure 2)**, we notice a superposition of the LAD and the intermediate artery on one view **(Figure 2C)**, and the presence of 50 to 60% lesion on the ostium of the LAD on the "spider" view, despite the foreshortening of this projection **(Figure 2D)**. Therefore, according to the available pictures, we are not totally convinced about the "severity" of the ostial LAD lesion as stated by the authors.

This patient has also undergone invasive imaging assessment with intravascular ultrasound at follow-up. It is important to state that the ideal IVUS "cut-off" value to treat (or not) an intermediate coronary lesion remains unclear and is subject to a lot of criticism due to the tendency of this imaging modality to overestimate lesion severity and induce unnecessary revascularisation procedures. The initial studies with IVUS pointed to a value of 4.0 mm^2 as the limit to decide on the need to revascularise a coronary lesion. Contemporary studies have suggested lower "cut-off" values (as low as 2.0 to 2.4 mm^2), which might also vary according to lesion location (proximal vs. distal coronary segments). **Table 1** summarises the main studies on this topic. However, despite the criticism in terms of finding a "number" to justify the treatment, the literature is unanimous in pointing out the safety of IVUS in deferring revascularisation in patients with minimum lumen area larger than 4.0 mm^2, as in the current scenario.

Furthermore, IVUS gave very interesting and potentially useful information in this case: most of the lumen restriction in the ostium of the LAD is secondary to its entrapment by the LCx Absorb BVS,

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Table 1. Studies comparing intravascular ultrasound (IVUS) to functional assessment (non-invasive and invasive) in intermediate lesions.

	Abizaid et al[9]	Nishioka et al[10]	Briguori e cols[11]	Takagi et al[12]	Kang et al[13]	Ben-Dor et al[14]	Waksman et al (FIRST trial)[15]	Stone et al (VERDICT Pilot and F1RST) trials*
Comparator	CFR	MIBI	FFR	FFR	FFR	FFR	FFR	FFR
	112	70	53	51	201	92	367	303/241(total=544)
Reference vessel diameter, mm	≥2.75 <3.5	N/I	N/I	≥2.5 <3.5	>2.5	≥2.5	≥2.5	≥2.5 <4.0 (Pilot) ≥2.75 <4.0 (F1RST)
IVUS "cut-off" value for MLA, mm^2	≥4.0	≤4.0	≤4.0	<3.0	<2.4	3.2	<3.07 (overall) <2.4 (vessels <3.0) <2.7 (vessels 3.0- 3.5) <3.6 (vessels > 3.5)	2.9
Accuracy, %	89	N/I	79	90.2	68	74	66	66
Sensitivity, %	N/A	90	92	83	90	69.2	64	66.3
Specificity, %	N/A	88	56	92.3	60	68.3	64.9	65.9

CFR: coronary flow reserve; FFR: fractional flow reserve; IVUS: intravascular ultrasound; MLA: minimum lumen area; N/A: data not available; *Unpublished data (presented at TCT 2012). Additional to greyscale IVUS, this trial also used radiofrequency IVUS (Virtual Histology™), which failed to improve greyscale IVUS accuracy to identify intermediate lesions provocative of ischaemia.

which will soon "vanish away" and might result in late enlargement of this area. Of course, our current understanding of bioresorbable technology is relatively limited and it might, for instance, happen that, in the final stages of the bioresorption, the inflammation produced by the process might aggravate the adjacent LAD lesion. However, at present, this is just speculation and should not substantiate the difficult decision whether to intervene in this patient.

Therefore, in a simple way, our best answer would be the following. For now, keep the patient under optimal medical therapy, but follow him carefully with non-invasive tests (scintigraphy and stress echo are the best options in this case).

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Conflict of interest statement

The authors have no conflicts of interest to declare.

How did I treat?

ACTUAL TREATMENT AND MANAGEMENT OF THE CASE

Though an angiogram in the right anterior oblique caudal view showed severe stenosis at the left anterior descending artery (LAD) ostium, we elected to defer intervention in view of the negative fractional flow reserve (FFR) result. Aggressive medical therapy and follow-up coronary angiography in two years was the recommended treatment plan.

Previous studies[16-18] have demonstrated that angiographic or intravascular ultrasound-based decision making for the treatment of side branch (SB) stenosis after main branch crossover stenting may frequently lead to unnecessary procedures. Therefore, functional assessment with post-stenting FFR has been recommended as a guide for the treatment of angiographically "jailed" side branches. Despite a recent study[19] showing only a weak correlation between diameter stenosis and functional significance, treatment of angiographically significant SB lesions post-stent (scaffold) implantation in the main branch remains a matter of debate. Clinical, angiographic and imaging follow-up of side branches jailed by a bioresorbable vascular scaffold (BVS) are of particular interest, given that scaffold struts at the orifice of the side branch can be bioresorbed and/or form a neointimal bridge/membrane[2]. The OCT study arm of the ABSORB cohort B trial demonstrated that the SB ostium area free from BVS struts reached a nadir at 12 to 24 months after BVS implantation. Subsequently, and up to 36 months of follow-up, the strut-free area increased significantly due to absorption of the polymer backbone.

In the current case, the procedure was performed 12 months after index PCI, a timeframe which coincides with the nadir in the lumen area of the SB ostium area free of BVS struts. Furthermore, despite angiographic appearance suggestive of a significant ostial LAD lesion, functional assessment ruled out haemodynamic significance. Is it justified then to wait for the absorption of the BVS struts, which would theoretically lead to an increased SB ostium strut-free area?

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Online data supplement

Moving image 1. Final angiogram at index percutaneous coronary intervention. Right anterior oblique, caudal view.

Moving image 2. Final angiogram at index percutaneous coronary intervention. Left anterior oblique, caudal view.

Moving image 3. 12-month follow-up angiogram demonstrating the narrowing of the left anterior descending artery ostium. Right anterior oblique, caudal view.

Moving image 4. 12-month follow-up angiogram demonstrating the narrowing of both the left anterior descending artery and the intermediate artery ostium. Left anterior oblique, caudal view.

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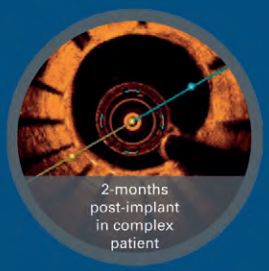

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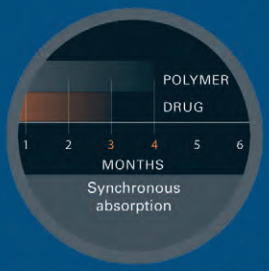

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