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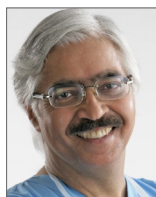
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AICT-AsiaPCR: a new global platform in Asia Pacific for education, research and innovation in cardiovascular interventions



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We are all looking forward to attending the 14th “Asian Interventional Cardiovascular Therapeutics” (AICT) Meeting in Hong Kong in September this year. This official annual scientific and educational forum of the Asian Pacific Society of Interventional Cardiology (APSIC) also happens to be the last AICT in its present form. This is because next year will see the birth of a new landmark annual meeting for the Asia-Pacific region: “AICT-AsiaPCR” – the official meeting of APSIC. This fresh and exciting educational collaboration between APSIC and PCR will be launched with its first meeting in July of 2019 in Singapore. AICT-AsiaPCR is being designed to be the most valuable scientific platform to address the needs of healthcare professionals in the Asia-Pacific region with a mission to improve healthcare delivery and outcomes for patients. The far-reaching vision is “to provide for all professionals involved in interventional cardiology, a global platform in the Asia Pacific to share education, promote and present research and showcase innovation”. AICT-AsiaPCR is different from other meetings because it combines the ethos of APSIC and AICT – “the spirit of participation, ownership and support

from interventional cardiologists (IC) across Asia Pacific Region” with the strength of PCR – “a tradition of excellence, education, research and highly visible global networking”. AICT-AsiaPCR, under the passionate course directorship of Christoph Naber, Upendra Kaul, Ashok Seth, Mohd. Ali Rosli, and Huay Cheem Tan (there will be a 6th Course Director who will be the representative of a national interventional society and the holder of the post will rotate yearly) and mentorship of William Wijns and Jean Fajadet, is expected to be the largest Pan-Asian interventional cardiology platform. Therefore, the future is not only exciting but has the potential to elevate the delivery of cardiac care in this region.

As we embark on this ambitious journey, I just cannot help reminiscing about the growth and development of interventional cardiology in this region over the last quarter of a century. I also feel fortunate to have been a part of that memorable journey and to have contributed to it in many ways.

APSIC was born out of informal discussion amongst 11 leading interventional cardiologists of this region, over evening drinks on 26 March 1993 during an intervention workshop in

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Sydney. Present were Drs Richard Ng, Arthur Tan, Dray Hong, John Ormiston, Upendra Kaul, Kenneth Chin, myself and others whom my memory fails to recall (**Figure 1** – courtesy Richard Ng). APSIC was formalised as a society in Singapore in July 1993 with Richard Ng as the first president and Arthur Tan (followed after two years by Y.L. Lim) as the secretary. The presidency of APSIC has rotated every two years with the post being held by representatives of 10 different countries from 1994 to 2018. In parallel, AICT was born independently from informal discussion in 2003 between Huay Cheem Tan, myself and some other leading interventional cardiologists (IC) of the region to create a participatory, practical, educational live demonstration interventional cardiology course for the Asia-Pacific region which could be free from the biases and politics of either a society-run or single-centre organised meeting. AICT grew through the interest, participation and contribution of every leading interventional cardiologist of the region. There was a highly successful first meeting in 2004 in Singapore run by Huay Cheem Tan and a second meeting in New Delhi run by myself in 2006, which was inaugurated by the Honourable President of India Dr Kalam. This set the stage for a highly valuable meeting, which has been organised in 12 different countries over the last 14 years. The Board of Trustees of AICT has, since its inception, included the leaders of the best centres of interventional cardiology in the region, the representatives of National Interventional Societies of the countries and office-bearers of APSIC. APSIC and AICT were brought closer together when the First Fellowship Ceremony of APSIC (FAPSIC) was held with great pomp and show at the 2nd AICT in New Delhi in 2006 and it has been held annually at every AICT thereafter.

It would be appropriate to acknowledge the transformational contribution of Huay Cheem Tan after taking over as President of APSIC in 2014, and the mentorship of Richard Ng. Dr Tan's futuristic and far-sighted vision of promoting education and knowledge through consolidation and partnership received support from the Boards of APSIC and AICT which had many members in common. Thus, in 2014 AICT became an official scientific meeting of APSIC with Europa Organisation Asia as the meeting organisers. Finally, early this year the educational partnership with PCR was cemented to create the largest interventional cardiology meeting for the region "AICT-AsiaPCR: the official meeting of APSIC".

As we move into this exciting transformational phase from 2019 onwards, we aim to bring into the fold a whole generation of



Figure 1. *The birth of APSIC.*

young IC by providing value in sharing of knowledge, promoting research and showcasing their expertise and talent.

The co-directors and associate directors of "AICT-AsiaPCR" are being meticulously selected across countries through their proven track records of being passionate about excellence, education, and organisational and innovative thought leadership in the field. A number of young-generation IC have been included in the programme-building committee, and cardiology fellows, nurses and allied professionals are being encouraged to contribute and participate in a most beneficial manner. The single factor which binds together the spectrum of course directors, co-directors and associate directors from countries across Asia Pacific is "commitment" towards the mission and vision of AICT-AsiaPCR and their willingness to devote their time and energy to elevate interventional cardiology in the Asia-Pacific region.

Yes, dear friends, we are ready to enter another exciting era in the historic and meteoric development of interventional cardiology in the Asia-Pacific region. AICT-AsiaPCR has been created by all of us together to be truly representative of the Asia-Pacific interventional cardiology community. It is a global platform emanating from Asia Pacific, a platform which will reflect our excellence to the world and one which we will be proud of in times to come.

Conflict of interest statement

A. Seth is a founder board member of AICT and founder board member and President Elect of APSIC.

Thoughts on secondary prevention after percutaneous coronary intervention in Japan



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Currently, aspirin and statins are regarded as the bottom-line treatment regimen for secondary prevention after percutaneous coronary intervention. However, even after implementation of aspirin and statin therapy, there remains a residual risk of cardiovascular events. Endeavours to reduce cardiovascular events further have been targeted at more intensive antithrombotic and lipid-lowering therapies.

Putting the results from the previous trials into perspective, the use of more intensive antithrombotic therapy could reduce ischaemic cardiovascular events, but has consistently increased the bleeding events in patients with stable coronary artery disease (CAD) including post-PCI patients¹⁻³. Furthermore, there are signs emerging of increased mortality in the case of prolonged dual antiplatelet therapy (DAPT) as compared with shorter DAPT⁴. Therefore, we should balance the benefits and risks when considering more intensive antithrombotic therapy as a secondary preventive measure in patients with stable CAD after PCI. Theoretically, more intensive antithrombotic therapy would be best suited in those patients with a high thrombotic risk but low bleeding risk, who should be identified by estimating the thrombotic and bleeding

risks separately and individually. We should estimate the absolute thrombotic and bleeding risks of the individual patients by applying the appropriate risk scores to the most contemporary long-term follow-up database in the geographic and/or ethnic population of interest. Therefore, we have developed the CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome study in Kyoto) thrombotic and bleeding risk scores from a large Japanese database of patients who underwent first coronary revascularisation⁵. The CREDO-Kyoto thrombotic and bleeding risk scores have demonstrated modest accuracy in stratifying the thrombotic risk and bleeding risk separately in the validation cohort from other Japanese PCI studies. We found substantial overlap of the predictors between the thrombotic and bleeding risk scores. Chronic kidney disease, atrial fibrillation, peripheral vascular disease and heart failure emerged as the common predictors for both thrombotic and bleeding events. Reflecting the overlap of the risk predictors, a large proportion of high thrombotic risk patients also had high bleeding risk. For this group of patients, a more intensive antithrombotic therapy would not be appropriate (**Figure 1**). Patients with high thrombotic risk but low bleeding risk accounted

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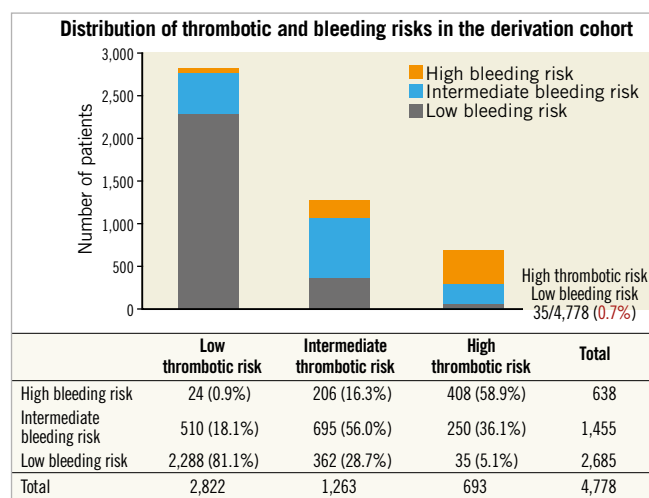


Figure 1. Distribution of thrombotic and bleeding risk based on the CREDO-Kyoto thrombotic and bleeding risk scores. A large proportion of high thrombotic risk patients also had a high bleeding risk. Patients with high thrombotic risk but low bleeding risk represented a very small proportion of the Japanese CAD population. CAD: coronary artery disease; CREDO-Kyoto: Coronary REvascularization Demonstrating Outcome study in Kyoto

for a very small proportion of the Japanese CAD population, which could be explained by the relatively lower thrombotic risk but comparable bleeding risk in Japanese patients as compared with Western patients. Therefore, more intensive antithrombotic therapy might not be the way to go for further prevention of cardiovascular events in the vast majority of Japanese patients with stable CAD after PCI.

More intensive lipid-lowering therapy is much safer than more intensive antithrombotic therapy. Based on the several previous “more versus less statins” trials, the current American College of Cardiology (ACC)/American Heart Association (AHA) guideline recommends high-intensity statin therapy in patients with clinical atherosclerotic cardiovascular disease⁶. However, high-intensity statin therapy is not widely implemented in daily clinical practice, particularly in Asia, at least partly because there has been no previous “more versus less statins” trial in Asia. We conducted a large randomised controlled trial comparing high-dose (4 mg/day) versus low-dose (1 mg/day) pitavastatin in 13,054 Japanese patients with stable CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease [REAL-CAD]), which is the largest ever “more versus less statins” trial, and the first trial of this type conducted in Asia. High-dose as compared with low-dose pitavastatin significantly reduced the risk of the primary endpoint (a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischaemic stroke, or unstable angina requiring emergency hospitalisation) (4.3% versus 5.4%, respectively, HR 0.81, 95% CI: 0.69-0.95, $p=0.01$)⁷. The favourable effect of high-dose pitavastatin was demonstrated regardless of the baseline low-density lipoprotein cholesterol (LDL-C) level. Relative risk reduction for the primary endpoint in the REAL-CAD trial conducted in Japan was remarkably comparable to that in the Treating to New Targets

(TNT) trial conducted outside Japan, although the absolute event rate was much higher in the TNT trial than in the REAL-CAD trial (Figure 2)⁸. A positive result in a large randomised controlled trial does not always lead to a strong recommendation to adopt the tested intervention in real clinical practice. However, in the case of high-dose statins, we should strongly recommend adopting it in Japanese clinical practice, considering the robust risk reduction seen in Japanese patients, proven safety of long-term statin use during more than 30 years of clinical experience, its reasonably low cost, and the issue of “what is the optimal statin dose?”.

Beyond the high-intensity statins, the efficacy of non-statin LDL-C-lowering agents in reducing cardiovascular events has long been debated. A few years ago, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated that ezetimibe inhibiting intestinal absorption of cholesterol significantly reduced cardiovascular events with a 6.4% relative risk reduction in 18,144 patients with acute coronary syndrome (ACS)⁹. More recently, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and ODYSSEY Outcomes trials demonstrated that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab, respectively) promoting LDL receptor recycling significantly reduced cardiovascular events with a 15% relative risk reduction in 27,546 patients with atherosclerotic cardiovascular disease and in 18,924 patients with ACS¹⁰. These non-statin LDL-C-lowering agents also appeared to be safe, and might be promising for secondary prevention in very high-risk patients. However, in real-world clinical practice, the decision to implement more intensive intervention should be based on consideration of the efficacy (relative risk reduction) and safety of a given intervention, absolute cardiovascular event risk of a given patient, and the cost of the intervention. The role of more

Primary endpoint results

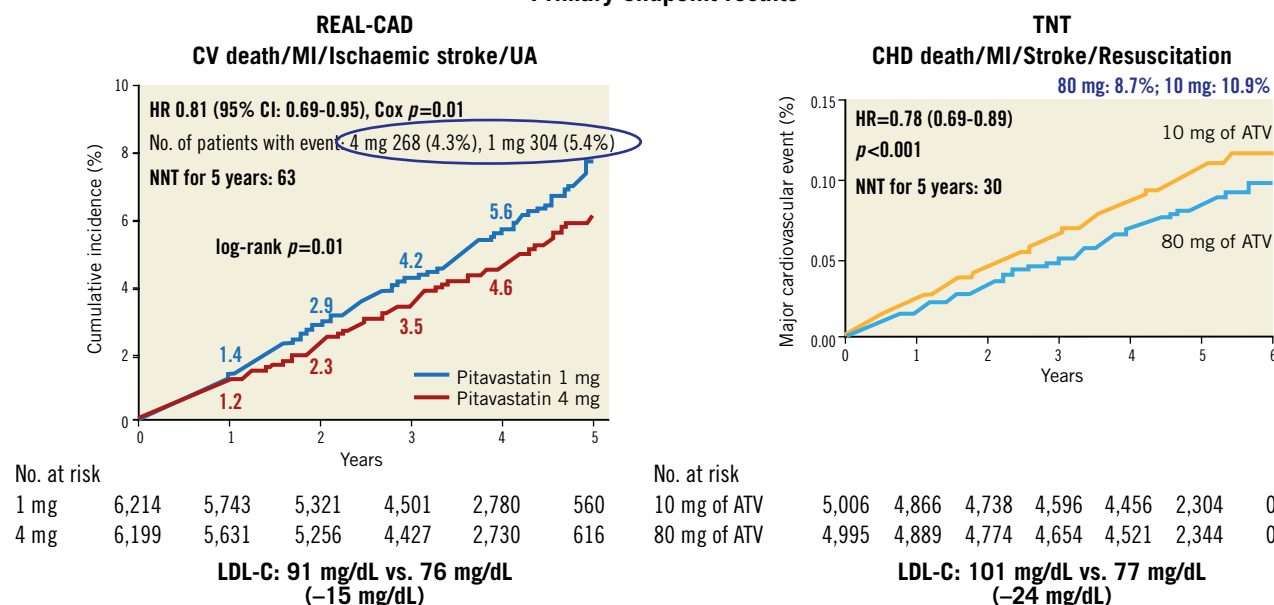


Figure 2. Primary endpoint results in the REAL-CAD and TNT trials. ATV: atorvastatin; CHD: coronary heart disease; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol; MI: myocardial infarction; NNT: number needed to treat; REAL-CAD: Randomised Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease; TNT: Treating to New Targets; UA: unstable angina

intensive lipid-lowering interventions beyond “high-intensity statin” therapy would be very limited in Japanese CAD patients, in whom the cardiovascular event risk is relatively low, and therefore the cost-effectiveness balance is unfavourable for these expensive interventions.

Conflict of interest statement

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Is a biodegradable polymer stent really superior to a durable polymer stent?



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While first-generation drug-eluting stents (DES) with durable polymers have been shown to be effective in reducing angiographic and clinical restenosis compared with bare metal stents, they were beset with problems of late and very late stent thrombosis attributed to delayed healing and re-endothelialisation¹. The durable polymer (DP) coatings are deemed to play an important causative role in inciting chronic inflammatory reaction in the vascular wall, leading to late events². The recently developed biodegradable polymer (BP)-coated DES, which offer similar or better control of drug delivery and release dynamics (without the long-term sequelae of durable polymer), are theoretically superior to DES with durable polymer coatings in reducing long-term adverse events. They aim to combine the efficacy of DES with the long-term safety of a bare metal stent.

There are various BP-DES on the market, ranging from the early bulky stainless steel stents, such as the biolimus-eluting BioMatrix™ stent (Biosensors, Morges, Switzerland), to new cobalt-chromium stents such as the sirolimus-eluting Ultimaster® (Terumo Corp., Tokyo, Japan) and Orsiro (Biotronik AG, Bülach,

Switzerland) stents, and the everolimus-eluting platinum-chromium SYNERGY™ stent (Boston Scientific, Marlborough, MA, USA). Polymer degradation can range from three to four months to over 12 months. In general, there are three types of synthetic biodegradable polymer: polyglycolic acid (PGA), polylactic acid (PLA) and poly glycolic-co-lactic acid (PLGA). PLA and PGA have lactic acid and glycolic acid that are ultimately converted to water and carbon dioxide through the action of enzymes in the tricarboxylic acid cycle and excreted via the respiratory system. PLA is more resistant to hydrolytic attack than PGA and increasing the PLA:PGA ratio in the PLGA copolymer will result in delayed degradability³.

The strongest purported benefit of biodegradable polymer stents is the fact that there is complete dissolution of the polymer after one year with no residual drug to cause persistent long-term vascular inflammation. Numerous studies have been performed to compare the efficacy and safety of BP-DES versus DP-DES. The first such comparator study was that of a BP biolimus-eluting stent (BES) (BioMatrix) with the CYPHER® stent (Cordis, Cardinal Health, Milpitas, CA, USA) in the LEADERS trial⁴. While similar

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rates of the composite endpoint of cardiac death, myocardial infarction (MI), and clinically indicated target vessel revascularisation (TVR) were observed within nine months of DES implantation (9.2% with BP-BES versus 10.5% with DP-SES; p for non-inferiority=0.003), there was a numerically lower incidence of the primary endpoint with BP-BES vs. SES (22.3% vs. 26.1%, p for non-inferiority <0.0001, p for superiority=0.069) at five years⁵. There was also a significant reduction in very late definite ST from one to five years with BES vs. SES (0.7% vs. 2.5%, $p=0.003$).

In this issue of AsiaIntervention, Chung et al⁶ compared a BP sirolimus-eluting stent (Orsiro) with a durable polymer, sirolimus-eluting stent (CYPHER) to determine if late failure of the CYPHER is caused by the polymer or sirolimus.

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The results showed that, at two years of follow-up, the composite outcome of cardiac death, stent thrombosis, and clinically driven target lesion revascularisation (TLR) occurred in 3.0% of the Orsiro group and 9.6% of the CYPHER group.

Among the 344 (79.9%) patients who were followed up from nine months to two years, stent failure occurred significantly less in the BP-SES group than in the DP-SES group (1.6% vs. 7.7%, HR 0.25, 95% CI: 0.06–0.74, $p=0.011$). The investigators performed multivariable Cox regression analysis which showed that the Orsiro stent was a significant independent predictor of clinical events two years after PCI. They concluded that late CYPHER failure is attributable to its durable polymer and not to the antiproliferative drug sirolimus, since both DES share the same drug.

The conclusion of this study could be somewhat questionable, as it is too simplistic to attribute the difference in stent failure rates to mere differences in the type of polymer coating, namely durable vs. biodegradable polymer. The two stents share the same type of drug and concentration (1.4 $\mu\text{g}/\text{mm}^2$) but differ in all other aspects including the types of polymer, stent alloy used, stent design, stent strut thickness and drug elution kinetics, with each of these characteristics having the potential to impact on the clinical performance of a stent.

It is known that, among the many BP-DES on the market, they differ in terms of their clinical performance. BP-BES were shown to have a higher incidence of stent thrombosis compared to a cobalt-chromium everolimus-eluting stent (Co-Cr EES)⁷. This was attributed to the thin-strut backbone of 81 μm for the EES and its novel polymeric drug carrier which consists of a non-inflammatory ultrapure fluorinated copolymer versus the thick struts of the BP-DES stainless steel design⁸.

Early studies in the bare metal stent (BMS) era had conclusively demonstrated that thin-strut stents fared better than thick-strut stents in reducing the restenosis and target vessel revascularisation rates^{9,10}. In the SORT OUT VII study which compared the thin-strut BP sirolimus-eluting Orsiro stent versus the thick-strut BP biolimus-eluting Nobori[®] stent (Terumo Corp.) in unselected patients, the Orsiro stent was associated with a reduced risk of definite stent thrombosis (0.4% vs. 1.2%, $p=0.03$)¹¹. In a comparison of the thin-strut BP-SES Orsiro with the thin-strut Pt-Cr EES

SYNERGY stent and a thin-strut DP zotarolimus-eluting stent (ZES) in the BIORESORT trial, the target lesion failure rate at 12 months was 4% for the patients treated with a BP-DES (either the SES Orsiro stent or the EES SYNERGY stent) versus 5.0% for the DP-ZES, which was not significant¹². A recent meta-analysis of 16 randomised controlled trials comparing BP-DES with second-generation DP-DES demonstrated similar safety and efficacy profiles, even after accounting for the type of antiproliferative drug used, stent platform, kinetics of polymer degradation/drug release, strut thickness, and duration of dual antiplatelet therapy¹³.

While all comparator studies of the new generation of thin-strut BP-DES showed clinical parity with second-generation EES, one exception was the BIOFLOW V trial. This study showed that the BP-SES Orsiro outperformed Co-Cr EES in 1,334 randomised patients with a significant reduction in target lesion failure rates (4% vs. 7%, $p=0.03$). The difference was observed as early as 30 days, predominantly driven by a difference in MI. At the 12-month primary endpoint, target lesion failure was 6% in the BP-DES group versus 10% in the DP-DES group, $p=0.04$ ¹⁴. Despite the positive results seen in favour of BP-SES, one has to be cautious in attributing this to the biodegradable polymer concept. The higher incidence of MI observed for Orsiro versus XIENCE (Abbott Vascular, Santa Clara, CA, USA) (5% vs. 8%, $p=0.0155$) was most likely due to a tighter definition of MI compared with other studies and the ultrathin-strut design of the Orsiro stent. The true litmus test of the Orsiro with its biodegradable polymer will only be known in a long-term follow-up study when the biodegradable polymer is fully resorbed after one year.

Given the many variables among different DES, the results of any direct comparator studies can only apply to the stents being studied. One can only conclude from Chung et al's study that the Orsiro stent performed better than the first-generation CYPHER stent in safety and efficacy because of its inherent design. The exact component driving the difference in outcomes remains speculative and is probably multifactorial, something which cannot be fully answered in this study.

Biodegradable polymer technology with its potential to reduce vessel inflammation and consequent neoatherosclerosis, late stent thrombosis and restenosis will continue to generate interest in the field. Whether this will be transformed into safety benefit in the long term needs to be validated in longer and larger studies. Until then, we can be sure that there will be many such comparator studies carried out.

Conflict of interest statement

J.P. Loh and H.C. Tan report research funding from Boston Scientific.

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Systems of care for STEMI in developing countries – the way forward



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Early reperfusion in ST-segment elevation myocardial infarction (STEMI) improves cardiovascular outcomes. Primary percutaneous coronary intervention (PPCI) is the preferred modality of reperfusion if it can be performed on a timely basis. The randomised clinical trials proving the superiority of PPCI over fibrinolytics resulted in a concerted effort to increase timely access to PCI in the developed countries and the commencement of regional STEMI systems. “A STEMI system was defined as an integrated group of separate entities focused on reperfusion therapy for STEMI within a geographic region that included at least one hospital that performs percutaneous coronary intervention and at least one emergency medical service agency”¹. These systems help to redirect the patients with STEMI to PCI-capable hospitals through emergency medical service (EMS) protocols and timely inter-hospital transfer, thereby curbing the time delays to reperfusion. Systems of care have radically altered the way patients with STEMI are treated in the developed countries. The Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments (RACE) project which started in 2003 decreased the median door-in to door-out time at transfer hospitals from 120 to 71 minutes, and median time to beginning treatment at a receiving hospital fell from 149 minutes to 106 minutes. In 2007, the American Heart Association (AHA) launched “Mission:

Lifeline”, the first national initiative to improve quality of care and outcomes in STEMI patients; 80% of states established a Mission: Lifeline Task Force within the first year². Europe has also witnessed similar success stories in the treatment of STEMI. The Vienna STEMI registry showed that, after establishing the central triage organisation via the Viennese Ambulance System, there was a marked decrease in the proportion of patients who received no reperfusion therapy, from 34% to 13.4%. PPCI usage increased from 16% to 60%, and in-hospital mortality decreased from 16% to 9.5%³. After the initiation of a STEMI network with the support of the Stent for Life (SFL) initiative in Central Romania, there was an increase in the reperfusion rate from 26.9% to 87.2%, mainly driven by an increase in the rate of PPCI (from 10.9% to 78.6%)⁴.

Although these systems are effective, they are resource intensive. This approach presupposes the availability of a fairly evenly distributed catheterisation laboratory density along with an effective EMS system and physical infrastructure for transportation. In developing countries, however, huge gaps exist in STEMI care as a result of limited healthcare infrastructure, financial barriers, poor knowledge and accessibility of acute medical services for the majority of the population⁵. Time delays are crucial: PPCI loses its advantages over fibrinolytic therapy when door-to-balloon times exceed door-to-drug times by 60 to 90 minutes. The concern that

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enthusiasm for PPCI has the inadvertent consequence of delaying reperfusion for patients presenting to hospitals without PCI capability and needing transfer mandates the inclusion of the “pharmaco-invasive (PI) strategy” – a concept of timely reperfusion by fibrinolytics with a routine and systematic coronary angiogram within 24 hours followed by PCI if indicated. A PI strategy compared well with PPCI in the STREAM and STEPP-AMI trials^{6,7}, showing better results than stand-alone fibrinolysis⁸. Integrating the PI strategy into the systems improved STEMI care via increased number of PCIs and resulted in better mortality rates at one year⁹. Routine use of the PI strategy in a system of care may also help in redirecting the much needed transfer resources to more critical patients such as those with contraindications to fibrinolysis, cardiogenic shock or out-of-hospital cardiac arrest.

The challenges to execute STEMI systems of care in low and middle income countries (LMICs) are formidable because of several non-clinical, system-level factors¹⁰. The most important limitations arise from poverty, and the fact that many of these patients may not have medical insurance and have to pay “out of pocket” for their treatment even in case of emergencies. This divide hinders uniformity of treatment protocols and fragments the healthcare delivery system. There is a great variation in the accessibility as well as the capability of EMS services and PCI-capable hospitals in LMICs. Technology gaps, dearth of standardised protocols, operational complexity and lack of centralised policies hamper designing STEMI systems to best match the needs of a community. Despite the challenges, few developing countries have made headway in the management of STEMI. In India, “STEMI India”, a private non-profit organisation, launched an innovative and sustainable system of care. The design of this system is based on a hub and spoke model with each unit called a “STEMI cluster”. The treatment protocols combine a dual approach of PPCI and a PI strategy of reperfusion. Linking public-private partnership EMS, state insurance schemes for vulnerable populations, and innovative information technology platforms with existing hospital infrastructure are the crucial aspects of this system. When implemented across the southern state of Tamil Nadu, this system of care reported increased rates of coronary angiography (35.0% vs. 60.8%; $p<0.001$) and PCI (29.5% vs. 46.5%; $p<0.001$) during the post-implementation phase. One-year mortality was also lower in the post-implementation phase (17.6% vs. 14.2%; $p=0.04$). This difference remained consistent after multivariable adjustment⁹.

In this issue of AsiaIntervention, Dharma et al report “Hospital outcomes in STEMI patients after the introduction of a regional STEMI network in the metropolitan area of a developing country”¹¹.

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Dharma et al also previously published an interesting article about the success of the Jakarta Cardiovascular Care Unit Network System, the STEMI network which was introduced as an integral part of the government project in 2010/2011¹². The present study compared the outcomes before and five years after implementation of the STEMI system. The proportion of patients with STEMI presenting late (>12 hours duration) has decreased significantly (37%

vs. 29%, $p<0.01$) and the number of patients with inter-hospital referral has increased (55% vs. 68%, $p<0.001$) post implementation, suggesting better connectivity in the STEMI system. There was greater use of PPCI (28% vs. 56%, $p<0.001$), possibly contributed to by the creditable healthcare coverage, where all costs related to acute reperfusion therapy are covered by the government healthcare insurance system¹². Better door-to-device times (94 min vs. 82 min, $p<0.001$) and, most importantly, reduction in the number of patients with “no reperfusion strategy” (59% vs. 37%, $p<0.001$) after the implementation of the STEMI system are perhaps the reasons for fewer deaths.

Although the authors should be congratulated for their efforts to build effectual regional STEMI systems of care in a developing country (appropriate to their country’s healthcare system), there could be improvement at several levels. There is non-availability of data, especially of patients who underwent fibrinolysis, their timelines, follow-up angiograms and their outcomes. To develop a system of care in developing countries, it is important to recognise that PPCI as the exclusive mode of reperfusion is not feasible, and a PI strategy must be included in the treatment protocol. Categorising and equipping the referring hospitals will avoid delay in the initiation of treatment. As in other countries, effective management of STEMI at the community level will require executing proven treatment protocols along with efficient and rapid inter-hospital transfer within coordinated hospital networks.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Long-term clinical outcomes with biodegradable polymer sirolimus-eluting stents versus durable polymer sirolimus-eluting stents



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KEYWORDS

- ACS/NSTE-ACS
- clinical research
- stable angina
- STEMI

Abstract

Aims: The purpose of this study was to compare the long-term outcomes of a biodegradable polymer, sirolimus-eluting stent (Orsiro) with a durable polymer, sirolimus-eluting stent (CYPHER) to determine if late failure of the CYPHER is caused by the polymer or sirolimus.

Methods and results: A total of 447 patients who underwent percutaneous coronary intervention (PCI) with one of the study stents were retrospectively analysed. The composite of cardiac death, stent thrombosis, and clinically driven target lesion revascularisation (TLR) within two years after PCI occurred in 3.0% of the Orsiro group and 9.6% of the CYPHER group. Multivariable Cox regression results indicated that the Orsiro stent was a significant independent predictor of a lower occurrence of the composite outcome (adjusted HR 0.37, 95% CI: 0.14-0.87), stent thrombosis (adjusted HR 0.07, 95% CI: 0.00-0.65), clinically driven TLR (adjusted HR 0.26, 95% CI: 0.09-0.69), and stent failure (adjusted HR 0.26, 95% CI: 0.09-0.69) within two years after PCI.

Conclusions: This study has demonstrated that late CYPHER failure is attributable more to its durable polymer than to the antiproliferative drug, sirolimus. This suggests that sirolimus-based, new-generation drug-eluting stents are relatively safe and are expected to show long-term outcomes superior to those of the CYPHER.

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Abbreviations

| | |
|---------------|--|
| ACC | American College of Cardiology |
| AHA | American Heart Association |
| BMS | bare metal stent(s) |
| BP-SES | biodegradable polymer sirolimus-eluting stent(s) |
| CI | confidence interval |
| DES | drug-eluting stent(s) |
| DP-EES | durable polymer everolimus-eluting stent(s) |
| DP-SES | durable polymer sirolimus-eluting stent(s) |
| HR | hazard ratio |
| LVEF | left ventricular ejection fraction |
| PCI | percutaneous coronary intervention |
| PSS | peri-stent contrast staining |
| SD | standard deviation |
| TIMI | Thrombolysis In Myocardial Infarction |
| TLR | target lesion revascularisation |

Introduction

First-generation drug-eluting stents (DES) with durable polymers for the controlled release of antiproliferative sirolimus have significantly reduced in-stent restenosis compared with bare metal stents (BMS)^{1,2}. However, unexpectedly, first-generation DES brought new problems, i.e., late and very late stent thrombosis³. Synthetic non-absorbable polymers or antiproliferative drugs were considered important stimuli for vascular wall inflammation responses subsequent to a hypersensitivity reaction. According to previous pathological studies of the CYPHER® (Cordis, Cardinal Health, Milpitas, CA, USA) durable polymer sirolimus-eluting stent (DP-SES), hypersensitivity to the polymer was the most likely mechanism for the inflammatory reaction of the coronary artery wall^{4,5}. Although studies were in an *in vitro* setting, there were concerns that sirolimus caused impairment of relaxation to serotonin and bradykinin of vascular smooth muscle cells subsequent to endothelial dysfunction and enhanced platelet aggregation⁶⁻⁸.

Numerous trials have been undertaken to determine the factors associated with CYPHER stent failure. However, until now, there have been no head-to-head comparisons of DP and biodegradable polymers (BP) in stents with the same antiproliferative drug, sirolimus, to clarify whether CYPHER stent failure could have been caused by the polymer or the sirolimus.

Therefore, we compared the relative long-term safety and efficacy of BP-SES (Orsiro; Biotronik, Bülach, Switzerland) with DP-SES (CYPHER) in patients undergoing percutaneous coronary intervention (PCI).

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Methods

STUDY DESIGN AND PATIENTS

This retrospective, observational single-centre study was undertaken at the Seoul National University Boramae Medical Center in Seoul, Republic of Korea. A total of 447 consecutive patients who underwent PCI from May 2008 to June 2016 with one of the study stents, BP-SES Orsiro or DP-SES CYPHER, were retrospectively analysed.

The enrolment period of the DP-SES was from May 2008 to May 2011, and of the BP-SES from September 2013 to July 2016. There were no limitations to the number of treated lesions, lesion length and location, reference vessel diameter, and concomitant use of other BMS or DES. As early death is rarely correlated with the scope of late complications associated with either drug or polymer and is affected by patients' disease severity at initial presentation and procedural success, patients who died within 48 hours after PCI were excluded from the analysis. The Seoul National University institutional review board and ethics committee approved the study protocol.

PROCEDURES

PCI procedures were performed according to the current procedural standard. All patients received a 300 mg loading dose of aspirin and a 600 mg loading dose of clopidogrel, a 60 mg loading dose of prasugrel or a 180 mg loading dose of ticagrelor before or during PCI, unless they had previously received these antiplatelet drugs. During the PCI, weight-adjusted unfractionated heparin was given to keep the activated clotting time in the range of 250-350 seconds. The use of glycoprotein IIb/IIIa receptor inhibitors, intravascular ultrasound or post-dilatation after stent implantation was left to the operator's discretion. Pre- and post-PCI coronary flows were graded by applying Thrombolysis In Myocardial Infarction (TIMI) grading⁹. Coronary lesions were classified according to the American College of Cardiology/American Heart Association (ACC/AHA) coronary lesion classification system¹⁰.

OUTCOMES AND DEFINITIONS

The primary outcome was the composite of cardiac death, stent thrombosis, and clinically driven target lesion revascularisation (TLR) occurring within two years of PCI. Secondary outcomes were cardiac death, stent thrombosis, clinically driven TLR, and stent failure defined as a composite of stent thrombosis and clinically driven TLR within two years of PCI. To investigate the late adverse effect of the polymer, a landmark analysis of the primary and stent failure outcomes from month 9 to month 24 post PCI was undertaken.

Cardiac death was defined as death from cardiac causes including myocardial infarction, decompensated heart failure, fatal arrhythmia, or sudden death of unknown cause. Stent thrombosis was defined as probable or definite stent thrombosis according to the Academic Research Consortium definitions¹¹. TLR was defined as revascularisation with PCI or coronary artery bypass graft surgery performed for a $\geq 50\%$ diameter stenosis within the index stent or within 5 mm proximal and/or distal to the implanted stents after documentation of recurrent symptoms, new electrocardiographic changes, or positive functional study suggesting ischaemia in a territory distal to the stented lesion at the time of the index procedure, or if the stenosis diameter was more than 70% in the index lesion, irrespective of the presence or absence of ischaemic signs and symptoms. Severe calcification was characterised by the presence of radiopacities noted without cardiac motion before contrast injection and generally compromising both

sides of the arterial lumen¹². Clinical follow-up was carried out every one to six months and whenever any clinical event took place. All events were identified by the physician in charge and confirmed by the principal investigator.

STATISTICAL ANALYSIS

The results are presented as mean±standard deviation (SD) values for continuous variables and as a percentage for categorical variables. Continuous variables were analysed by using the Student's t-test. Categorical variables were analysed by using the Pearson's chi-squared test or Fisher's exact test, as appropriate. Survival curves for study outcomes were constructed by using Kaplan-Meier estimates and were compared with the log-rank test result to evaluate the difference in clinical event rates according to stent type. Cox regression analysis with Firth's penalised likelihood method was performed to determine independent associations of stents with clinical outcomes after PCI. In the multivariable analysis, prior history of myocardial infarction, clinical diagnosis, total stent length, minimal stent diameter, severe calcification of lesion, and left ventricular ejection fraction (LVEF) were included as covariates. All analyses were two-tailed, and statistical significance was defined as $p < 0.05$. Statistical analyses were performed with the statistical packages SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA) and R programming language version 3.3.1 with package coxphf (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between May 2008 and July 2016, 447 consecutive patients with coronary artery disease underwent PCI with either Orsiro or CYPHER stents and survived for more than 48 hours after the index PCI. All were included in the analysis (**Figure 1**). In the

CYPHER group, the first case was undertaken in May 2008 when CYPHER was still popular, and the last case was in May 2011. In the Orsiro group, the first case was in September 2013, and the last case was in July 2016.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The mean age of the study patients was 67.3 ± 11 years, 285 (63.8%) patients were male, and 372 (83.2%) patients presented with acute coronary syndrome (ACS). Among the 447 patients, 177 patients underwent PCI with DP-SES for 270 lesions, and 270 patients with BP-SES for 358 lesions. Among the previous medical history and cardiovascular risk factors, the prevalence of dyslipidaemia was higher, while that of previous myocardial infarction was lower in the BP-SES group than in the DP-SES group. In terms of clinical diagnosis, ACS was less prevalent, whereas multivessel disease was more prevalent in the BP-SES group than in the DP-SES group. At discharge, a beta-blocker was prescribed less and a statin was prescribed more in the BP-SES group than in the DP-SES group. The rate of dual antiplatelet use was similar in the two groups at one year after PCI but was significantly lower in the BP-SES group than in the DP-SES group at two years after PCI (**Table 1**). Newer-generation antiplatelet agents such as prasugrel or ticagrelor were prescribed only in the Orsiro group, in which only 18.1% of the patients received them.

BASELINE ANGIOGRAPHIC AND PROCEDURAL CHARACTERISTICS

Total stent length was shorter, whereas post-dilatation and final TIMI flow grade 3 in the target vessel were more common in the BP-SES group than in the DP-SES group. With regard to individual lesion characteristics, the rate of thrombus-containing lesions was less prevalent whereas severely calcified lesions were more prevalent in the BP-SES group than in the DP-SES group (**Table 2**).

CLINICAL OUTCOMES

The cumulative clinical outcomes of the study patients are summarised in **Table 3** and Kaplan-Meier survival curves are shown in **Figure 2**. The primary outcome occurred significantly less often in the BP-SES group than in the DP-SES group (BP-SES vs. DP-SES, 3.0% vs. 9.6%, hazard ratio [HR] 0.41, 95% confidence interval [CI]: 0.17-0.91, $p = 0.028$). As for secondary outcomes, cardiac death occurred at similar rates in both groups (1.1% vs. 1.1%, HR 1.42, 95% CI: 0.27-8.84, $p = 0.679$). However, stent thrombosis (0.0% vs. 3.4%, HR 0.07, 95% CI: 0.00-0.56, $p = 0.008$), clinically driven TLR (1.9% vs. 9.0%, HR 0.28, 95% CI: 0.10-0.70, $p = 0.005$), and stent failure (1.8% vs. 9.0%, HR 0.28, 95% CI: 0.10-0.70, $p = 0.005$) occurred significantly less often in the BP-SES group than in the DP-SES group.

Among the study population, 354 (79.2%) of the 447 patients in total had a nine-month angiographic follow-up. One patient in each group had a stent fracture at the nine-month follow-up ($p = 0.653$). Peri-stent contrast staining (PSS) was observed

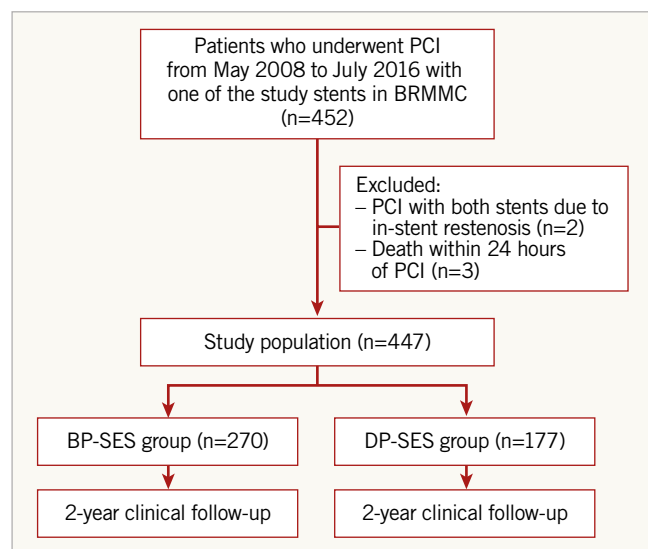


Figure 1. Flow chart of the study groups established for analysis of stent type. BRMMC: Boramæ Medical Center

Table 1. Demographic and baseline clinical characteristics of study patients.

| Variables | BP-SES (n=270) | DP-SES (n=177) | p-value |
|---|-------------------|-------------------|---------|
| Demographics | | | |
| Age, years | 67.32±11.17 | 67.27±10.83 | 0.965 |
| Male | 178 (65.9) | 107 (60.5) | 0.239 |
| Body mass index (kg/m ²) | 24.50±3.29 | 25.99±17.62 | 0.188 |
| Comorbidities and risk factors | | | |
| Hypertension | 184 (68.1) | 128 (72.3) | 0.348 |
| Diabetes | 118 (43.7) | 62 (35.0) | 0.067 |
| Dyslipidaemia | 184 (68.1) | 101 (57.1) | 0.017 |
| Heart failure | 19 (7.0) | 13 (7.3) | 0.902 |
| Cerebrovascular disease | 30 (11.1) | 31 (17.5) | 0.054 |
| Chronic kidney disease | 15 (5.6) | 9 (5.1) | 0.829 |
| Current smoker | 63 (23.3) | 45 (25.4) | 0.614 |
| Family history of coronary artery disease | 27 (10.0) | 21 (11.9) | 0.534 |
| Previous myocardial infarction | 24 (8.9) | 43 (18.1) | 0.004 |
| LVEF | 60.16±13.28 | 59.28±14.50 | 0.512 |
| LV dysfunction (LVEF ≤40%) | 33 (12.7) | 26 (15.0) | 0.488 |
| Clinical diagnosis | | | |
| Stable angina | 55 (20.4) | 20 (11.3) | 0.002 |
| Unstable angina | 128 (47.4) | 84 (47.5) | |
| NSTEMI | 57 (21.1) | 33 (18.6) | |
| STEMI | 30 (11.1) | 40 (22.6) | |
| Acute coronary syndrome | 215 (79.6) | 157 (88.7) | 0.012 |
| Total number of diseased vessels | | | |
| 1 vessel | 43 (15.9) | 46 (26.0) | 0.006 |
| 2 vessels | 89 (33.0) | 65 (36.7) | |
| 3 vessels | 138 (51.1) | 66 (37.3) | |
| Multivessel disease | 227 (84.1) | 131 (74.0) | 0.009 |
| Left main disease | 35 (13.0) | 15 (8.5) | 0.141 |
| Medication at discharge | | | |
| Aspirin | 270 (100.0) | 177 (100.0) | – |
| P2Y ₁₂ inhibitors | 265 (98.1) | 172 (97.2) | 0.496 |
| Newer antiplatelets (prasugrel or ticagrelor) | 49 (18.1) | 0 (0) | <0.001 |
| DAPT at 1 year | 129/160 (80.6) | 121/138 (87.7) | 0.098 |
| DAPT at 2 years | 18/66 (27.3) | 76/127 (59.8) | <0.001 |
| RAS blockers | 167 (61.9) | 108 (61.0) | 0.859 |
| Beta-blockers | 136 (50.4) | 112 (63.3) | 0.007 |
| Statin | 244 (90.4) | 139 (78.5) | <0.001 |

Values are n (%) or mean±standard deviation. ACC: American College of Cardiology; AHA: American Heart Association; DAPT: dual antiplatelet therapy; LV: left ventricle; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; RAS: renin-angiotensin system; RVD: reference vessel diameter; STEMI: ST-segment elevation myocardial infarction

in six patients in the CYPHER group only (p=0.017) (**Figure 3**). However, none of them experienced any clinical event during the whole follow-up period.

Among 447 patients, 344 patients were followed up from nine months to two years after PCI and were included in the nine months to 24 months landmark analysis of clinical outcomes after PCI. The composite of cardiac death, stent thrombosis, and clinically driven TLR occurred significantly less often in the BP-SES group than in the DP-SES group (2.1% vs. 7.7%, HR 0.33, 95% CI: 0.10-0.91, p=0.032). Similarly, stent failure after nine months of PCI occurred significantly less in the BP-SES group than in the DP-SES group (1.6% vs. 7.7%, HR 0.25, 95% CI: 0.06-0.74, p=0.011). Interestingly, even patients who did not take the newer antiplatelet therapy experienced fewer primary outcomes in the BP-SES group than in the DP-SES group (2.7% vs. 10.7% during the whole follow-up period, p=0.001; 2.1% vs. 9.0% during the nine-month landmark analysis, p=0.009). Additionally, the 49 patients who had received the newer antiplatelet therapy did not experience any cardiac death, stent thrombosis, or TLR events after discontinuation of the prasugrel or ticagrelor after 12 months.

The results of the multivariable Cox regression analysis revealed that BP-SES was a significant independent predictor of a lower occurrence of the primary outcome (adjusted HR 0.37, 95% CI: 0.14-0.87, p=0.022), stent thrombosis (adjusted HR 0.07, 95% CI: 0.00-0.65, p=0.015), clinically driven TLR (adjusted HR 0.26, 95% CI: 0.09-0.69, p=0.006), and stent failure (adjusted HR 0.26, 95% CI: 0.09-0.69, p=0.006) within two years after PCI. The multivariable Cox regression analysis for outcomes from nine months to 24 months after PCI demonstrated similar results. Compared to the DP-SES, the use of the BP-SES was significantly associated with a lower occurrence of the composite of cardiac death, stent thrombosis, or clinically driven TLR (adjusted HR 0.34, 95% CI: 0.10-0.97, p=0.043) and stent failure (adjusted HR 0.23, 95% CI: 0.06-0.74, p=0.012) from nine months to 24 months after PCI (**Table 4**).

To determine whether the outcomes according to stent type were consistent, we calculated the HR for the primary outcome in various subgroups. The results revealed that there were no significant interactions between stent type and primary outcome in any of the subgroups even though, in subgroups of patients without diabetes, with severely calcified lesions, with a lesion longer than 24 mm, and with LVEF more than 40%, the BP-SES patients had significantly better clinical outcomes than the DP-SES patients (**Figure 4**).

Discussion

In this observational study, we showed that the clinical efficacy of DP stents was inferior to that of BP stents with the same anti-proliferative drug, sirolimus. The incidence of clinical outcomes, including stent thrombosis, clinically driven TLR, and other composite outcomes was significantly higher in the DP-SES group than in the BP-SES group during the two-year follow-up period. In particular, the differences in outcomes increased at and after

Table 2. Angiographic and procedural characteristics.

| Variables | | BP-SES | DP-SES | p-value |
|--|--|-------------|-------------|---------|
| Per patient characteristics | | n=270 | n=177 | |
| Total number of stents | | 1.53±0.84 | 1.66±0.95 | 0.136 |
| Total stent length (mm) | | 36.01±23.62 | 43.09±26.26 | 0.003 |
| Minimal stent diameter (mm) | | 2.88±0.42 | 2.82±0.33 | 0.069 |
| At least 1 vessel RVD ≤2.75 mm | | 149 (55.2) | 113 (63.8) | 0.069 |
| At least 1 lesion length >24 mm | | 84 (31.1) | 71 (40.1) | 0.051 |
| At least 1 ACC/AHA B2 or C lesion | | 199 (73.7) | 130 (73.4) | 0.952 |
| At least 1 preprocedural TIMI flow grade 0-2 | | 56 (20.7) | 47 (26.6) | 0.153 |
| At least 1 moderate or severe angulation | | 18 (6.7) | 6 (3.4) | 0.133 |
| At least 1 chronic total occlusion | | 17 (6.3) | 12 (6.8) | 0.839 |
| At least 1 severe calcification | | 88 (32.6) | 47 (26.6) | 0.174 |
| At least 1 ostial lesion | | 57 (21.1) | 37 (20.9) | 0.958 |
| Adjuvant ballooning of all treated lesions | | 185 (68.5) | 84 (47.5) | <0.001 |
| Post-procedural TIMI flow grade 3 of all vessels | | 267 (98.9) | 170 (96.0) | 0.047 |
| Per lesion characteristics | | n=358 | n=270 | |
| Target lesion coronary artery | Left main | 15 (4.2) | 12 (4.4) | 0.551 |
| | Left anterior descending | 150 (41.9) | 106 (39.3) | |
| | Left circumflex | 87 (24.3) | 69 (25.6) | |
| | Right coronary artery | 106 (29.6) | 81 (30.0) | |
| | Bypass graft | 0 (0.0) | 2 (0.7) | |
| ACC/AHA lesion class | A | 31 (8.7) | 33 (12.2) | 0.502 |
| | B1 | 84 (23.5) | 63 (23.3) | |
| | B2 | 118 (33.0) | 88 (32.6) | |
| | C | 125 (34.9) | 86 (31.9) | |
| | B2 or C lesions | 243 (67.9) | 174 (64.4) | 0.367 |
| Preprocedural TIMI flow grade | 0 | 34 (9.5) | 37 (13.7) | 0.392 |
| | 1 | 5 (1.4) | 4 (1.5) | |
| | 2 | 20 (5.6) | 12 (4.4) | |
| | 3 | 299 (83.5) | 217 (80.4) | |
| | Preprocedural TIMI flow grade 0-2 | 59 (16.5) | 53 (19.6) | 0.307 |
| Lesion angulation | Mild (<45°) | 340 (95.0) | 264 (97.8) | 0.150 |
| | Moderate (≥45° and <90°) | 16 (4.5) | 6 (2.2) | |
| | Severe (≥90°) | 2 (0.6) | 0 (0.0) | |
| | Angulated lesion (≥45°) | 18 (5.0) | 6 (2.2) | 0.069 |
| Total occlusion | No | 322 (89.9) | 230 (85.2) | 0.107 |
| | <3 months | 19 (5.3) | 26 (9.6) | |
| | ≥3 months | 17 (4.7) | 14 (5.2) | |
| | Chronic total occlusion | 17 (4.7) | 14 (5.2) | 0.803 |
| Lesion calcification | No | 187 (52.2) | 195 (72.2) | <0.001 |
| | Mild | 26 (7.3) | 3 (1.1) | |
| | Moderate | 37 (10.3) | 11 (4.1) | |
| | Severe | 108 (30.2) | 61 (22.6) | |
| Other characteristics | Severely calcified lesion | 108 (30.2) | 61 (22.6) | 0.034 |
| | Thrombus present | 40 (11.2) | 86 (31.9) | <0.001 |
| | Ostial lesion | 62 (17.3) | 45 (16.7) | 0.830 |
| | Adjuvant ballooning after stent implantation | 257 (71.8) | 152 (56.3) | <0.001 |
| | Long lesion (>24 mm) | 156 (43.6) | 157 (58.1) | <0.001 |
| | Small vessel (RVD ≤2.75 mm) | 178 (49.7) | 156 (57.8) | 0.045 |
| | Post-procedural TIMI flow grade 3 | 355 (99.2) | 262 (97.0) | 0.063 |

Values are n (%) or mean±standard deviation. ACC: American College of Cardiology; AHA: American Heart Association; RVD: reference vessel diameter; TIMI: Thrombolysis In Myocardial Infarction

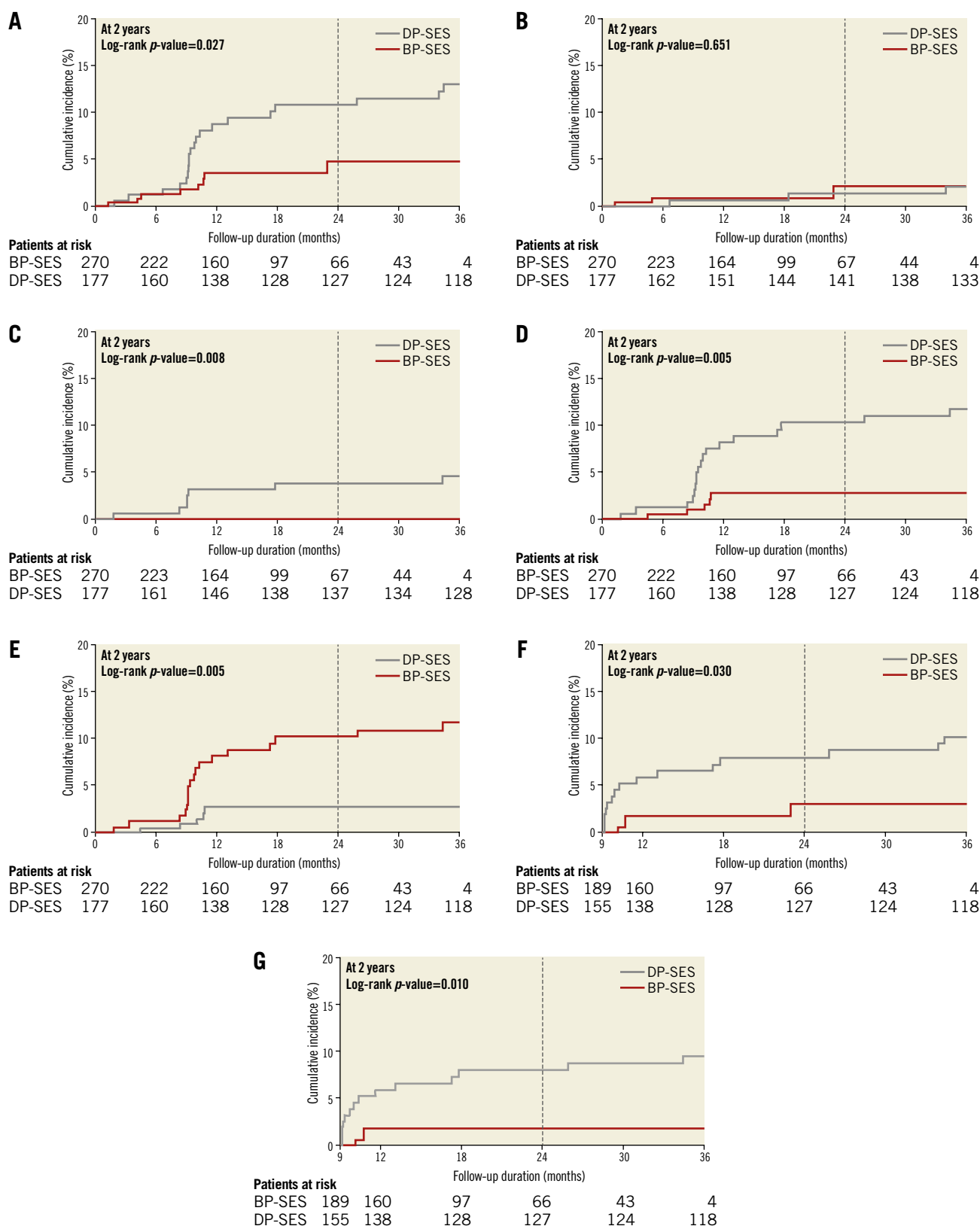


Figure 2. Kaplan-Meier curves of clinical outcomes. A) Cumulative incidence of the primary outcome, a composite of cardiac death, stent thrombosis, and target lesion revascularisation (TLR). B) Cumulative incidence of cardiac death. C) Cumulative incidence of stent thrombosis. D) Cumulative incidence of TLR. E) Cumulative incidence of the composite of stent thrombosis or TLR. F) Cumulative incidence of the composite of cardiac death, stent thrombosis, and TLR at and after nine months of PCI. G) Cumulative incidence of stent thrombosis or TLR at and after nine months of PCI.

Table 3. Clinical outcomes at 2-year follow-up.

| Variables | BP-SES (n=270) | DP-SES (n=177) | HR (95% CI) | p-value |
|---|-------------------|-------------------|------------------|---------|
| Cardiac death, stent thrombosis or clinically driven TLR | 8 (3.0) | 17 (9.6) | 0.41 (0.17-0.91) | 0.028 |
| Cardiac death | 3 (1.1) | 2 (1.1) | 1.42 (0.27-8.84) | 0.679 |
| Stent thrombosis | 0 (0.0) | 6 (3.4) | 0.07 (0.00-0.56) | 0.008 |
| Clinically driven TLR | 5 (1.9) | 16 (9.0) | 0.28 (0.10-0.70) | 0.005 |
| Stent thrombosis or clinically driven TLR | 5 (1.9) | 16 (9.0) | 0.28 (0.10-0.70) | 0.005 |
| Cardiac death, stent thrombosis or clinically driven TLR after 9 months | 4/189 (2.1) | 12/155 (7.7) | 0.33 (0.10-0.91) | 0.032 |
| Stent thrombosis or clinically driven TLR after 9 months | 3/189 (1.6) | 12/155 (7.7) | 0.25 (0.06-0.74) | 0.011 |

Values are n (%), unless otherwise stated. Hazard ratio provided as hazard BP-SES/hazard DP-SES. Stent thrombosis defined as probable or definite stent thrombosis according to the Academic Research Consortium definition. Target lesion revascularisation defined as revascularisation by percutaneous or surgical methods. CI: confidence interval; HR: hazard ratio; TLR: target lesion revascularisation

nine months post PCI. The differences were mainly driven by the contribution of the clinically driven TLR outcome. Notably, there was an absence of stent thrombosis in the BP-SES group, whereas there were six stent thromboses in the DP-SES group. All stent thrombosis cases were proven by performing coronary angiography and all were successfully revascularised with PCI.

Sirolimus has potent immunosuppressant properties and an anti-proliferative action that inhibits both cytokine- and growth factor-mediated proliferation and migration of vascular smooth muscle cells¹³. These antiproliferative and antimigratory properties are responsible for the efficacy of sirolimus therapy, which results from the suppression of neointimal hyperplasia in the PCI field¹⁴.

The superiority of SES over BMS in late lumen loss was described in previous trials^{1,2}. Although DES significantly reduced in-stent angiographic (binary) restenosis and repeat revascularisation compared with the levels associated with BMS, some data

Table 4. Adjusted hazard ratios of clinical outcomes in multivariable model.

| Variables | Adjusted HR* | 95% CI | p-value |
|---|--------------|------------|---------|
| Cardiac death, stent thrombosis or clinically driven TLR (primary endpoint) | 0.37 | 0.14-0.87 | 0.022 |
| Cardiac death | 2.13 | 0.25-26.66 | 0.484 |
| Stent thrombosis | 0.07 | 0.00-0.65 | 0.015 |
| Clinically driven TLR | 0.26 | 0.09-0.69 | 0.006 |
| Stent thrombosis or clinically driven TLR | 0.26 | 0.09-0.69 | 0.006 |
| Cardiac death, stent thrombosis or clinically driven TLR after 9 months | 0.34 | 0.10-0.97 | 0.043 |
| Stent thrombosis or clinically driven TLR after 9 months | 0.23 | 0.06-0.74 | 0.012 |

Hazard ratio provided as hazard BP-SES/hazard DP-SES. *adjusted for previous myocardial infarction, clinical diagnosis, total stent length, minimal stent diameter, severe lesion calcification, and left ventricular ejection fraction. CI: confidence interval; HR: hazard ratio; TLR: target lesion revascularisation

from large registries have indicated a high risk for late and very late stent thrombosis with first-generation DES, which is rarely seen with BMS^{15,16}.

Several factors, including procedure-, patient-, lesion-, and stent-related factors, are thought to have a role in stent thrombosis in DES^{15,17,18}. Of the stent-related factors, the drugs eluted from stents play an important role. Sirolimus not only reduces neointimal formation by impeding vascular smooth muscle cell proliferation and migration, but also impairs endothelialisation and the normal healing processes of the injured arterial wall¹⁹. Another stent-related factor, the polymer that carries the antiproliferative drug, was also doubted as a key factor associated with late stent thrombosis. Polymers have been shown to cause delayed healing, impaired endothelialisation on stent struts, and hypersensitivity reactions^{4,5}. Preclinical experience in a pig model showed a progressive increase of granulomatous reactions, including eosinophilic infiltrate, starting at 28 days after CYPHER DP-SES

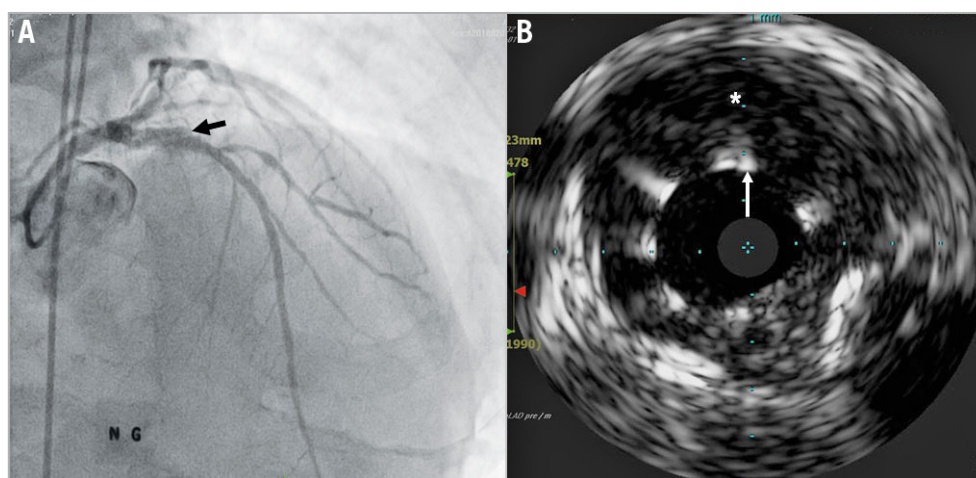


Figure 3. A typical example of peri-stent staining and very late malapposition in the CYPHER group. A) Black arrow indicates peri-stent contrast staining. B) White arrow indicates a stent strut; the asterisk denotes peri-stent space formed by malapposition.

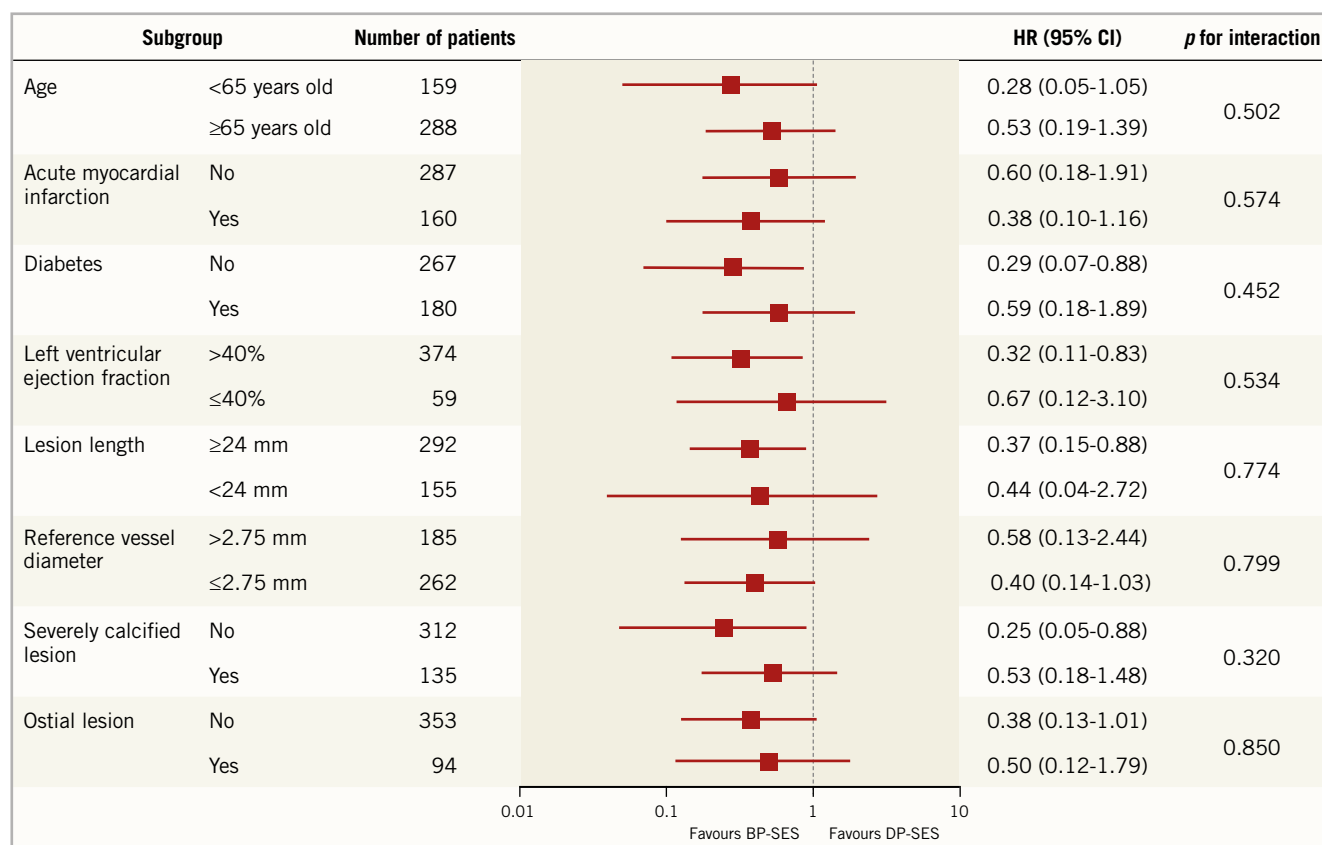


Figure 4. Forest plot of the composite of cardiac death, stent thrombosis, and target lesion revascularisation.

implantation. This finding suggests that the hypersensitivity reaction peaks after the complete release of the eluted drugs and is probably related to the polymer²⁰.

There were some clinical trials investigating the efficacy and safety of second-generation DES with newer polymers and antiproliferative drugs. However, despite extensive and thorough studies, researchers could not determine which stent feature (antiproliferative agent or polymer type) was more causative of late stent-related adverse events since all of the studies compared stents with different antiproliferative drugs and/or different polymers.

To the best of our knowledge, this study is the first to compare the safety of stents with different polymers (durable versus biodegradable) but the same antiproliferative drug, sirolimus. As shown in our results, the use of a BP-SES has been demonstrated to be more efficacious and safer than that of a DP-SES. This indicates that the late failures associated with the CYPHER DP-SES were more likely to be caused by the DP than the sirolimus.

Despite our results showing superiority of BP-DES over DP-DES, it is uncertain whether a BP is safer than all DP because there are different kinds of DP than that used in CYPHER stents. The present study simply indicates that the specific DP used in the CYPHER stent is vasculotoxic. Actually, some clinical studies have shown other types of DP to be safe when compared to other BPs²¹⁻²⁴.

At present, SES are produced by a variety of manufacturers and are used in the treatment of coronary patients, though the

CYPHER DP-SES is no longer commercially available due to safety concerns. However, a clinical implication of the present study is that sirolimus is quite effective as an antiproliferative drug for use in DES, even though many kinds of antiproliferative drug are available. Therefore, recently developed SES adopting other drug-carrier technologies, whether DP or BP, should be investigated with the results of this study in mind.

Limitations

There are several limitations in this study. First, the present study was not a randomised study. Thus, the results may have been subject to bias, even though multiple potential variables were adjusted in the analyses. In particular, mean stent length, one of the significant factors affecting TLR, was significantly greater in the DP-DES group than in the BP-SES group. Second, the stent material and structure, other than the polymer, are markedly different in the two stent types tested. The CYPHER DP-SES has a closed cell design and is made of stainless steel, and the stent strut thickness is 140 µm thick, whereas the Orsiro BP-SES has an open cell design and is made of cobalt-chromium L-605, and the stent strut is thinner (60 or 80 µm). The coating thickness of the stent is 7 µm for the CYPHER stent and 3.5 or 7.5 µm for the Orsiro stent depending on the strut thickness. These structural differences may have influenced the study results. However, as was shown in the BMS era, when the strut was as thick as that in the DP-SES

used in this study, late failure was seldom seen^{25,26}. Moreover, it should be borne in mind that PSS and very late stent malapposition (**Figure 3**) were very rare after BMS implantation. Third, although the drug dose of both stents is 1.4 µg/mm², the drug elution from the two stents is different: the CYPHER releases 80% of the drug within 30 days of implantation while the Orsiro releases about 50% of the drug within 30 days. This difference in drug release may influence the inflammation of the vessel wall. Fourth, the separate enrolment periods for patients treated with DP-SES and BP-SES may have influenced the study results. For example, recent increases in the use of fractional flow reserve-based PCI could have affected the results.

Most of the technical advances have occurred in the field of stent technology, in dedicated devices for chronic occlusion and in antiplatelet agents as well as in breakthroughs for procedural success and rescue. We have shown no difference in the lesion complexity or in the proportion of chronic occlusions between the two groups. Stents were successfully implanted and the final TIMI flow was grade 3 in almost all cases. We do not believe that the potent antiplatelet agents affect our results because the BP-SES was superior without any newer-generation antiplatelet agents as shown.

Finally, the relatively low two-year clinical follow-up rate compared to those in other trials^{21,27} might have affected the results, especially those related to clinically driven TLR in the BP-SES group. Despite these limitations, this is the first study to compare different polymers in stents with the same antiproliferative drug, thus allowing a conclusion regarding the reason for the late failures associated with CYPHER stents.

Conclusions

In conclusion, the Orsiro BP-SES was superior to the CYPHER DP-SES with respect to the clinical outcomes at two years post PCI. Incidences of adverse clinical outcomes in the Orsiro BP-SES were significantly lower than those in the CYPHER DP-SES. What clinicians should learn from the so-called “CYPHER failure” is that the failure is mainly attributable to the use of an inappropriate DP, indicating the need for thorough investigation of stent polymers. Regardless, sirolimus is still a useful antiproliferative drug for coronary stents.

Impact on daily practice

Sirolimus is a potent antiproliferative drug which is still used for newer-generation drug-eluting coronary stents. Earlier CYPHER stent failure left some concerns that these newer-generation stents could adversely affect vascular wall and clinical outcomes. The present study has shown that sirolimus-eluting stents are quite safe and effective when they are embedded in another kind of polymer. It is expected that the currently used sirolimus-eluting stents will demonstrate markedly improved long-term outcomes whether the polymers are biodegradable or newly durable.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Selective use of drug-eluting stents in high-risk versus bare metal stents in low-risk patients according to predefined criteria confers similar four-year long-term clinical outcomes



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KEYWORDS

- bare metal stents
- clinical research
- drug-eluting stents

Abstract

Aims: The aim of the study was to evaluate the long-term outcomes following selective implantation of drug-eluting stents (DES) in patients at high risk of restenosis versus bare metal stents (BMS) in low-risk patients, according to predefined criteria.

Methods and results: Patients who underwent elective percutaneous coronary intervention (PCI) between May 2002 and April 2004 were enrolled in this retrospective, single-centre study. All patients received a BMS while undergoing PCI, unless they fulfilled at least two entry criteria that warranted DES usage. The study endpoints were major adverse cardiac events (MACE), comprising death, myocardial infarction, stent thrombosis (ST), and target vessel revascularisation (TVR), at four years between the DES and BMS groups. A total of 1,250 patients were enrolled in the study, among whom 1,095 (88%) received BMS and the rest received DES. At four years, there was no difference in the cumulative incidence of MACE: death (4.5% in DES vs. 5.8% in BMS, $p=0.531$), myocardial infarction (2.6% in DES vs. 3.1% in BMS, $p=0.722$), TVR (9.7% in DES vs. 7.9% in BMS, $p=0.461$), and ST (1.9% in DES vs. 0.8% in BMS, $p=0.183$). The event-free survival rate at four years was similar in the two groups (87.1% in DES vs. 86.1% in BMS; $p=0.741$).

Conclusions: In elective PCI, a strategy of selective use of DES in patients at high risk of restenosis based on predefined criteria confers the same favourable long-term clinical outcomes as BMS in low-risk patients.

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Abbreviations

| | |
|-------------|------------------------------------|
| BMS | bare metal stent(s) |
| DES | drug-eluting stent(s) |
| MACE | major adverse cardiac events |
| PCI | percutaneous coronary intervention |
| ST | stent thrombosis |
| TVR | target vessel revascularisation |

Introduction

Percutaneous coronary intervention (PCI) with implantation of stents has become the most commonly performed therapeutic procedure worldwide¹. In comparison to bare metal stents (BMS), the use of drug-eluting stents (DES) has been shown to be more effective in reducing the rate of restenosis². The overall benefit associated with the use of DES was largely due to a reduction in target lesion revascularisation, without effect on all-cause mortality. In the Norwegian Coronary Stent Trial, there were no significant long-term effects on the rates of death or spontaneous myocardial infarction between patients receiving contemporary DES and those receiving BMS³. In large registries such as Ontario and the Swedish database, the benefit with DES, compared to BMS, was most apparent in patients at risk of developing restenosis. These high-risk patients are identified by clinical and angiographic factors such as the presence of diabetes mellitus, small calibre target vessels, diffuse lesions, and the complexity of target lesions^{4,5}.

The majority of current-generation DES carry a risk of late and very late stent failure due to the persistence of the polymer. The duration of dual antiplatelet therapy is longer with DES, at least in part due to delayed neointimal coverage^{6,7}. In addition, DES come at a much higher cost (up to three to four times) compared to BMS, and the rapid growth of their use has raised important concerns about cost from both institutional and societal perspectives^{8,9}. It is against this background that we analysed our data retrospectively, comparing DES versus BMS.

Methods

STUDY DESIGN AND POPULATION

This is a retrospective, single-centre study from a tertiary care teaching hospital comparing the selective use of DES in patients at high risk of restenosis versus BMS in low-risk patients according to predefined criteria. In the initial period of coronary stenting, it was the institution's practice to select patients carefully based on predefined criteria and to employ a strategy for the targeted use of DES. We conducted a retrospective analysis of the first 1,250 patients from May 2002 in order to evaluate the long-term clinical outcomes of such a strategy. All patients in the two-year period between May 2002 and April 2004 received a BMS while undergoing elective PCI in our centre, unless they fulfilled at least two entry criteria which warranted DES usage. These criteria included the presence of diabetes mellitus, diffuse lesion as defined by a lesion length of more than 20 millimetres, small vessel (<3.0 mm), proximal lesion, restenosis following PCI, and ostial or bifurcation stenting. Patients who underwent an emergency PCI for acute coronary

syndrome and those who received hybrid stenting with BMS and DES were excluded. The study was approved by the National Ethics Committee and the Hospital Research Board.

DATA COLLECTION AND STUDY OUTCOMES

Baseline demographics, clinical characteristics, and procedural data were collected retrospectively from our institution's cardiac database. These patients had clinical follow-up for four years and outcomes were analysed. The study endpoints were the major adverse cardiac events (MACE) of death, myocardial infarction, stent thrombosis (ST), and target vessel revascularisation (TVR) at four years between the BMS and DES groups. ST was classified according to the Academic Research Consortium criteria. The clinical endpoints were reviewed and adjudicated by members of the study team.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS, Version 18 (SPSS Inc., Chicago, IL, USA). Patients' demographic and clinical data were summarised descriptively. Categorical and quantitative data are presented as frequency (percentage) and mean±standard deviation, respectively. The categorical variables were compared between those receiving BMS and DES using either the chi-square test or Fisher's exact test where applicable, while numerical variables were compared using either the two-sample t-test or the Mann-Whitney U test. The occurrence of the clinical outcomes such as death, myocardial infarction, TVR, and ST were compared using either the chi-square test or Fisher's exact test between the two groups. Multivariate analysis was performed with logistic regression models for the prediction of MACE. The known predictive factors such as diabetes mellitus, diffuse disease, ostial lesion, bifurcation lesion, American Heart Association type C lesion, location of lesion in the left main or left anterior descending artery, and stent diameter less than 3 mm were included in the multivariate model. This selection was based on the well-described association of these variables with MACE. All statistical tests were performed at a 5% level of significance and with 95% confidence intervals.

Results

Between May 2002 and April 2004, a total of 1,250 patients were enrolled in the study, among whom 1,095 (88%) received BMS and the rest received first-generation DES, which included the CYPHER® (Cordis, Cardinal Health, Milpitas, CA, USA) sirolimus-eluting stent and TAXUS® (Boston Scientific, Marlborough, MA, USA) paclitaxel-eluting stent. The baseline demographic and risk factor profiles are shown in **Table 1**. The mean age was 57 years in both groups and three fourths of the patients were male. There was no difference in the prevalence of hypertension, hyperlipidaemia, and family history of premature coronary artery disease between the two groups. Patients who received DES were more likely to be diabetic when compared to those in the BMS group (44.5% in the DES group vs. 36.3% in the BMS group, $p=0.049$).

The lesion and stent characteristics of the study population are shown in **Table 2** and **Table 3**. Patients who received DES

Table 1. Baseline demographic data.

| | BMS | DES | p-value |
|---------------------------------|-------------|-------------|---------|
| Number of patients | 1,095 | 155 | |
| Age (years) | 57.4±11.0 | 57.4±10.2 | 0.932 |
| Males | 835 (76.3%) | 117 (75.5%) | 0.813 |
| Diabetes | 397 (36.3%) | 69 (44.5%) | 0.049 |
| Hypertension | 670 (61.2%) | 93 (60.0%) | 0.777 |
| Hyperlipidaemia | 775 (70.8%) | 113 (72.9%) | 0.585 |
| Family history of premature CAD | 27 (2.5%) | 4 (2.6%) | 0.931 |
| Smoker | Current | 374 (34.2%) | 0.009 |
| | Ex | 219 (20.0%) | |
| | Non | 502 (45.8%) | |

BMS: bare metal stents; CAD: coronary artery disease; DES: drug-eluting stents

Table 2. Lesion characteristics.

| | BMS (n=1,095) | DES (n=155) | p-value |
|-------------------------------------|---------------|-------------|---------|
| Diffuse | 243 (22.2%) | 62 (40.1%) | <0.001 |
| AHA type C | 246 (22.5%) | 66 (42.7%) | <0.001 |
| Ostial | 42 (3.9%) | 10 (6.4%) | 0.063 |
| Eccentric | 763 (69.7%) | 114 (73.8%) | 0.173 |
| Calcification | 105 (9.6%) | 18 (11.6%) | 0.297 |
| Angulation | 128 (11.7%) | 20 (13.1%) | 0.507 |
| Bifurcation | 188 (17.2%) | 29 (18.4%) | 0.655 |
| Left main and LAD lesion | 488 (44.6%) | 90 (58.1%) | <0.001 |
| Mean diameter stenosis pre-PCI (%) | 84.6±10.9 | 82.9±10.0 | 0.02 |
| Mean diameter stenosis post-PCI (%) | 9.62±7.96 | 8.98±5.96 | 0.213 |
| Multivessel PCI | 194 (17.8%) | 35 (22.6%) | 0.154 |

AHA: American Heart Association; BMS: bare metal stents; DES: drug-eluting stents; LAD: left anterior descending artery; PCI: percutaneous coronary intervention

Table 3. Stent characteristics.

| | BMS | DES | p-value |
|-----------------------------------|----------|----------|---------|
| Mean number of stents per patient | 1.1±0.4 | 1.2±0.5 | <0.001 |
| Mean number of stents per lesion | 1.1±0.5 | 1.3±0.6 | <0.001 |
| Mean stent diameter (mm) | 3.2±1.0 | 2.8±0.3 | <0.001 |
| Mean stent length (mm) | 18.7±6.6 | 21.8±6.6 | <0.001 |

BMS: bare metal stents; DES: drug-eluting stents

had a higher prevalence of diffuse lesions and American Heart Association type C lesions. Patients with a lesion in the left main and left anterior descending artery were more likely to receive a DES. There was no difference in the incidence of multivessel PCI between the two groups (22.6% in the DES group vs. 17.8% in the BMS group, $p=0.154$). There were more stents implanted per patient and per lesion in the DES group compared with the BMS group (1.2±0.5 and 1.3±0.6 in the DES group vs. 1.1±0.4 and 1.1±0.5 in the BMS group, $p<0.001$). The DES used were significantly longer in length and smaller in diameter than the BMS

(21.8±6.6 mm and 2.8±0.3 mm in the DES group vs. 18.7±6.6 mm and 3.2±1.0 mm in the BMS group, $p<0.001$).

The incidence of MACE at four years was similar between the two groups (**Table 4**). Cumulative death rates at four years were 5.8% in the BMS group and 4.5% in the DES group ($p=0.531$). Cumulative rates of myocardial infarction at four years were 3.1% in the BMS group and 2.6% in the DES group ($p=0.722$). The cumulative TVR rates at four years were 7.9% in the BMS group and 9.7% in the DES group ($p=0.461$). The event-free rates at four years between the two groups were similar (86.1% in the BMS group and 87.1% in the DES group, $p=0.741$). There was no significant difference between the two groups even after adjusting for significant covariates (**Table 5**). Diabetes mellitus was a significant predictor of death and TVR, while the presence of diffuse disease was a predictor of death and myocardial infarction.

Table 4. Major adverse cardiac events at four years.

| MACE | BMS n=1,095 | DES n=155 | p-value |
|---------------------|-------------|-----------|---------|
| Death | 64 (5.8%) | 7 (4.5%) | 0.531 |
| MI | 34 (3.1%) | 4 (2.6%) | 0.722 |
| TVR | 87 (7.9%) | 15 (9.7%) | 0.461 |
| Stent thrombosis | 9 (0.8%) | 3 (1.9%) | 0.183 |
| Event-free rate (%) | 86.1 | 87.1 | 0.741 |

BMS: bare metal stents; DES: drug-eluting stents; MACE: major adverse cardiac events; MI: myocardial infarction; TVR: target vessel revascularisation

There was no difference in the ST rate at four years (0.8% in the BMS group and 1.9% in the DES group, $p=0.183$). On further analysis of this subgroup of patients, nine patients in the BMS group and three patients in the DES group developed ST. In the BMS group, five were classified as definite ST and four were classified as probable ST. In the DES group, all three patients had definite ST. For patients with definite ST, three in the BMS group were classified as early (0 to 30 days) and two as late (30 days to one year). In the DES group, two were classified as early and one as late. There were no cases of very late ST in this study (**Table 6**).

Discussion

This is a retrospective, single-centre study comparing the strategy of the selective use of DES based on high-risk characteristics that increase the likelihood of developing in-stent restenosis versus BMS in patients undergoing elective PCI. Based on predefined criteria, we did not find a significant difference between DES and BMS in the rates of death, myocardial infarction, TVR, or ST during four years of follow-up. The event-free rates at four years were similar between the two groups.

Since their introduction, DES have substantially changed the practice of interventional cardiology. Various studies have consistently demonstrated a significant reduction in restenosis with the use of DES when compared with BMS¹⁰. Although DES are used in the majority of PCI cases, there is debate as to whether the devices are too often being used inappropriately¹¹. In addition, it

Table 5. Multivariate analysis for the occurrence of major adverse cardiac events of death, myocardial infarction, target vessel revascularisation and stent thrombosis.

| | Death | | MI | | TVR | | ST | |
|--------------------------|----------------------|---------|----------------------|---------|----------------------|---------|----------------------|---------|
| | Adjusted OR [95% CI] | p-value | Adjusted OR [95% CI] | p-value | Adjusted OR [95% CI] | p-value | Adjusted OR [95% CI] | p-value |
| DES vs. BMS | 0.588 (0.254-1.363) | 0.216 | 0.537 (0.178-1.622) | 0.27 | 1.211 (0.658-2.229) | 0.539 | 1.752 (0.43-7.136) | 0.434 |
| Diabetes mellitus | 2.088 (1.276-3.415) | 0.003* | 1.45 (0.751-2.8) | 0.268 | 2.091 (1.379-3.17) | 0.001* | 1.036 (0.323-3.326) | 0.952 |
| Diffuse disease | 2.476 (1.367-4.483) | 0.003* | 2.347 (1.075-5.123) | 0.032* | 1.286 (0.747-2.215) | 0.364 | 2.065 (0.502-8.501) | 0.315 |
| Ostial lesion | 1.768 (0.603-5.184) | 0.299 | 0.731 (0.097-5.537) | 0.762 | 0.494 (0.117-2.094) | 0.339 | — | — |
| Bifurcation lesion | 0.925 (0.477-1.791) | 0.817 | 0.827 (0.333-2.054) | 0.683 | 0.862 (0.479-1.55) | 0.619 | 0.33 (0.042-2.615) | 0.294 |
| Stent diameter <3 mm | 1.152 (0.658-2.018) | 0.621 | 1.972 (0.983-3.956) | 0.056 | 0.784 (0.472-1.303) | 0.349 | 2.901 (0.875-9.623) | 0.082 |
| AHA type C lesion | 0.835 (0.437-1.595) | 0.585 | 1.111 (0.49-2.517) | 0.801 | 1.115 (0.642-1.936) | 0.699 | 0.552 (0.114-2.679) | 0.461 |
| Left main and LAD lesion | 1.158 (0.7-1.915) | 0.568 | 1.077 (0.55-2.109) | 0.829 | 1.006 (0.656-1.541) | 0.979 | 1.521 (0.468-4.945) | 0.486 |

*Statistically significant. AHA: American Heart Association; BMS: bare metal stents; DES: drug-eluting stents; LAD: left anterior descending artery; MI: myocardial infarction; ST: stent thrombosis; TVR: target vessel revascularisation

Table 6. Stent thrombosis rates at four years.

| Stent thrombosis | BMS – 9 out of 1,095 patients | DES – 3 out of 155 patients |
|------------------|-------------------------------|-----------------------------|
| Definite | 5 | 3 |
| Early | 3 | 2 |
| Late | 2 | 1 |
| Probable | 4 | 0 |

BMS: bare metal stents; DES: drug-eluting stents

has been demonstrated that unrestricted use of DES is less cost-effective and unlikely to reflect effective utilisation of available healthcare resources^{9,12}. Hence, the use of DES could be restricted to patients in certain high-risk groups.

In the Ontario registry, the benefit of DES in reducing the need for TVR was limited to those patients with two or three risk factors for restenosis (presence of diabetes mellitus, vessel diameter of <3 mm, and lesions of ≥ 20 mm in length), but not among low-risk patients⁴. Similarly, in the Swedish Coronary Angiography and Angioplasty Registry, the benefit of DES compared with BMS was most apparent when any one of these high-risk features was present⁵. In our institution, it was a routine clinical practice to risk-stratify patients into the likelihood of developing restenosis following PCI. Any patient fulfilling two or more of the predefined risk factors was considered for a DES. In our study, the patients in the two groups were well matched in their baseline demographics, except for a higher prevalence of diabetes mellitus in the DES group, reflecting our predefined clinical criteria. Patients who received DES also had a higher prevalence of diffuse lesions and American Heart Association type C lesions. The DES implanted were significantly narrower in diameter and longer in length than the BMS, which suggests that the DES were being placed in more diffuse lesions in smaller calibre vessels. This reflects the criteria of reserving DES for complex coronary lesions. The BASKET-PROVE study found no significant difference among patients requiring stenting of large coronary arteries in the DES and BMS groups regarding the rates of death or myocardial infarction at two years¹³. Similar findings were observed in the Norwegian Coronary Stent Trial at

six-year follow-up, comparing contemporary DES with BMS³. In our study, a strategy of the selective use of DES reserved for high-risk patients for restenosis based on predefined criteria conferred the same favourable long-term clinical outcomes as BMS for low-risk patients. Thus, an identification of established predictors of restenosis is important during PCI and should guide the choice of stent selection. Interestingly, our data did not suggest a higher incidence of TVR in the BMS group, nor were there higher rates of ST in the DES group as observed in some analyses¹⁴⁻¹⁷.

Our study suggests that a DES is not required for all patients undergoing elective PCI. In fact, BMS should continue to have a place in this era of PCI, with reasonable safety and efficacy. This is one of the few studies to address the use of DES compared with BMS in South-East Asia, with long-term clinical outcomes. This may be especially important in the Asian context, in which selective utilisation of stents based on predefined criteria may prove to be safe, efficacious, and lead to significant cost savings.

Study limitations

This is a retrospective study with inherent limitations. The sample size for this retrospective study was not adequately powered. This is one of the major limitations of the study. Our findings are based on a single-centre experience and may not be applicable to other institutions with different study populations. The study population consisted of only stable patients who underwent elective PCI. The study compared BMS with the first-generation DES, and not the current generation of stents, which may have influenced the outcome. Stent designs have been refined, resulting in a significant improvement in clinical outcomes. We did not perform an analysis of cost-effectiveness comparing DES versus BMS. As it was a non-randomised study, there may still have been unmeasured confounding factors that contributed to our findings. It was not possible to ascertain retrospectively the compliance and duration of dual antiplatelet therapy in each individual patient.

Conclusions

In the setting of elective PCI, our strategy of the selective use of DES reserved only for patients at high risk of restenosis based on

predefined criteria confers the same favourable long-term clinical outcomes as BMS for low-risk patients. Such a strategy may prove to be cost-effective in most healthcare systems.

Impact on daily practice

DES are effective in reducing restenosis when compared to BMS. Limited data are available on long-term outcomes following selective implantation of DES in patients at high risk of restenosis versus BMS in low-risk patients. In this retrospective study, the selective use of DES reserved only for patients at high risk of restenosis based on predefined criteria conferred the same favourable long-term clinical outcomes as BMS for low-risk patients. This strategy may lead to significant cost savings and provide a platform for evaluation of the current generation of DES against BMS.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Hospital outcomes in STEMI patients after the introduction of a regional STEMI network in the metropolitan area of a developing country



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KEYWORDS

- miscellaneous
- plaque rupture
- STEMI

Abstract

Aims: Data on the long-term outcomes of STEMI patients treated via a network in Asian countries are very limited. We aimed to evaluate the characteristics and outcomes of STEMI patients at two different periods, before and five years after the establishment of a regional STEMI network in Jakarta, Indonesia.

Methods and results: Out of 6,291 patients with STEMI admitted to hospital between January 2008 to January 2016, we compared the characteristics and outcomes of STEMI patients from two different periods, January 2008 to July 2009 (before instalment of the STEMI network, N=624), and from January 2015 to January 2016 (five years after the start of the network, N=1,052). The PCI hospital is an academic tertiary care cardiac hospital and initiated the regional STEMI network in 2010. Logistic regression was used to determine the adjusted association between treatment in the latter period and mortality. Compared with data from 2008/2009, in the 2015/2016 period, more primary PCI procedures were performed (N=589 [56%] vs. N=176 [28%], $p<0.001$), fewer patients did not receive reperfusion therapy (37% vs. 59%, $p<0.001$), and median door-to-device (DTD) times were shorter (82 vs. 94 minutes, $p<0.001$). Overall in-hospital mortality decreased from 9.6% to 7.1% (adjusted odds ratio 0.72, 95% CI: 0.50 to 1.03, $p=0.07$).

Conclusions: Half a decade after the implementation of the STEMI network in Jakarta, Indonesia, the result is better and faster care for patients with STEMI and this has been associated with lower in-hospital mortality.

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Abbreviations

| | |
|--------------|--|
| AHA | American Heart Association |
| AMI | acute myocardial infarction |
| CI | confidence interval |
| DTD | door-to-device |
| ED | emergency department |
| ECG | electrocardiography |
| ESC | European Society of Cardiology |
| GP | general practitioners |
| IU | international unit |
| JAC | Jakarta Acute Coronary Syndrome |
| MI | myocardial infarction |
| OR | odds ratio |
| PCI | percutaneous coronary intervention |
| STEMI | ST-segment elevation myocardial infarction |

Introduction

Both the European Society of Cardiology (ESC)¹ and American Heart Association (AHA)² guidelines on ST-elevation myocardial infarction (STEMI) emphasise the importance of STEMI networks in order to facilitate a rapid acute reperfusion therapy. Several established STEMI networks have consistently demonstrated that rapid transfer to a PCI centre is effective in reducing the mortality of STEMI patients in the region³⁻⁵. In contrast with the STEMI networks in developed countries, there are few data reporting the benefit of setting up STEMI networks in developing countries. The Jakarta Cardiovascular Care Unit Network System was set up in 2010 in Jakarta, Indonesia, in order to optimise the care of patients with acute myocardial infarction (AMI) in the region^{6,7}. We compared the characteristics and outcomes of patients with STEMI seen during two time periods, before (2008-2009) and five years after establishment of the regional STEMI network (2015-2016) in a primary percutaneous coronary intervention (PCI) centre that implemented a regional STEMI network in 2010.

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Methods

PATIENT POPULATION

A retrospective analysis of the Jakarta Acute Coronary Syndrome (JAC) registry was performed. Data consisted of all STEMI patients admitted to the emergency department of an academic tertiary care cardiac hospital (National Cardiovascular Center Harapan Kita) between January 2008 and January 2016. The hospital provides a 24/7 primary PCI service and it is the largest tertiary academic cardiovascular hospital across the nation, located in the capital city (Jakarta). In 2015, the hospital performed approximately 2,300 PCIs.

The STEMI network (Jakarta Cardiovascular Care Unit Network System) is the first regional STEMI system in the country and is coordinated by the STEMI call centre at the emergency department (ED) of the PCI hospital. The network was established as a multiple hubs system involving many PCI centres in the region and pioneered the development of the national emergency call centre. An ECG transmission system was adopted in

the network through several methods of transmission (facsimile, email, WhatsApp or web-based) along with wide application of the pre-hospital triage protocols^{8,9}.

The JAC registry was introduced and has been coordinated by the ED of the hospital since 2007. It is used as the main source of data for measuring the performance of the STEMI network in the region, as well as in the PCI hospitals. All consecutive patients admitted to the ED with an acute coronary syndrome (ACS) were recorded in the database of the registry. Data consist of demographic, clinical characteristics and acute care of the patients. The organisation of the network and registry was created in close collaboration with the local government of Jakarta and the Ministry of Health, Republic of Indonesia.

STUDY SAMPLE

Out of 86,489 patients admitted to the ED of the hospital between January 2008 and January 2016, 6,291 were STEMI patients. The number of STEMI patients admitted between January 2008 and July 2009 was 624 and 1,052 for the period between January 2015 and January 2016 (**Figure 1**). We compared the characteristics and outcomes of STEMI patients between the two periods.

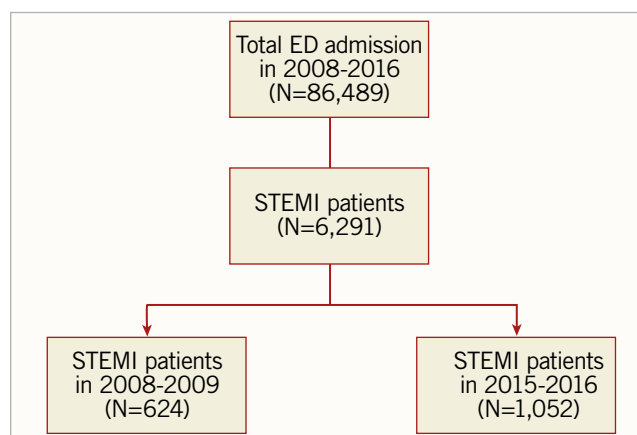


Figure 1. Study flow chart. ED: emergency department; STEMI: ST-elevation myocardial infarction

MANAGEMENT PROTOCOL

The treatment protocol for patients with STEMI in the hospital is in accordance with the ESC guidelines on STEMI². Primary PCI is recommended as the first choice of acute reperfusion therapy. A standardised pre-hospital triage form and check list for possible fibrinolytic therapy were used in the pre-PCI hospital as part of the STEMI network programme⁷.

Patients with STEMI who underwent primary PCI were pre-treated with 160-320 mg acetylsalicylic acid and 600 mg clopidogrel or ticagrelor 180 mg orally before primary PCI, followed by daily administration of 75 mg clopidogrel or 90 mg of ticagrelor twice daily for six to 12 months and 80-100 mg acetylsalicylic acid indefinitely. Fibrinolytic therapy (streptokinase or alteplase) was given either in the ED of the PCI hospital or in the referring centre. Not

all health centres have the ability to perform fibrinolytic therapy. Unfractionated heparin was administered intravenously in the catheterisation laboratory (100 IU/kg) for all patients with STEMI who underwent primary PCI. The use of a glycoprotein IIb/IIIa inhibitor was at the operator's discretion. PCI of the culprit lesion only was applied in the majority of the primary PCIs.

DATA COLLECTION

Demographic and clinical characteristic data were collected from the JAC registry electronic database. The quality of the registry data is maintained by a monthly evaluation of the data set by the primary investigator of the JAC registry (SD).

STUDY OUTCOME AND DEFINITIONS

The primary outcome of the study was the characteristics of STEMI patients, by means of the proportion of patients receiving acute reperfusion therapy (primary PCI or fibrinolytic therapy) between the two periods. Other outcomes were numbers of patients who did not receive reperfusion therapy, door-to-device time and in-hospital mortality.

The period of 2008-2009 was defined as the period before the STEMI network was introduced, while the period 2015-2016 was categorised as five years after STEMI network introduction.

Diagnosis of STEMI was made based on the presence of ischaemic symptoms and persistent (>20 minutes) ST-segment elevation in at least two contiguous leads, a new left bundle branch block, or a true posterior myocardial infarction confirmed by posterior leads². Non-reperused patients were defined as patients who did not receive any acute reperfusion therapy (either primary PCI or fibrinolytic therapy).

The JAC registry was approved by the local institutional review board committee.

STATISTICAL ANALYSIS

We grouped patients into two groups based on time of admission (2008-2009 and 2015-2016). Clinical characteristics, in-hospital mortality and time metrics data were compared between the two groups. Normally distributed continuous variables were expressed as mean±standard deviation or median and quartile range for skewed distribution. Differences between continuous variables were compared with the Student's t-test or the Mann-Whitney U test. Categorical variables were expressed as percentages, and differences between groups were compared with the chi-square test or Fisher's exact test as appropriate. Logistic regression analyses were used to examine the association between the time period and incidence of all-cause mortality during hospitalisation. Several baseline characteristics that are listed in **Table 1** (symptom onset, time of admission, gender, location of MI) were considered as potential confounders for the in-hospital mortality and were included in the analysis.

All statistical tests were two-tailed and a p-value <0.05 was considered significant. Statistical analyses were performed with SPSS for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Characteristics of STEMI patients between the two periods (N=1,676).

| | Year 2008/2009 (N=624) | Year 2015/2016 (N=1,052) | p-value |
|---|------------------------------|--------------------------------|---------|
| Age, years | 55.59±10.36 | 55.71±10.23 | 0.76 |
| Age >65 years, n (%) | 104 (16.6%) | 169 (16%) | 0.74 |
| Male, n (%) | 532 (85%) | 895 (85%) | 0.92 |
| Off-hours admission, n (%) | 466 (74%) | 820 (78%) | 0.12 |
| Anterior MI, n (%) | 377 (60%) | 579 (55%) | 0.03 |
| Symptom onset >12 hrs, n (%) | 232 (37%) | 306 (29%) | <0.01 |
| CAD risk factors, n (%) | | | |
| Smoker | 414 (66%) | 660 (63%) | 0.13 |
| Hypertension | 334 (53%) | 560 (53%) | 0.90 |
| Diabetes mellitus | 190 (30%) | 282 (27%) | 0.10 |
| Dyslipidaemia | 297 (47%) | 315 (30%) | <0.001 |
| Family history | 162 (26%) | 172 (16%) | <0.001 |
| Source of referral, n (%) | | | |
| Inter-hospital referral | 343 (55%) | 715 (68%) | <0.001 |
| Killip class 2 to 4, n (%) | 204 (32%) | 317 (30%) | 0.27 |
| TIMI risk score >4, n (%) | 238 (38%) | 436 (41%) | 0.18 |
| Dual antiplatelet therapy within 24 hrs, n (%) | | | |
| Salicylic acid | 589 (94%) | 1,038 (98%) | <0.01 |
| Clopidogrel | 594 (95%) | 1,014 (96%) | 0.23 |
| Acute reperfusion therapy, n (%) | | | |
| Primary PCI | 176 (28%) | 589 (56%) | <0.001 |
| Fibrinolytic therapy | 75 (12%) | 69 (6.5%) | <0.001 |
| Non-reperfusion therapy, n (%) | 373 (59%) | 389 (37%) | <0.001 |
| Time metrics evaluation, minutes | | | |
| Door-to-device time | 94 (72-122) | 82 (67-103) | <0.001 |
| In-hospital mortality, n (%) | 60 (9.6%) | 75 (7.1%) | 0.07 |
| CAD: coronary artery disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction | | | |

Results

A total of 1,676 patients with STEMI were included in the final analysis, consisting of 624 patients admitted during 2008-2009 and 1,052 patients admitted during 2015-2016.

Compared with the recent year (2015-2016), patients who were admitted during 2008-2009 had more anterior MI, dyslipidaemia and family history of coronary artery disease. Late onset STEMI patients (symptom onset >12 hrs) were found less frequently in the recent year (37% vs. 29%). The majority of STEMI patients were admitted through a transfer process (inter-hospital transfer) (**Table 1**). Most of the patients received salicylic acid and clopidogrel within the first 24 hrs after admission (**Table 1**).

Compared with data from 2008-2009, STEMI patients who were admitted in 2015-2016 had more primary PCI procedures

(N=588 [56%] vs. N=176 [28%], $p<0.001$) and there were fewer patients who did not receive reperfusion therapy (37% vs. 59%, $p<0.001$). Use of fibrinolytic therapy was lower during the recent time period (6.5% vs. 12%, $p<0.001$) (**Table 1, Figure 2**).

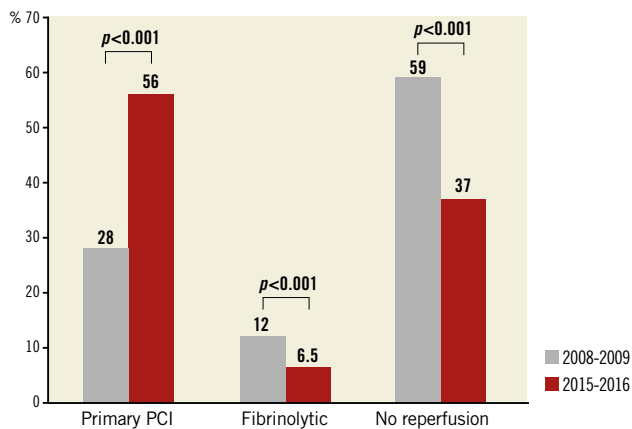


Figure 2. The characteristics of acute reperfusion therapy between the two periods. PCI: percutaneous coronary intervention

The median door-to-device (DTD) time was significantly shorter during the recent time period (82 vs. 94 minutes, $p<0.001$) (**Table 1**).

The overall in-hospital mortality of STEMI patients was lower in the recent year (7.1% vs. 9.6%; unadjusted odds ratio [OR] 0.72, 95% confidence interval [CI]: 0.50 to 1.02, $p=0.07$) (**Table 2, Figure 3**). After adjustment of several variables, the OR was 0.72, 95% CI: 0.50 to 1.03, $p=0.07$ (**Table 3**).

Table 2. Bivariate analysis of in-hospital mortality.

| | Odds ratio | 95% confidence interval | p-value |
|----------------|------------|-------------------------|---------|
| Year 2015/2016 | 0.72 | 0.50-1.02 | 0.07 |

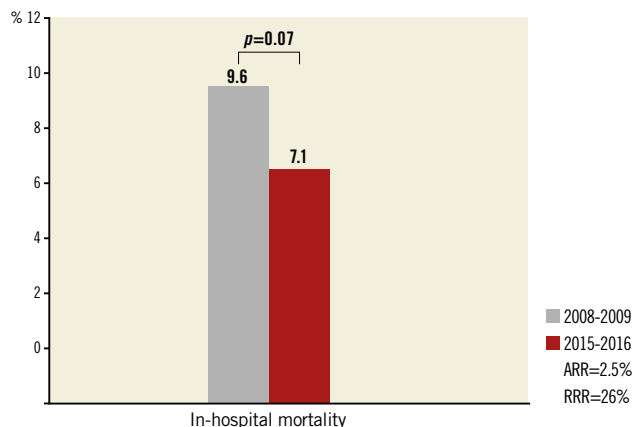


Figure 3. In-hospital mortality. ARR: absolute risk reduction; RRR: relative risk reduction

Table 3. Multivariate analysis of in-hospital mortality of STEMI patients.

| | Odds ratio | 95% confidence interval | p-value |
|-----------------------|------------|-------------------------|---------|
| Year 2015/2016 | 0.72 | 0.50-1.03 | 0.07 |
| Symptom onset >12 hrs | 1.08 | 0.74-1.58 | 0.66 |
| Off-hours admission | 1.42 | 0.90-2.24 | 0.12 |
| Female | 1.63 | 1.05-2.51 | 0.02 |
| Anterior MI | 1.15 | 0.80-1.66 | 0.44 |

Discussion

This study shows that, five years after the introduction of a STEMI network, more patients underwent primary PCI, fewer patients did not get reperfusion therapy, and DTD times were shorter, resulting in a numerically lower in-hospital mortality compared with the period before initiation of the STEMI network.

The benefits of regional STEMI networks have been described in many developed countries³⁻⁵. In Jakarta, Indonesia, the STEMI network was initiated in 2010 with the goal of offering reperfusion therapy to all STEMI patients in the metropolitan area⁶⁻⁹. This study suggests that it took several years to obtain a significant improvement in the processes of care for STEMI within the network. Furthermore, the results of the present study indicate that there was a shift in choice of reperfusion therapy from 2008 to 2015, whereby primary PCI has markedly increased and the use of fibrinolysis therapy has declined (**Figure 2**).

It was also observed that the proportion of late STEMI presenters (symptom onset >12 hrs) has dropped significantly (29% vs. 37%, $p<0.01$). These results suggest that the pre-hospital time delay has improved recently. The awareness of the population of the importance of early treatment might have improved since more patients were coming to a health centre to seek help early after onset of symptoms. In addition, better knowledge of the benefits of reperfusion therapy by the primary physicians (mostly general practitioners) has probably played a significant role as well, as suggested by the higher numbers of STEMI patients transferred to the PCI hospital.

In spite of the progress made over recent years, the Jakarta STEMI network is still facing many serious challenges. City traffic during day time often results in huge delays, many PCI centres in Jakarta do not provide a 24/7 primary PCI service and the number of catheterisation labs and interventional cardiologists is low when compared with Western countries.

In order to select the best reperfusion strategy for a particular patient, collaboration among primary physicians, the emergency ambulance service, the STEMI call centre and the interventional cardiologists all working with a commonly agreed protocol is needed. When timely primary PCI is not possible, e.g., because the ambulance is stuck in a traffic jam, a pharmaco-invasive strategy as studied in the STREAM trial^{10,11} and in many registries may need to be developed in the near future.

TIME DELAYS IN THE PCI HOSPITAL

It is often difficult to achieve a DTD time <90 minutes in all primary PCI cases, as recommended by both the ESC and AHA guidelines^{12,13}. The DTD time in our hospital has improved in recent years (median 94 vs. median 82 minutes, $p<0.001$). This means that the flow of STEMI patients in the hospital has improved starting from admission to the ED and transferring the patient to the catheterisation laboratory. The improvement is due to the centralisation of all administration processes in the ED, an increase in the number of interventional cardiologists in the hospital, and the presence of on-site cardiologists and nurses in the catheterisation laboratory 24/7. Similar to the USA¹⁴, the key indicator used by the Ministry of Health Republic of Indonesia to evaluate the performance of our hospital as the national cardiovascular centre is that a DTD time ≤ 90 minutes should be achieved in more than 80% of primary PCI. However, delays in reperfusion therapy are more often due to sub-optimal pre-hospital care¹⁵. Therefore, improving STEMI care in the referring hospitals is critically important. This should include informing and training of GPs and nurses in the use of a common protocol. This training programme has been carried out routinely in our ED and was initiated in close collaboration with the local government.

IN-HOSPITAL MORTALITY

The in-hospital mortality of patients with STEMI has been lower in recent years (7.1% vs. 9.6%, $p=0.07$) (**Figure 3**). This absolute difference was borderline significant and corresponds with a 26% relative reduction of in-hospital mortality since the initiation of the network. After adjustment for several clinical variables, the odds ratio remained unchanged (OR 0.72; $p=0.07$). The mortality reduction achieved in recent years is the result of more patients getting reperfusion therapy, higher numbers of primary PCI and shorter DTD time.

In order to make further progress, education of GPs and nurses who are working in the referring centres focusing on all aspects of pre-PCI care is critically important.

The pre-hospital triage form should also be used in the ambulance setting along with improvement of the ambulance navigation system. PCI centre performance can be improved by sending patients directly to the catheterisation laboratory (bypassing the ED). Furthermore, a public promotion campaign to encourage the population to dial the emergency medical service number (1-1-9) in case of chest pain may be helpful as well. A public campaign has been associated with an improved system of care of AMI¹⁶.

Finally, the JAC registry (www.jacregistry.pjnhk.go.id) which is currently the main source of data to evaluate the performance of the STEMI network in the region should be used and updated on a regular basis.

Study limitations

We have limited data on the details of the fibrinolytic therapy that was given in the pre-PCI centres, or the number of patients with a pharmaco-invasive strategy. Furthermore, the results of the present analysis cannot be generalised to other hospitals in the region

due to differences in the numbers of catheterisation laboratories and those that do not provide a 24/7 primary PCI service.

Conclusions

Half a decade after the implementation of the STEMI network in Jakarta, Indonesia, the result is better and faster care of patients with STEMI and this has been associated with lower in-hospital mortality.

Impact on daily practice

The results of this study will increase the awareness of treating patients with STEMI in the region and may encourage other developing countries in Asia to carry out routine performance measures of their STEMI networks in order to give insights into improving patient care.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Retrograde algorithm for chronic total occlusion from the Asia Pacific Chronic Total Occlusion club



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KEYWORDS

- calcified stenosis
- chronic coronary total occlusion
- stable angina

Abstract

Retrograde CTO PCI is an effective method to improve the success rate of CTO PCI. Despite several comprehensive and detailed descriptive papers on the retrograde techniques, retrograde CTO PCI remains difficult for many interventionists. We, the Asia Pacific CTO club, propose a new retrograde CTO PCI algorithm, which focuses on three specific problems in the retrograde approach. First, how to overcome the tough proximal cap. Then, how to cross the collateral channels safely and efficiently. Finally, how to cross the CTO and, in particular, the problems of reverse CART. We explain our new philosophy of contemporary reverse CART. We hope that this algorithm will provide the tools for operators to overcome the difficulties of retrograde CTO PCI and that it will become a platform for discussion, training, and proctoring for the retrograde approach.

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Abbreviations

| | |
|--------------|--|
| APCTO | Asia Pacific Chronic Total Occlusion club |
| BAM | balloon-assisted microdissection |
| BASE | balloon-assisted subintimal entry |
| CART | controlled antegrade and retrograde tracking |
| CTO | chronic total occlusion |
| EBW | end balloon wiring |
| FFR | fractional flow reserve |
| IVUS | intravascular ultrasound |
| LAO | left anterior oblique |
| PCI | percutaneous coronary intervention |
| PDA | posterior descending artery |
| RAO | right anterior oblique |

Introduction

The retrograde approach to chronic total occlusion (CTO) percutaneous coronary intervention (PCI) was popularised by Japanese operators in 2006¹. The impressive success rates achieved by retrograde CTO PCI, demonstrated in many live case conferences, have led to its worldwide adoption. CTO lesions occur in 10%-20% of cases²⁻⁴; furthermore, retrograde CTO PCI accounts for 25%-50% of CTO PCI cases⁵. Therefore, retrograde procedures are a substantial part of interventional cardiology work. However, for many interventionists, the retrograde techniques remain inaccessible due to the technical challenges of channel crossing and reverse CART, the inherent traps that have potential to lead to horrific complications⁶, and the need to learn and understand the philosophy and concepts of retrograde CTO PCI. The landmark work of Wu et al⁷ provided the first detailed description of the retrograde techniques. Joyal et al⁸ and Brilakis et al⁹ have given the most comprehensive step-by-step description of the retrograde approach to date. However, the techniques, equipment and, more importantly, the concepts of retrograde CTO PCI have changed considerably since 2012. We, the Asia Pacific Chronic Total Occlusion (APCTO) club, propose a new algorithm for retrograde CTO PCI (**Figure 1**). This algorithm builds upon the work of Wu⁷, Joyal⁸, and Brilakis⁹ to provide an up-to-date algorithm that focuses on the concepts of retrograde CTO PCI. Unlike the previous work, this is not a detailed step-by-step teaching method for retrograde techniques but rather an algorithm to help interventionists overcome problems encountered in retrograde CTO PCI. There is substantial focus on channel crossing and reverse CART, the two major hurdles to retrograde CTO PCI. It is hoped that this algorithm will serve as the basis for future retrograde CTO PCI proctoring and training.

The APCTO club recommends the use of the JCTO score cut-off of 2¹⁰ to determine whether a CTO should be undertaken under the guidance of a proctor. While every CTO patient should undergo evaluation to determine the clinical indication for CTO PCI, the threshold for engaging in retrograde CTO PCI should be even higher. A careful balance between the risks and benefits of CTO PCI, acknowledging the higher risks of the retrograde approach, should be made. Only the symptomatic patient with a large territory of proven viable ischaemic territory should undergo retrograde CTO PCI.

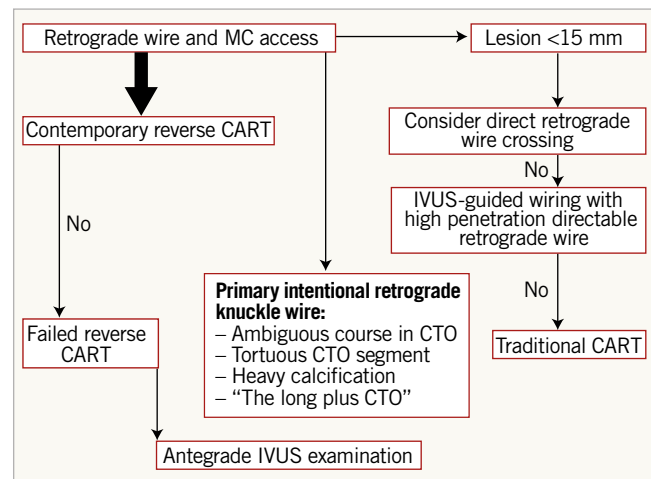


Figure 1. Asia Pacific Chronic Total Occlusion (APCTO) club algorithm for crossing a CTO lesion via the retrograde approach.

PROXIMAL CAP

ANTEGRADE PREPARATION FIRST PHILOSOPHY

The APCTO club promotes a strong “antegrade preparation first” philosophy¹¹, even in planned retrograde cases. “Antegrade preparation first” reduces the time that the retrograde system is engaged in the donor artery, CTO territory ischaemic time, and donor artery risks. It is especially important to carry out antegrade preparation when the proximal cap is tough or ambiguous, as the retrograde gear may have to be engaged for an extended period of time in the “retrograde first approach” if the operator struggles to obtain proximal cap puncture. It also encourages going directly to reverse controlled antegrade retrograde tracking (CART), which is the most efficient way to attain retrograde wire crossing. Finally, the “antegrade preparation first” philosophy removes the risks of single retrograde wire crossing in ostial lesions. However, there are some circumstances where antegrade preparation may be unnecessary, e.g., in short CTO where single retrograde wire crossing is planned or in a previously attempted case where the antegrade route is clear and there is no proximal cap problem to overcome. We also recognise that intravascular ultrasound (IVUS)-guided proximal cap puncture is a difficult technique to master, requiring experience as well as the availability of IVUS. For operators without the experience or availability, the retrograde first approach with knuckle wiring from the retrograde side to remove proximal cap ambiguity is a valid alternative.

AMBIGUOUS PROXIMAL CAP

Ambiguity of the proximal cap should be overcome with IVUS guidance. The IVUS catheter should be placed in the branch nearest to the proximal cap and withdrawn to look for the CTO site. Sometimes calcium overlaps with the proximal cap, making it impossible to locate the exact origin of the proximal cap on IVUS. However, a sudden increase in the size of the vessel will tell us roughly where the proximal cap is located. Contrast angiography

should be undertaken when the IVUS is next to the CTO proximal cap. We can then use the angiogram as a guide to where the proximal cap is. Simultaneous IVUS-guided wiring of the proximal cap requires an 8 Fr system and is difficult, as the IVUS catheter often interferes with wire manipulation. Our solution is to place a low-profile dual-lumen catheter (SASUKE®; Asahi Intecc, Nagoya, Aichi, Japan) onto the wire that has a short monorail segment (OptiCross™ IVUS catheter; Boston Scientific, Marlborough, MA, USA) on it and use the over-the-wire port of the SASUKE to wire the CTO while simultaneously observing the wiring under IVUS.

TOUGH PROXIMAL CAP

The tough proximal cap presents two barriers to antegrade preparation: inability to pass a wire and inability to pass devices.

A stepwise algorithmic approach to overcome these two problems is suggested.

If the first CTO wire fails to puncture the proximal cap, a high penetration force wire (**Table 1**) should be used. Where a suitable side branch is available near the tough proximal cap, support by a twin lumen catheter is recommended. The balance between the risk of perforation and penetration power should be considered in each individual case. A higher penetration force wire can be used if the vessel course is clear and a more stepwise intermediate penetration force wire where there is ambiguity of vessel course (**Table 1**). The next step is to use a side branch anchor balloon to anchor the twin lumen catheter in the side branch to improve penetration power. This can be performed with 7 Fr guiding catheters but is much less restrictive with 8 Fr. Alternatively, a side branch anchor balloon with a microcatheter jammed up against the proximal cap and the Conquest Pro 8-20 guidewire (Asahi Intecc) would usually be able to puncture the proximal cap. Finally, “power anchor puncture” with a large balloon inflated in the proximal vessel just proximal to the proximal cap anchoring the microcatheter underneath the balloon provides extreme puncturing force to overcome the tough proximal cap. If the high penetration wire has gone outside the vessel, we should remove the wire and check for perforation. Antegrade balloon tamponade of the vessel should be carried out to control perforation before proceeding again. Antegrade bypass by knuckle wire is also possible by “scratch and go” - using a Conquest Pro 12 guidewire (Asahi Intecc) to puncture into the proximal vessel wall and start a knuckle wire into

the subintimal space to go beside the proximal cap. Alternatively, balloon-assisted subintimal entry (BASE) can be performed where a balloon is used to create dissection in the proximal vessel for a wire to enter into the subintimal space for knuckle wiring.

For operators without access to IVUS, a similar method to puncture the proximal cap with a high penetration wire followed by tipping in of the microcatheter and knuckle wiring can be used to overcome ambiguity.

If the wire can pass into the proximal cap but no device can follow, we suggest a two-tier approach.

The tier-one methods are applicable to all CTO interventionists. These include the use of a side branch anchor balloon or coaxial guiding catheter extension catheter (e.g., GuideLiner® [Vascular Solutions, Minneapolis, MN, USA]; Guidezilla™ [Boston Scientific]) to push the lowest profile balloon into the lesion and inflate and deflate the balloon consecutively to break the cap. A side branch anchor balloon provides more force than a coaxial guiding catheter extension catheter in the majority of cases, especially if the side branch is near the proximal cap of the CTO. These techniques can be combined with balloon-assisted microdissection (BAM)¹², which is the deliberate rupture of the balloon, by inflation to 30 atm to cause dissection of the proximal cap. In about 50% of the cases, the next balloon after BAM would pass into the proximal cap¹². It is important to use a small balloon for BAM and to deflate as soon as there is loss of balloon inflation pressure. Using these techniques as described, Vo et al¹² did not find any vessel perforation. The convenience and controllability of BAM has made the Carlino technique for the proximal cap¹³ much less used nowadays, although the Carlino technique is still useful to elucidate vessel course and to make progress in very difficult cases¹³. The use of Tornus (Asahi Intecc) or Turnpike® Gold catheters (Vascular Solutions, Minneapolis, MN, USA) with side branch balloon anchor or coaxial guiding catheter extension catheter should be tried next. In our experience, 90% of the tough proximal caps can be overcome with the tier-one methods described above.

Tier-two methods should be undertaken by those who are familiar with their use or under proctorship. Subintimal rotablation, using a microcatheter to exchange for a cut Rotawire™ (Boston Scientific) (with 80% of the distal radiopaque part cut off) and then using a 1.25 mm burr to ablate the proximal cap, is difficult as often the cut Rotawire cannot retrace the previous CTO wire's course. There is a risk of vessel perforation in subintimal

Table 1. Wires. Wires classified according to use for proximal cap puncture, for retrograde channel crossing and for reverse CART, listed in order of recommended preference.

| | Proximal cap puncture | Reverse CART | Channel crossing |
|--------------------------------------|--|---|---|
| High penetration force wires | Conquest/CONFianza 12g, Pro 9g, Hornet 14 (Boston Scientific) | Gaia Third, Conquest/CONFianza 12g, Hornet 14 | NA |
| Intermediate penetration force wires | Pilot 200, Miracle 12g, Gaia Second (if vessel course unclear) | Gaia Second, Gaia Third | NA |
| Low penetration force wires | NA | XT-A (for single wire retrograde crossing) | SION, SUOH 03, Sumarai RC (Boston Scientific), XT-R, SION black |
| NA: not applicable | | | |

rotablation, so it is important to rotablate only the proximal cap and not to push the rotablation burr beyond. Excimer laser with contrast-assisted proximal cap ablation is another option, but there are costs and expertise limitations. Also, included in this tier are methods that bypass the proximal cap. Retrograde knuckle wiring to pass the proximal cap and performing reverse CART proximal to the CTO entry cap, so-called “extended reverse CART”, is a good method to bypass the proximal cap. The antegrade equivalent of this is to use the “scratch and go” or BASE method (mentioned above) to bypass the CTO proximal cap. BASE or “scratch and go” can also be used to pass a wire in the subintimal space outside the proximal cap and, by inflating a 2.5 mm balloon on this wire, we can perform “external cap crush” to weaken the proximal cap, allowing devices to pass on the initial wire through the proximal cap¹⁴. If the retrograde channel can accommodate an over-the-wire balloon, a 2.5 mm over-the-wire balloon can be passed through the channel and inflated to perform traditional CART. After successful CART, the antegrade wire can be anchored in the distal true lumen with the retrograde balloon providing strong wire traction force to allow a small balloon to penetrate into the proximal cap. Reverting to traditional CART and retrograde knuckle wire bypass of the proximal cap are the two easiest methods to use of the tier-two methods.

CROSSING THE COLLATERAL CHANNELS (Table 2)

Careful analysis of the collateral channels with frame-by-frame study and the set-up required for retrograde CTO PCI, including guiding shortening⁷, has been well described elsewhere^{8,9} and will not be covered here. The availability of coaxial guiding extension catheters has greatly lessened the need for short guiding. Lesions in the donor artery should be stented to prevent donor artery thrombosis. Intermediate donor artery lesions that are fractional flow reserve (FFR) negative may still cause ischaemia or thrombosis when a microcatheter sits inside the artery further reducing the lumen size or causing the accordion phenomenon. Some of these intermediate lesions should be treated before commencing the retrograde approach. Critical lesions not in the path of the retrograde route but in the donor side of the coronary system should also be stented before the retrograde approach. Non-critical but

significant lesions not in the path of the retrograde route can be treated after the CTO procedure is completed.

LEFT TO RIGHT SEPTAL CHANNELS

Left to right septal channels should be wired with a workhorse wire loaded onto a 150 cm long microcatheter. When the microcatheter is engaged into the proximal segment of the channel, selective injection should be carried out in RAO caudal and LAO views (Table 2). It is advisable to aspirate blood from the microcatheter before selective injection to minimise the chance of channel damage. If we fail to aspirate blood, we should move the microcatheter back and retry aspiration. The SION™ wire (Asahi Intecc) should be used to negotiate the channel. Contrary to the experience of others^{8,9}, channel haematoma or rupture caused by selective injection rarely occurs when selective injection is performed in the proximal part of the left to right septal channels before any wiring has started. Selective injection after channel surfing may cause septal haematoma due to channel damage from wiring and therefore a pre-wiring selective angiogram is recommended. If wiring proves to be difficult, more distal selective angiography using rotational angiography from RAO caudal to LAO caudal (or multiple view angiography if rotational angiography is not available) is useful. There are now many specifically designed wires for channel crossing (Table 1) which should be used instead of the Fielder™ FC (Asahi Intecc) type polymer jacketed hydrophilic wires that were used commonly and recommended in 2012^{8,9}. The main advantage of dedicated channel wires is that they can be controlled to rotate with one-to-one torque transmission allowing accurate wiring of the channel. The newer wires also have lower tip load (SION 0.7g, SUOH 03 0.3g [Asahi Intecc] compared to Fielder FC 0.8g) and less risk of channel damage. The Fielder™ XT-R wire (Asahi Intecc) should also not be used as a first-line wire for channel crossing as its tapered tip increases the risk of channel perforation and damage. Negotiating the proximal part of the left to right septal channels can be difficult due to branching. This can be overcome with a non-selective angiogram and increasing the tip curve of the SION wire.

Distal channel anatomy determines the wiring strategy. If the majority of the septal channels are relatively straight but small or

Table 2. Tips for channel crossing.

| Channel | Angio | Tips | First wire | Second choice small channel | Second choice for tortuous channel | Third choice for tortuous channel |
|---------------|---|--|------------|-----------------------------|------------------------------------|--|
| L → R septals | Selective injection* | Further distal selective injection with rotational angiogram | SION | XT-R | SUOH 03 | SION black |
| R → L septals | Non-selective injection (or via twin lumen) | Twin lumen catheter to overcome retroflex ostium | SION | XT-R | SUOH 03 | SION black |
| Epicardial | Selective injection* | Microcatheter follows the wire technique | SUOH 03 | XT-R/SION | SION/XT-R | SION black if large epicardial channel |

* Selective angiography should be performed with biplane or rotational angiography.

even invisible, channel surfing is often successful. We recommend using the SION or Fielder XT-R wires for channel surfing. The SION should be used when a more deliberate directional wiring strategy is used to cross the collateral channels, especially in channels which are moderate in size (cc2) or are tortuous. Corkscrew channels can be crossed if they are of good size: the SUOH 03 is particularly useful for larger corkscrew channels while the Fielder XT-R is useful for smaller calibre ones. We recommend switching from SION to SUOH 03, then XT-R, then SION® black (Asahi Intecc) for septal channel crossing.

RIGHT TO LEFT SEPTAL COLLATERAL CHANNELS

Right to left septal collateral channels are considerably more difficult to cross. The difficulties arise from the retroflex take-off of the channel from the posterior descending artery (PDA), and tortuosity. In retroflex take-off anatomy, the use of a twin lumen catheter such as the SASUKE or Twin-Pass® (Vascular Solutions) can be helpful (Table 2). We do not recommend a routine selective angiogram from the proximal part of right to left septal collaterals as there is an increased risk of channel rupture and haematoma due to the back and forth motion of the microcatheter from PDA tortuosity. However, selective injection through a microcatheter in the PDA or through a twin lumen catheter in the PDA is often helpful to elucidate the channel course.

OTHER EPICARDIAL COLLATERAL CHANNELS

The development of the SUOH 03 wire has dramatically improved epicardial channel wiring success. The SUOH 03 has a 0.3 gram weight tip and a very flexible distal end, allowing it to find its own way through very tortuous epicardial channels. It comes in two types, pre-shaped and straight. The pre-shaped SUOH 03 is suitable for the vast majority of epicardial channels but the straight allows the operator to make a special bend in order to conform to a particularly troublesome bend in the channel. The SUOH 03, if available, should be the first-line wire to use in epicardial collaterals. With the use of the SUOH 03 it is rarely necessary to use the “microcatheter follows the wire” technique of wiring epicardial channels. The “microcatheter follows the wire” technique (Table 2) is used when the wire is unable to pass a bend in the epicardial channel. The microcatheter is tracked to 15 mm from the distal end of the wire and the wire is gently pulled back just to relax the forward pressure and manipulated again through the

bend. After this, the microcatheter and the wire can be manipulated forward together as one unit to overcome tortuosity, always keeping the microcatheter tip 15 mm proximal to the wire tip. However, in tortuous epicardial channels where there is much to and fro movement of the microcatheter, the operator should not remove the wire and expose the tip of the microcatheter to the channel in a bend in case of channel injury or perforation. If removal of the wire for exchange is needed, it should be done when the tip of the microcatheter is in a relatively straighter segment of the channel and the operator should try to minimise the time required for such an exchange. If the SUOH 03 is not available, the SION wire with a small but large-angled tip bend should be used for epicardial channel tracking.

MICROCATHETER CROSSING

In septal channels, a long torque transmitting microcatheter such as the Turnpike, Turnpike LP (Vascular Solutions), or Corsair (Asahi Intecc) should be the initial channel dilator. If the Corsair fails to cross, we recommend switching to the Turnpike LP, which can be rotated for channel dilatation and has a lower profile (Table 3). If the Turnpike LP is not available, a new Corsair or Caravel (Asahi Intecc) should be tried as the tip coating of the Corsair catheter is easily roughened by manipulation and a new Corsair often will pass. The use of a short Corsair with better torque transmission to dilate the channel is also an option. A very low-profile microcatheter, such as the Finecross® GT (Terumo, Tokyo, Japan) or the Mizuki (Kaneka Medix, Osaka, Japan), can often pass the channel even if the Corsair, Caravel, or Turnpike LP has failed; however, these provide less support for CTO crossing and they pass better after Corsair or Turnpike dilatation of the channel and therefore should be reserved as second-line. If these methods fail, a 1.25 mm balloon dilated at 4-6 atm to the channel using the push forward and dilate method described by Wu et al⁷ can be used to dilate the septal channel and the Corsair can often pass after this dilatation. Never dilate an epicardial channel as dilatation does not enlarge an epicardial channel and can cause channel rupture and tamponade.

In epicardial channels, the choice of microcatheter is determined by channel anatomy and CTO anatomy. If the channel is large enough to accommodate a Corsair/Turnpike and the body of the CTO is such that the operator anticipates the need for rotational drilling of the Corsair to cross the CTO, then a Turnpike or

Table 3. Tips for crossing microcatheter through channel.

| Channel | Corsair/Turnpike will not cross | Switched microcatheter will not cross | Failure to cross after balloon dilatation |
|---|---------------------------------|---------------------------------------|---|
| L → R septal | Switch to Caravel/Turnpike LP* | 1.25 mm balloon to dilate channel | Side branch anchor balloon |
| R → L septal | | | Beware too tortuous PDA to septal channel angle |
| Epicardial | | Switch to Finecross | Beware too small channel |
| * If septal ostium stented → dilate septal ostium with small balloon. | | | |

Corsair should be used. Conversely, in smaller epicardial channels and softer CTO, a Finecross could be used. If a Corsair or Finecross cannot cross the channel, a Turnpike LP is again a good option for these cases. Alternatively, other lower-profile microcatheters such as the Mizuki or Caravel could be used. If none of these microcatheters can cross, a reassessment of the channel and guiding catheter is needed. If the operator considers the channel to be robust enough to pass a retrograde microcatheter and the operator feels that a lack of guiding support is in part the reason for failing to cross the channel, then an anchor balloon placed into the main branch just distal to the take-off of the channel can be used to support the microcatheter crossing. We advise caution in using this technique due to the risks of epicardial channel rupture.

HOW TO CONNECT ANTEGRADE AND RETROGRADE SPACE THE PHILOSOPHY OF CONTEMPORARY REVERSE CART

The majority of retrograde CTOs should be crossed with contemporary reverse CART (**Figure 1**).

One of the main motivations for the APCTO club to write a new retrograde algorithm is the change in philosophy of reverse CART. Although CTO operators have differing ideas about what contemporary reverse CART is, we all agree that the contemporary reverse CART era started with the availability of more directable retrograde wires, such as the Gaia wires (Asahi Intecc), which allowed successful reverse CART to be performed with much smaller 2.0 or 2.5 mm antegrade balloons. At the beginning of the reverse CART era, which began with the introduction of the Corsair as the dominant retrograde crossing microcatheter in 2009 (**Table 3**)¹⁵, the wires available for retrograde wiring were limited and were very difficult to control. Consequently, the only method to complete reverse CART was to make the antegrade target space bigger. Therefore, in that era, we started using IVUS to size the vessel so that we could use the largest possible balloon to perform reverse CART. If that failed, we used a coaxial guiding catheter extension catheter to perform reverse CART, and ultimately adopted stent reverse CART which produced the largest possible antegrade space. These techniques all rely on making the antegrade target space larger.

In the contemporary reverse CART era, there was a sudden decrease in antegrade target space size as it was no longer necessary to make a large space since the retrograde wire was much more controllable. Unfortunately, despite being five years into the contemporary reverse CART era, we have still not learnt to maximise the advantage of directable retrograde wires. If the solution to retrograde wire crossing in the reverse CART era was to make the antegrade target space larger, then the solution to retrograde wire crossing in the contemporary reverse CART era is to make the retrograde wire more controllable. Therefore, the philosophy of contemporary reverse CART is to maximise the retrograde wire control in four main ways. 1) Antegrade preparation first to allow an antegrade target to be set up before retrograde wiring. This results in minimal retrograde wire manipulation. 2) Back-up force to support the retrograde wire and choosing a site for reverse

CART that maximises retrograde wire control. 3) Virgin territory wiring of the retrograde wire. Finally, 4) the end balloon wiring (EBW) technique. These four together form the EBW method for reverse CART.

IMPROVING RETROGRADE WIRE CONTROL – BACK-UP FORCE AND REVERSE CART SITE

Wire control is improved with good back-up force and, conversely, lack of back-up force leads to poor wire control. Therefore, it is important to drill the retrograde microcatheter into the distal cap of the CTO and keep the retrograde microcatheter near the tip of the retrograde wire to afford the best back-up and enhance the retrograde wire control. It is also easier to control a wire in a straight segment of the vessel as opposed to a tortuous part. Therefore, a relatively straight part of the vessel should be chosen as the reverse CART site before we start wiring in either the antegrade or the retrograde side of the CTO. This premeditated site of reverse CART should be at least 15 mm proximal to the distal cap to allow the retrograde microcatheter to anchor into the CTO to give support to the retrograde wire.

IMPROVING RETROGRADE WIRE CONTROL – VIRGIN TERRITORY AND WIRE SPACE EXPANSION

Wire control is much better when the wire is travelling through virgin territory. When a wire first enters a CTO, it makes a 0.014-inch hole and all around this wire is solid plaque. If you turn the wire and push forward, the solid plaque surrounding the wire would support the wire, enhancing both its torque control and its penetration power. However, after a period of wire manipulation inside the CTO, the wire enlarges the space surrounding it. The wire is no longer surrounded by solid plaque but rather by blood-filled spaces. When you torque a wire inside a blood-filled space, the wire tip catches on some plaque but the wire body continues to turn. This leads to the whip phenomenon and loss of wire control. Therefore, to maximise wire control we should hit our target on the first virgin run of the wire into the CTO and avoid over-torquing of the wire and enlarging the wire space. Performing antegrade preparation first and minimising retrograde wiring can improve retrograde wire control.

IMPROVING RETROGRADE WIRE CONTROL – END BALLOON WIRING (EBW)

Wires are forward-moving devices: the majority of the force the wire exerts is immediately in front of the wire. Most retrograde operators today still overlap the antegrade and retrograde wires in the CTO and then inflate the antegrade balloon for reverse CART. This sets up the retrograde wire parallel to the balloon and the retrograde wire will be directed to enter the side of the balloon (**Figure 2A**). They assume that the retrograde wire will easily move sideways into the antegrade balloon space (**Figure 2B**), but wires are much more controllable and have higher penetration force when wiring into something in front of the wire. The penetration force in front of the wire tip is much

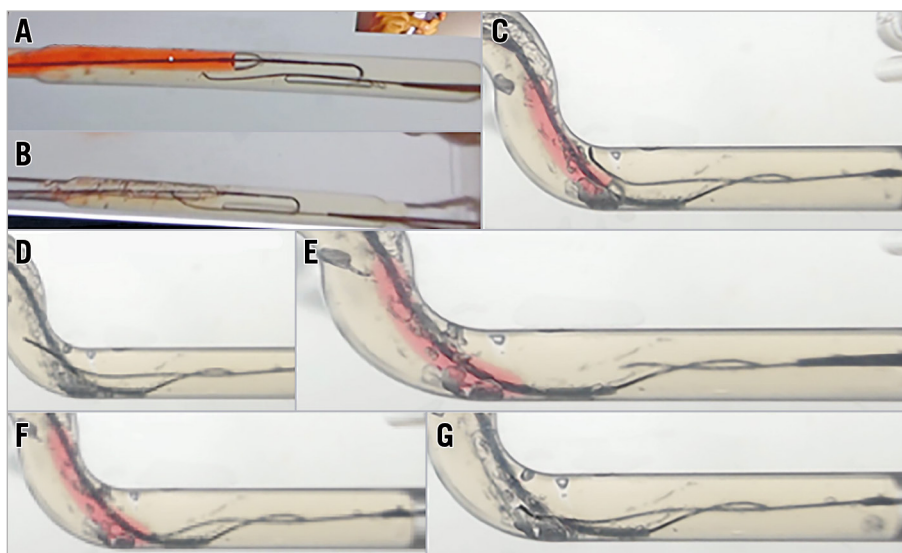


Figure 2. Different ways the retrograde wire moves in reverse CART to illustrate end balloon wiring. A) Parallel starting position of contemporary reverse CART balloon and retrograde wire. B) Presumed side wiring into antegrade balloon space. C) Wire easily goes through the space to the opposite wall. Wire going up parallel to the balloon if starting at the side. D) Wire going through antegrade space into the opposite wall. E) End balloon wiring (EBW) start position. F) End balloon wiring. G) Successful end balloon wiring into the antegrade balloon space.

higher than the penetration force going to the side. Therefore, wires often go up parallel to the balloon (**Figure 2C**) or through the antegrade balloon space into the opposite wall and enter the subintimal space again (**Figure 2D**). To maximise wire control, we should inflate the antegrade balloon before the wires overlap (**Figure 2E**). Then the retrograde wire can be manipulated through virgin CTO body territory aiming for the end tip of the balloon (**Figure 2F**) (EBW) and can be controlled into the balloon space quickly and easily (**Figure 2G**).

In the contemporary reverse CART era, the main method of wire crossing in retrograde CTO PCI should be contemporary reverse CART. The EBW method of contemporary reverse CART should be possible unless the retrograde wire has already gone subintimal or there has been extensive retrograde wire manipulation. However, our algorithm recognises two exceptions to contemporary reverse CART: the short CTO, and the long and tortuous or ambiguous or calcified CTO, which we label as “long-plus CTO” (**Figure 1**).

THE EXCEPTIONS TO CONTEMPORARY REVERSE CART

THE SHORT CTO – SINGLE WIRE CROSSING

Once the retrograde wire and microcatheter have crossed the channel, contrast injection through the microcatheter should be performed to elucidate distal cap morphology. The true length of the CTO and the distal cap characteristics can then be known. The majority of CTOs requiring a retrograde approach are longer than 15 mm but, if the true length of the CTO is less than 15 mm, our algorithm (**Figure 1**) recommends attempting single retrograde wire crossing of the CTO, except when the CTO is in the ostial LAD or ostial LCx. This exception is to prevent subintimal

tracking of the retrograde wire into the left main which may cause haematoma formation, leading to compromise of the other artery (LAD or LCx). Therefore, in ostial LAD and LCx short CTO, we should carry out antegrade preparation first and wire crossing should be performed with reverse CART. In all other short CTOs, retrograde single wire crossing should be used.

If there is a suitable side branch at the proximal cap of the short CTO, single wire crossing should be carried out under IVUS guidance to prevent the loss of the side branch.

If single retrograde wire crossing fails in the short CTO, reverse CART is usually not a good bail-out technique because the retrograde wire is often in the subintimal space while the antegrade wire would be in the true lumen. The distance between the antegrade and retrograde wires is wide, and the retrograde wire has to travel sideways quite a long way within a short longitudinal distance to reach the antegrade space, which is often impossible. Persisting in attempting to perform reverse CART would often lead to the retrograde wire going into the subintimal space in the vessel proximal to the CTO site, leading to loss of the proximal side branch or proximal vessel haematoma. Therefore, we recommend antegrade IVUS-guided retrograde wiring as the first bail-out method.

If antegrade IVUS-guided retrograde wiring fails, we should bail out with traditional CART by removing the retrograde microcatheter with an extension wire, 1.25 mm balloon dilatation of the septal channel, and passing a 2.5 mm over-the-wire balloon to the distal lumen. In this situation, the antegrade wire and the retrograde balloon are both in the true lumen and the distance between them is short. Therefore, traditional CART is almost always successful.

THE LONG PLUS CTO – INTENTIONAL SUBINTIMAL TRACKING

The second exception to contemporary reverse CART is the “long plus CTO”. We do not believe that length alone is predictive of failure to cross the CTO body with traditional wiring techniques. However, when a long CTO is accompanied by tortuosity or calcium or ambiguity, so-called “long plus CTO”, traditional wiring is highly likely to fail and therefore intentional subintimal wiring should be used as recommended by the algorithm (**Figure 1**). The main method of intentional subintimal wiring from the retrograde side is knuckle wiring. For most retrograde operators, retrograde knuckle wiring is the fastest and safest way to cross these long plus CTOs. If a retrograde knuckle wire is used, we should use a large balloon for conventional reverse CART.

IVUS-GUIDED REVERSE CART (**Figure 3**)

When contemporary or conventional reverse CART fails, the next step should be IVUS examination on the antegrade wire using an end imaging IVUS catheter, such as the Eagle Eye® (Volcano Corp., San Diego, CA, USA). This is the recommendation not only of the APCTO club but also from established consensus papers¹⁶.

Although conventionally the result of IVUS examination is classified into four possible wire positions, our algorithm considers the IVUS examination results in three categories: 1) there is a connection between the antegrade wire and the retrograde wire; 2) there is no connection and the antegrade wire (and thus IVUS) is intraplaque; and 3) there is no connection and the antegrade wire is in subintimal space (**Figure 3**). The reason for this classification is because, when the antegrade wire is intraplaque, whether the retrograde wire is intraplaque or subintimal makes no difference to the subsequent methods needed to complete wire crossing. For beginner retrograde operators, this classification is much easier to read as

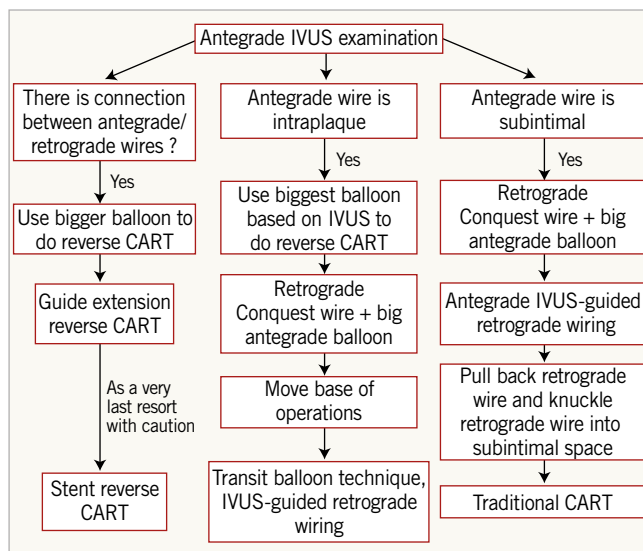


Figure 3. APCTO club algorithm for intravascular ultrasound (IVUS)-guided reverse CART.

there is no need to locate the retrograde wire position, which can be difficult on IVUS. Also, for operators without IVUS, this classification allows them to follow the steps of the algorithm based on whether they think the antegrade wire is intraplaque or subintimal, and whether the wires are connected – information that one can make an educated guess on from the fluoroscopic findings.

IVUS SHOWS THAT THE ANTEGRADE WIRE AND THE RETROGRADE WIRE ARE IN THE SAME SPACE

If there is a connection, using a larger balloon to perform reverse CART will usually succeed. If this fails, it is most commonly due to the retrograde wire being caught up in disease, dissection, or tortuosity between the connection point and the antegrade guiding ostium. This is particularly common in mid right coronary reverse CART. In these situations, one should go straight to coaxial guiding catheter extension catheter reverse CART (**Figure 3**). If this fails, we can use IVUS to locate the connection site and put a coaxial guiding catheter extension catheter at that site and try to wire it, or use the transit balloon technique¹⁷. Stent reverse CART – placing a stent by landing the distal end of the stent just at the connection point – can be carried out as a last resort.

IVUS SHOWS NO CONNECTION BUT THE ANTEGRADE WIRE IS INTRAPLAQUE

If there is no connection and the antegrade IVUS is in the plaque, our aim is to crack the plaque to make a connection. Therefore, the largest balloon sized by IVUS should be used to perform reverse CART. If this fails, we should use a retrograde high penetration force wire (Conquest 12) to puncture the antegrade space.

When this fails, one should move the reverse CART site (“move the base of operations” in hybrid terminology) to a more favourable site and reattempt reverse CART. The coaxial guiding catheter extension catheter assisted transit balloon technique is an extremely powerful technique to bail out these cases¹⁷ (**Figure 3**). IVUS-guided retrograde wiring is also possible but this requires great experience with IVUS-guided wiring. We do not recommend stent reverse CART if the IVUS does not show connection between the antegrade and retrograde wires.

IVUS SHOWS NO CONNECTION BUT ANTEGRADE IVUS IS SUBINTIMAL

Finally, the antegrade wire (and IVUS) is subintimal and there is no connection. This is the most difficult situation in which to perform successful reverse CART. Using a large balloon will not work, as the balloon will expand the subintimal space, stretching out the media and adventitia of the vessel, but once the balloon is deflated the space will just collapse, making it impossible to wire into. Therefore, we should start with large antegrade balloon inflation and retrograde Conquest wire puncture while the balloon is inflated. If this fails, we should pull back the retrograde wire and attempt to knuckle a PILOT® 200 (Abbott Vascular, Santa Clara, CA, USA) wire from the retrograde side, as the retrograde PILOT 200 will very likely go into subintimal space and

spontaneously make a connection to the antegrade wire space (**Figure 3**). After retrograde wire pullback and knuckle, IVUS can be repeated to confirm the connection and we can follow the algorithm for wires with connection. If knuckling fails to connect the wires, the next step is to revert to traditional CART. If even traditional CART fails, we can employ the confluent balloon technique¹⁸, which is an extremely powerful reverse CART tool.

As with any detailed retrograde CTO PCI technical paper, this work may encourage its readers to perform retrograde CTO PCI. Therefore, we feel it is our responsibility also to point out the inherent traps that can cause catastrophic complications in retrograde CTO PCI. However, this is beyond the scope of this paper; we refer our readers to our other work⁶.

Conclusions

In the retrograde CTO PCI field, there have been few technical overview papers, the most recent being more than five years ago. Many new devices and concepts have been developed since the last comprehensive review. We, the APCTO club, deemed it the right time to propose a new algorithm for retrograde CTO PCI. This algorithm builds upon the excellent work of the hybrid operators and avoids overlap by referring to their work. We hope this algorithm will form the next step to encourage safer and more efficacious retrograde CTO PCI procedures.

Impact on daily practice

This retrograde algorithm provides very practical advice to overcome the major hurdles of successful retrograde CTO PCI channel crossing and reverse CART. Different wires and techniques to overcome problems associated with particular retrograde channels are needed for success. The different methods to achieve retrograde/antegrade connection in different CTO morphologies are described and a detailed explanation of how to carry out IVUS-guided reverse CART is given. By following this algorithm, operators can markedly improve their retrograde CTO PCI success.

Conflict of interest statement

S. Harding has received honoraria for speaking from Boston Scientific, Medtronic and Asahi, and acted as a proctor for Boston Scientific and Bio-Excel. E. Tsuchikane is consultant for Boston Scientific, Nipro, and Asahi. E. Wu is a proctor for Boston Scientific and St. Jude Medical, and owns Medtronic shares. The other authors have no conflicts of interest to declare.

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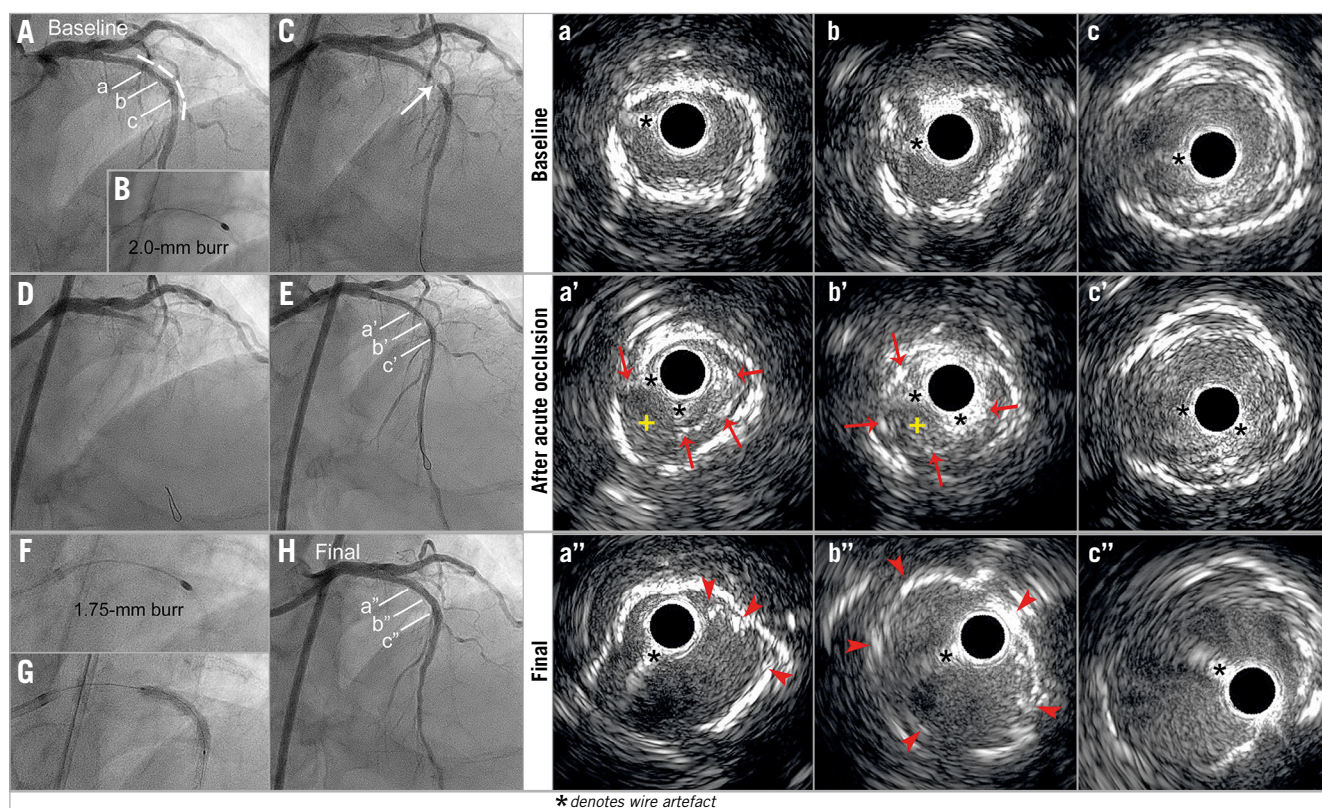
Acute coronary occlusion due to stent deformation caused by rotational atherectomy of an underexpanded, undilatable stent: an unusual complication and its bail-out



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



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An 83-year-old man was admitted for unstable angina. The angiogram showed in-stent restenosis of a 2.5 mm cobalt-chromium everolimus-eluting stent in the left anterior descending (LAD) artery (fractional flow reserve, 0.73) that had been underexpanded due to heavy calcification five years earlier (**Panel A**, dotted line, **Moving image 1**). Baseline intravascular ultrasound (IVUS) revealed the underexpanded stent in the area of continuous calcification with optimal stent apposition (**Panel a-Panel c**). Rotational atherectomy (RA) of the underexpanded stent was required; however, neither a 2.0 mm (**Panel B**) nor a 1.75 mm rotablation burr could cross the stent without significant deceleration, leading to subtotal occlusion with ST-segment elevation in the precordial leads (**Panel C**, arrow). A 2.0 mm balloon catheter or a 1.25 mm burr also could not cross; subsequently, the LAD became totally occluded (**Panel D**). As a bail-out procedure, a second floppy guidewire was used to pass through the other remaining lumen inside the occluded stent to restore coronary flow (**Panel E**). IVUS demonstrated that the distorted stent struts had been ablated by the rotablation burr (**Panel a'-Panel c'**: red arrows, yellow asterisks indicate the deformed stent that remained in a circle; **Moving image 2**). Following guidewire exchange for the ROTAWire™ Extra Support (Boston Scientific, Marlborough, MA, USA) with the aid of a microcatheter, we managed to ablate the deformed, undilatable stent using a 1.75 mm burr at 210,000 rpm with deceleration (7,000 rpm) (**Panel F**). Angioplasty with a 3.5 mm scoring balloon and 3.5 mm drug-coated balloon re-established good coronary flow with excellent stent expansion (**Panel G**, **Panel H**, **Panel a''-Panel c''**: red arrowheads; **Moving image 3**). No restenosis had occurred at the one-year follow-up.

This is the first report of acute coronary occlusion due to stent deformation caused by RA of an underexpanded stent. Use of a relatively large burr (burr artery ratio, 0.75) deformed and crushed the underexpanded stent, which caused thrombus formation and the accumulation of tissue fragments that led to acute coronary occlusion. RA of the deformed, undilatable stent was successful using the second guidewire in the remaining lumen, resulting in excellent stent expansion. For RA of the underexpanded stent in this case, a step-up procedure starting with a 1.5 mm burr (i.e., burr-to-artery ratio of 0.6) up to a 1.75 mm burr might have been a safer approach.

Conflict of interest statement

T. Fujita is a consultant for Terumo Corporation. The other authors have no conflicts of interest to declare.

Supplementary data

Moving image 1. Baseline intravascular ultrasound showing residual stent underexpansion with heavy and circumferential calcification.

Moving image 2. Intravascular ultrasound after the second guidewire crossing, demonstrating the distorted stent struts, suggestive of stent deformation caused by RA.

Moving image 3. Final intravascular ultrasound examination showing excellent stent expansion with correction of the deformed strut.

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



Feasibility and safety of non-occlusive coronary angioscopic observation using a 4 Fr guiding catheter



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KEYWORDS

- miscellaneous
- other imaging modalities
- radial

Abstract

Aims: Coronary angiography (CAS) is a robust imaging methodology for evaluation of vascular healing response after stenting. However, the procedure requires a guiding catheter with a diameter of more than 6 Fr, which is rather invasive at follow-up angiography. Recently, coronary angioscopes of a smaller diameter have been able to pass through a 4 Fr guiding catheter. This study aimed to investigate the feasibility and safety of slender CAS observation using a 4 Fr guiding catheter.

Methods and results: Thirty-three consecutive patients who underwent follow-up angiography were evaluated. Following usual angiography via the radial artery, the stent segment was observed by non-occlusive CAS through a 4 Fr guiding catheter. Low molecular weight dextran-L (4 mL/sec) was flushed from a guiding catheter to replace coronary blood. The success rate, anatomical or procedural factors related to the success, and incidence of adverse events were examined. The success rate was 84.8% (n=28/33). The luminal diameter at the orifice of the target vessel was larger in the successful than in the failed group (4.03±0.61 mm vs. 3.39±0.61 mm, respectively; p=0.009). The presence of deep engagement of the guiding catheter into the target vessel was a key factor for sufficient observation (100% in the successful group vs. 0% in the failed group; p<0.0001). No adverse events, such as dissection or acute coronary syndrome, were reported.

Conclusions: The new method of CAS through a 4 Fr guiding catheter demonstrated high feasibility and safety. This less invasive observation via CAS may be useful for stent follow-up.

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Abbreviations

| | |
|-------------|-----------------------------------|
| BVS | bioresorbable vascular scaffold |
| CAG | coronary angiography |
| CAS | coronary angiography |
| ECG | electrocardiogram |
| LMT | left main trunk |
| LAD | left anterior descending artery |
| LCx | left circumflex |
| QCA | quantitative coronary angiography |
| RCA | right coronary artery |
| VLST | very late stent thrombosis |

Introduction

Although thrombotic events have decreased markedly since the introduction of second-generation drug-eluting stents in daily practice, life-threatening very late stent thrombosis (VLST) will never vanish. VLST originates from delayed arterial healing (or a persistent uncovered stent), stent malapposition, hypersensitivity reaction to the stent polymer, and neoatherosclerosis¹. Furthermore, the bioresorbable vascular scaffold (BVS) is becoming common as a new device for the treatment of coronary artery diseases. At present, scaffold thrombosis is the main ongoing limitation of BVS, attributed to the large strut thickness^{2,3}.

In order to understand the pathogenesis of VLST or scaffold thrombosis in human beings, intravascular imaging is essential. Moreover, comprehending the vascular healing response in a stented segment provides helpful information about patient treatment and is therefore clinically significant.

Coronary angiography (CAS) is a unique intravascular imaging modality because the vessel lumen can be directly visualised. As shown in previous reports, growth of neointima and uncovered struts in the stented segment can be sufficiently evaluated by CAS⁴. In addition, CAS is capable of detecting intracoronary thrombi with high sensitivity. CAS is therefore one of the valuable tools for follow-up examination after coronary stenting. However, conventional CAS requires a guiding catheter with a diameter of more than 6 Fr which is rather invasive, because a 4 or 5 Fr sheath and a catheter of the same diameter are commonly used at the angiographic procedure for stent follow-up. CAS using a smaller diameter has recently become available, and an angioscope can pass through the lumen of a 4 Fr guiding catheter. Although the first-in-man case of CAS observation with a 4 Fr guiding catheter was reported previously, systematic data about this procedure are absent⁵.

The aim of this study was to investigate the feasibility and safety of a new procedure using CAS through a 4 Fr small diameter guiding catheter for clinical use at stent follow-up.

Methods

SUBJECTS

The present study prospectively investigated 58 consecutive patients who underwent coronary angiography (CAG) for stent follow-up at Nippon Medical School Chiba Hokusoh Hospital between September 2016 and December 2016. Twenty-five

patients were eliminated because of exclusion criteria, which were 1) an aorto-ostial stent segment such as the left main trunk (LMT) or right coronary artery (RCA) less than 10 mm from the orifice (n=7), 2) chronic renal failure (serum creatinine >2.0 mg/dL) (n=0), 3) decompensated heart failure (n=0), 4) history of anaphylactic shock caused by contrast media (n=0), 5) no consent to undergoing CAS examination (n=6), 6) in-stent restenosis (diameter stenosis >50%) (n=3), 7) *de novo* stenosis in a stented branch (n=9), and 8) stent segment in a bypass graft (n=0). Thirty-three patients underwent CAS to observe the condition of deployed stents. The study flow chart is shown in **Figure 1**. The study protocol was approved by the Ethics Committee of our institute and an informed consent was obtained from all patients participating in this study.

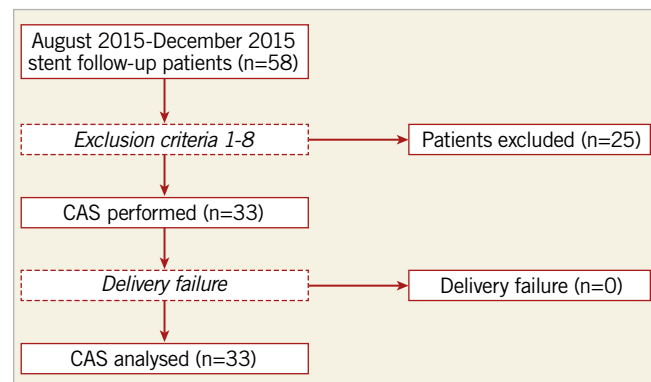


Figure 1. Study flow chart. Twenty-five out of 58 stent follow-up patients were excluded according to the exclusion criteria. No cases of angioscope delivery failure were reported.

PROCEDURES

All procedures were performed through the transradial approach using a 4 Fr sheath. Four thousand units of unfractionated heparin were administered before the procedure and 50 µg of nitroglycerine were administered to each coronary artery immediately before CAG. After ordinary CAG for stent follow-up, the stent segment was observed by CAS. A non-occlusive and short monorail type of coronary angioscope (Smart-i™ type S11; iHeart Medical Co. Ltd., Tokyo, Japan) (**Figure 2**) and a 4 Fr guiding catheter (Kiwami; Terumo Corp., Tokyo, Japan) were used. The diameters of the coronary angioscope were 1.2 mm at the tip and 0.6 mm at the shaft. The guiding catheter had a diameter of 0.055 inches (1.27 mm), enabling the angioscope to pass inside the catheter lumen. The appropriate shape of the guiding catheter was selected according to the anatomy of the coronary arteries, such as Judkins left (JL), Judkins right (JR), Amplatz left (AL), and Backup left (BL). After engagement of the guiding catheter into the target vessel, a 0.014-inch guidewire was crossed over the stent segment. The angioscope was advanced along the guidewire distal to the stent through the guiding catheter. For removal of coronary blood, low molecular weight dextran-L at a flow rate of 4 mL/sec (total

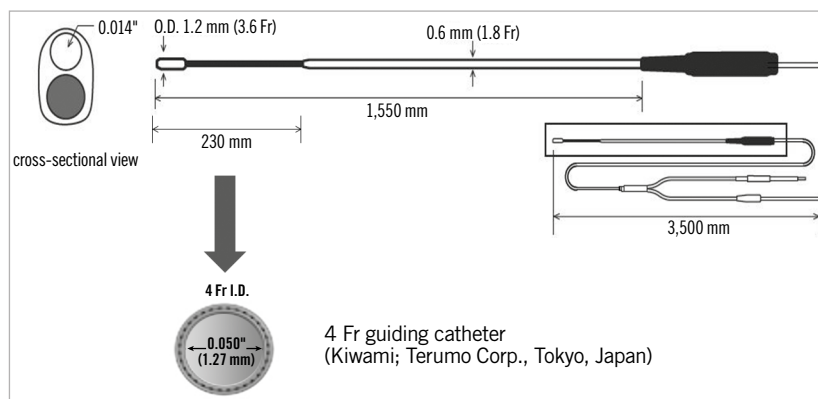


Figure 2. Profile of Smart-i™ (type S11) and guiding catheter. The tip of the angioscope was 1.2 mm and the inner diameter of the 4 Fr guidewire was 1.27 mm.

volume of 36 mL) was flushed from the guiding catheter using the auto-injector. In the target stent segment, the angioscope was pushed and/or pulled back slowly and gently during the flush.

ENDPOINT

The primary endpoint was the success rate of CAS observation. Image quality was used to divide the obtained images into two groups: the successful group in which the quality was sufficient for evaluation of the stent segment due to continuously clear images with complete replacement of the blood, and the failed group in which observation was insufficient due to discontinuous images or no image acquisition owing to residual blood.

In addition, we analysed lesion characteristics contributing to successful observation of CAS as follows: location of the target vessel (left anterior descending artery [LAD], left circumflex artery [LCx], or RCA) and the stent segment (just proximal, proximal, mid, or distal), ostial diameter of the target vessel, reference diameter in the stent segment, lumen diameter at the tip of the guiding catheter, deployed stent diameter, deployed stent length, and achievement of deep engagement of the guiding catheter into the target vessel. The just proximal segment was defined as the LAD or LCx ≤ 10 mm from the bifurcation. Vessel diameter and distance were analysed by quantitative coronary angiography (QCA) using QAngio XA, Version 7.2.34.0 (Medis medical imaging systems bv, Leiden, the Netherlands). Deep engagement of the left coronary artery was defined as selective insertion into the LAD or LCx, and that of the RCA was defined as adaptation more than 10 mm from the orifice.

The secondary endpoint was estimation of the safety of the 4 Fr coronary angioscope. Procedure-related adverse events, such as changes in the electrocardiogram (ECG) during the observation, and the occurrence of coronary dissection and acute coronary syndrome were checked.

STATISTICAL ANALYSIS

All data were analysed using Statistical Package for Social Sciences (SPSS) software, Version 22.0 (IBM Corp., Armonk, NY, USA).

All numerical data were expressed as the mean \pm standard deviation or the median (25-75% interquartile range), depending on normality. If the data were normally distributed, the values were expressed as the mean \pm standard deviation. If the data were not normally distributed, the values were expressed as the median (25-75% interquartile range). The t-test was used to compare quantitative variables between groups, and chi-square analysis was used to compare qualitative data between groups. A p-value of <0.05 was considered to be statistically significant.

Results

PATIENT CHARACTERISTICS

Patient and lesion characteristics are shown in **Table 1**. The right radial approach accounted for 84.8% (n=28) of cases and the left side was chosen in the others. Delivery failure to the stent segment was not reported. Types of guiding catheter used were JL in 14, BL in four, AL in four cases for the LAD; JL in two, BL in two cases for the LCx; and JR in five, AL in one, BL in one case(s) for the RCA.

The location of the stent segments is also shown in **Table 1**. Among 33 cases, four cases had LMT lesions and one case had an aorto-ostial RCA; these segments were excluded from the analysis because engagement of the guiding catheter conceals the stents in the aortic ostium. Finally, 60 segments of 33 vessels were analysed in this study.

SUCCESS RATE AND FACTORS OF SUCCESSFUL OBSERVATION

Among 33 patients, 28 patients (84.8%) were categorised as the successful group and five (15.2%) were placed in the failed group. Mean time of clear imaging in the successful group was 5.7 ± 2.5 sec. The proportion of cases in which the whole targeted stent was evaluated in the successful group was 42.9% (n=12/28). The ratio of observed length to whole targeted stent in the successful group was 85.4% (77.0-100%). Haemodynamics, including blood pressure and heart rate, laboratory data, and ejection fraction, were similar in both groups (**Table 2**). The success

Table 1. Patient and lesion characteristics.

| | | n=33 |
|---|-----------------------------|------------|
| Age (years) | | 67.8±9.4 |
| Gender, male (%) | | 24 (72.4%) |
| Body weight (kg) | | 64.1±10.0 |
| Height (cm) | | 162.4±7.5 |
| BMI (kg/m ²) | | 24.3±2.7 |
| Diagnosis before stenting | Acute coronary syndrome | 13 (39.4%) |
| | Stable angina | 12 (36.4%) |
| | Silent myocardial ischaemia | 8 (24.2%) |
| Diseased vessel | 1-vessel disease | 14 (42.4%) |
| | 2-vessel disease | 13 (39.4%) |
| | 3-vessel disease | 6 (18.2%) |
| AHA/ACC type | A | 3 (9.1%) |
| | B1 | 9 (27.3%) |
| | B2 | 17 (51.5%) |
| | C | 4 (12.1%) |
| Previous CABG | | 1 (3.0%) |
| Previous myocardial infarction | | 17 (51.5%) |
| Coronary risk factor | Hypertension | 25 (73.6%) |
| | Diabetes mellitus | 20 (60.6%) |
| | Dyslipidaemia | 28 (84.8%) |
| | Current smoking | 21 (63.6%) |
| Stent follow-up period (months) | | 17.8±18.2 |
| Ejection fraction on echocardiogram (%) | | 61.7±10.9 |
| Targeted vessel | LAD | 22 (66.7%) |
| | LCx | 4 (12.1%) |
| | RCA | 7 (21.2%) |
| Location of stent segment (60 total segments) | Just proximal | 17 (51.5%) |
| | Proximal | 20 (60.6%) |
| | Mid | 18 (54.5%) |
| | Distal | 5 (15.2%) |

Data are presented as mean±SD or number (%). AHA/ACC: American Heart Association/American College of Cardiology; BMI: body mass index; CABG: coronary artery bypass grafting

Table 2. Comparison of clinical factors between successful and failed groups.

| | | Successful group n=28 | Failed group n=5 | p-value |
|---|---------------------------------|--------------------------|---------------------|---------|
| Haemo-dynamics | Systolic blood pressure (mmHg) | 127.1±17.9 | 140.2±16.9 | 0.141 |
| | Diastolic blood pressure (mmHg) | 66.2±11.7 | 68.4±11.5 | 0.698 |
| | Heart rate (/min) | 67.0±14.3 | 65.8±10.4 | 0.860 |
| Labora-tory data | Haemoglobin (mg/dl) | 13.5±1.3 | 13.3±1.1 | 0.784 |
| | eGFR (ml/min) | 67.0±17.1 | 64.8±21.2 | 0.802 |
| | BNP (pg/ml) | 60.8±78.7 | 50.7±56.9 | 0.787 |
| Ejection fraction on echocardiogram (%) | | 61.8±10.8 | 61.4±12.5 | 0.951 |

Data are presented as mean±SD. The p-values between groups were determined using t-test. BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate

rate did not differ between the LAD, LCx, and RCA (86.4%, 75.0%, and 85.7%, respectively; $p=0.877$). The segment-by-segment success rate was 70.0% ($n=42/60$) and the rate per location was 17.6% ($n=3/17$) for the just proximal site, 85.0% ($n=17/20$) for the proximal site, 94.4% ($n=17/18$) for the middle site, and 100% ($n=5/5$) for the distal site. Just proximal segments showed a lower success rate than the other segments (just proximal segments 17.6% [$n=3/17$] vs. the other segments 90.7% [$n=39/43$]; $p<0.001$) (**Figure 3**). **Table 3** shows the results of QCA analysis. The reference diameter in the stent segment, lumen diameter at the tip of the guiding catheter, deployed stent diameter, and deployed stent length were not different between the successful and the failed groups. The ostial diameter of the target vessel was greater in the successful group than in the failed group (successful group: 4.14 ± 0.55 mm vs. failed group: 3.39 ± 0.61 mm; $p=0.009$). The success rate was significantly higher in patients with deep engagement of the guiding catheter than in patients

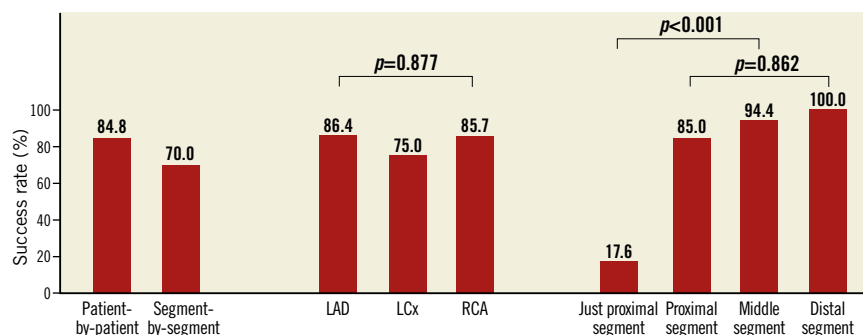


Figure 3. Success rate of 4 Fr CAS. Patient-by-patient success rate was 84.8% and segment-by-segment success rate was 70.0%. Just proximal segments showed a lower success rate than the other segments. p-values between groups were determined using the chi² test. LAD: left anterior descending; LCx: left circumflex; RCA: right coronary artery

Table 3. Findings of quantitative coronary angiography.

| | Successful group n=28 | Failed group n=5 | p-value |
|--|--------------------------|---------------------|---------|
| Ostial diameter of target vessel, mm | 4.14±0.55 | 3.39±0.61 | 0.009 |
| Reference diameter in stent segment, mm | 2.83±0.41 | 2.53±0.53 | 0.161 |
| Lumen diameter at tip of guiding catheter, mm | 3.09±0.43 | 2.75±0.54 | 0.124 |
| Deployed stent diameter, mm | 3.10±0.44 | 3.30±0.27 | 0.240 |
| Deployed stent length, mm | 30.6±15.2 | 25.2±17.8 | 0.678 |
| Data are presented as mean±SD. The p-values between groups were determined using t-test. | | | |

without. As shown in **Figure 4**, the successful group achieved 100% deep engagement of the guiding catheter, while the failed group achieved 0% ($p<0.001$).

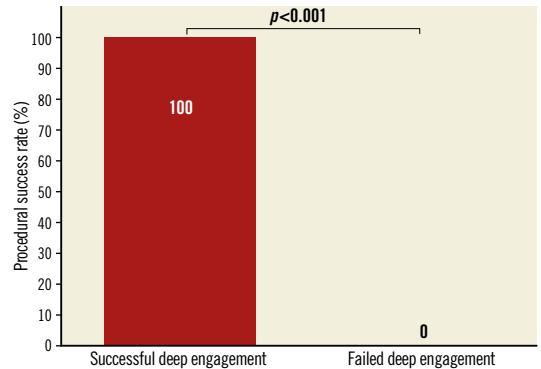


Figure 4. Association between procedural success and deep engagement of the guiding catheter. Deep engagement of the guiding catheter was the most important factor of the procedural success. p-values between groups were determined using the χ^2 test.

Representative cases are shown in **Figure 5**. These included the successful case and the failed case of 4 Fr CAS carried out for the LCx. The guiding catheter in the successful case achieved selective insertion to the LCx, while that in the failed case did not.

ADVERSE EVENTS RELATED TO CAS PROCEDURES

In all cases, no transient ST-T changes on the ECG were found during the observation. No serious adverse events, such as coronary dissection and acute coronary syndrome, were observed.

Discussion

The present investigation demonstrated that more than 80% of stent segments were sufficiently observed by slender CAS through a 4 Fr small diameter guiding catheter. The procedures were less invasive and quite safe.

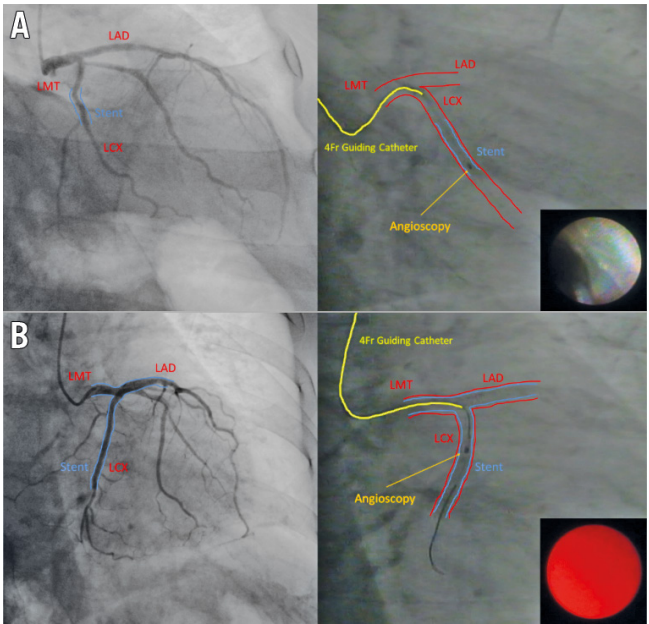


Figure 5. Representative cases of 4 Fr CAS for the LCx. Successful (A) and failed (B) cases are shown. The guiding catheter achieved a deep engagement position in the successful case (enabling the observation of neointimal stent coverage), while it did not in the failed case. The neointimal stent coverage of the successful case was Grade 1. Stent coverage could not be evaluated in the failed case due to the residual blood flow.

The innovation of fibre optics and laser technologies in the early 1980s helped the development of CAS⁶⁻⁹. As fibrescopes became flexible and thin, CAS was utilised for observation of coronary lumens in clinical practice. Two types of CAS catheters have been used, each of which has its advantages and disadvantages: balloon-occlusion (FULLVIEW NEO™; FiberTech Co., Ltd., Chiba, Japan) and non-occlusion (Visible™; FiberTech Co., Ltd.). The monorail type of balloon-occlusion angioscope provides continuous images without residual blood. However, this invites transient myocardial ischaemia during the observation and has low delivery performance due to its large diameter and high rigidity. In contrast, the non-occlusion angioscope is easily deliverable, but with inferior image quality as compared to the occlusion angioscope. Moreover, a guidewire inside a microcatheter (over-the-wire catheter) is replaced by a fibrescope, and the wire is lost for the observation. Both types require a guiding catheter of more than 6 Fr in diameter. The systems and procedures of CAS have changed little since the beginning of their development.

To the best of our knowledge, our study was the first to evaluate novel procedures using a slender CAS catheter. The current investigation was performed by a non-occlusive and 4 Fr-compatible system, which has the advantage of simplicity and less invasiveness over conventional procedures. In addition, a guidewire was left in the target vessel because of the monorail system of the

catheter. The guidewire is helpful for bail-out in case of unexpected complications including dissection, and this may help to guarantee procedural safety.

In our series, 84.8% of cases were sufficiently evaluated by the 4 Fr CAS system. Previous studies have reported that the success rate using an 8 Fr guiding catheter and the occlusion type of angioscope resulted in a success rate of 82-83%^{4,10}. The occlusion type of angioscope cannot be delivered in the presence of severe tortuosity or calcification proximal to the target lesion. No cases of delivery failure were reported in the present study, suggesting that the current CAS catheter produced a delivery capability under back-up force by a 4 Fr guiding catheter. Although the definition of procedural success and the exclusion criteria were different from the previous reports, our observation showed a similar success rate regardless of the small size of the 4 Fr guiding catheter. The first-in-man case of a 4 Fr CAS system was accomplished with flushing of iodine contrast media⁵. The current procedure, using low molecular weight dextran-L, was less invasive compared to the previous procedure.

According to our results, deep engagement of the guiding catheter into the target vessel and its diameter at the ostium were related to the success rate. In particular, deep engagement of the guiding catheter was a key factor of the procedural success. Deep engagement of the guiding catheter and consequent selective injection of low molecular weight dextran-L was able to wash out coronary blood efficiently, and this provided clear images without residual blood. The ostial diameter of the target vessel was another factor of the procedural success. In general, a large vessel makes CAS observation difficult because of the large amount of coronary blood that needs to be washed out. However, a large vessel diameter was a favourable condition for the observation. Although the precise reasons were unclear, large vessels may facilitate deep engagement of the guiding catheter and enable good washout of blood. The tip of the guiding catheter with a small diameter is flexible, and a 4 Fr guiding catheter may allow deep engagement easily and safely. This is the one of the most important advantages of a small diameter system when performing CAS. The 4 Fr system provides sufficient observation even when the mother-and-child catheter system is necessary if performing CAS with a larger diameter guiding catheter. No major complications were reported in this study. From the viewpoint of safety, our procedures were acceptable for clinical use.

Limitations

Several limitations in the present study must be noted. First, our report is a single-centre trial with a relatively small population and is limited to patients evaluated for neointimal stent coverage with no restenosis. In addition, the selection of the guiding catheter depended on each operator. Operators selected the tip shape of the guiding catheter according to the anatomy of each vessel. These biases may have affected the procedural success and occurrence of adverse events using 4 Fr CAS. Second, aorto-ostial lesions were excluded from the analysis. We excluded these lesions on

the grounds that the tip of the guiding catheter disturbs observation of the ostial RCA or LMT. Given the low success rate even in the just proximal segment of the LAD or LCx, 4 Fr CAS would be unsuitable to observe ostial lesions. However, this disadvantage might also be applicable to CAS with the larger diameter system. Actually, in balloon-occlusion type CAS, the ostium including the LMT is invisible because of the approximately 2 cm distance between the catheter tip and the occlusion balloon. Third, the present study categorised several cases into the successful group in which the neointimal coverage was only partially observed. We need to recognise the difficulty of observing just proximal segments, as shown above. Nevertheless, the average consecutive observation time of 5.7 sec and the observed length ratio of 85.4% against the whole targeted stent length in our successful group are considered to be relatively adequate to evaluate neointimal coverage after stent deployment. Fourth, the present study evaluated only procedure-related adverse events during the CAS procedure; it did not assess the events after the procedure such as 1-day, 7-day, or 30-day events. Nevertheless, no complications during the CAS procedure occurred in the present study. We consider that this result substantially endorses its safety.

Historically, CAS contributed towards the illumination of the pathogenesis of acute coronary syndrome⁴ and the identification of vulnerable plaques as its origin¹¹. Although we focused on implanted stents in this study, 4 Fr CAS could contribute considerably to every situation in daily practice, including stent follow-up and plaque evaluation. Moreover, it has the potential to become an important technique for follow-up of new devices (such as BVS) in the near future.

Conclusions

In conclusion, the present study is the first-in-man report showing the feasibility, safety, and lesser invasiveness of CAS with a 4 Fr slender system.

Impact on daily practice

CAS is a robust imaging methodology for evaluating vascular healing response after stenting. Conventional CAS generally requires a 6 Fr guiding catheter and is rather invasive for stent follow-up. This study demonstrated a high success rate and the safety of CAS with a slender 4 Fr system. It could contribute to every situation in daily practice, including stent follow-up and plaque evaluation.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Takayasu's arteritis: a review of the literature and the role of endovascular treatment



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KEYWORDS

- abdominal aortic aneurysm stent/prosthesis
- aneurysm
- renal artery stenosis
- thoracic aorta aneurysm

Abstract

Takayasu's arteritis (TA) is a chronic non-specific vasculitis with variable presentation in different ethnicities and countries. Treatment options vary and are dependent on the stage and presentation of the disease. We aimed to review current literature related to TA, focusing on the role of endovascular treatment in revascularisation. The temporal course of the disease and stage at presentation influence the management of TA. Treatment options include medical therapy, endovascular intervention or surgical vascular reconstruction. The decision to intervene is individualised according to vascular anatomy and the presence of haemodynamically significant lesions. There are currently no clear guidelines regarding the choice between the endovascular and open surgical approaches, but studies have shown that endovascular procedures are associated with slightly higher rates of restenosis while surgical procedures have higher rates of thrombosis. Periprocedural immunosuppression is suggested if the disease is active at the point of intervention. This improves outcomes but at the cost of immunosuppression-related side effects. Careful long-term follow-up is essential due to the risk of disease activation or flare-up, requiring appropriate evaluation of the diseased vessels.

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Abbreviations

| | |
|--------------|--|
| CABG | coronary artery bypass graft |
| CRP | C-reactive protein |
| CTA | computed tomography angiography |
| MACE | major adverse cardiac events |
| MRA | magnetic resonance angiography |
| PCI | percutaneous coronary intervention |
| PET | positron emission tomography |
| PTA | percutaneous transluminal angioplasty |
| TA | Takayasu's arteritis |
| TARAS | Takayasu's arteritis-induced renal artery stenosis |

Introduction

Takayasu's arteritis (TA) is a chronic non-specific granulomatous large-vessel vasculitis, which affects the aorta and its main branches. It may also affect the coronary and pulmonary arteries^{1,2}. TA has historically been described as having a strong association with female patients, though the degree of association with the female gender may vary for different populations³. In the Japanese population where TA was originally described, the majority (80-90%) of the TA patient population consists of females. By comparison, Indian, Thai and Israeli populations demonstrate greater gender heterogeneity, with a larger (31-38%) proportion of male patients^{3,4}. The disease commonly presents in the second or third decade of life regardless of ethnicity, although a small percentage may present in childhood^{2,4,5}. The incidence of TA has been described worldwide as up to 3.3 per million, and is generally considered to be most common in Asia⁶.

TA has been described as the infiltration of inflammatory cells into the adventitia and media resulting in a cell-mediated immune response, involving NK T cells and CD4 T cells which form characteristic granulomas and giant cells. This is different from atherosclerotic lesions which consist of the accumulation of lipid-laden foam cells involving the intima layer. These features make atherosclerotic lesions respond better to percutaneous transluminal angioplasty (PTA) as compared with TA lesions, with 15.5% residual stenosis after subclavian artery PTA in TA compared with only 8.3% in atherosclerotic lesions⁷.

CLINICAL MANIFESTATIONS

In a series of 60 patients described by Kerr et al, only 33% had systemic symptoms on presentation⁵. Hypertension is most often associated with renal artery stenosis. Sixty-eight percent (68%) of patients had extensive vascular disease; stenotic lesions were 3.6-fold more common than were aneurysms (98% compared with 27%)⁵. Most of the aneurysms were located in the thoracic aorta (83.3%), with a smaller proportion (19%) in the abdominal aorta⁸. It has been noted that the site of affected lesions differs amongst various countries, therefore causing different sets of symptoms. Occlusive disease seems to be more prevalent in Japan, the USA, and Europe, whereas aneurysmal disease is more common in India, Thailand, Mexico, and Africa⁹.

The clinical course of TA can be subdivided into two phases - the early or active phase, and the late, chronic, or inactive phase¹⁰. During the early or active phase, the initial intimal inflammation process is followed by oedema and subsequent infiltration of lipids and blood cells. The resultant calcification and intimal thickening that follows the inflammatory phase represents the chronic phase of TA, which is similar to atherosclerosis. Clinically, constitutional symptoms are predominant during the acute phase, whereas the chronic phase is characterised by symptoms related to arterial compromise¹¹. Though TA patients have often been described as having high rates of relapse despite being on medical treatment¹², a small cohort study (n=26) demonstrated that a significant proportion of patients (76%) had no angiographically significant relapse over more than three years¹³.

Geographically, TA demonstrated significant anatomical variability in terms of the site of the disease. This can potentially be explained by the heterogeneous genetic presentation of TA patients around the globe¹⁴. In Japan and South America, cervical and thoracic arterial lesions are more prevalent, but in Israel and other Asian countries abdominal lesions are more frequent¹⁵. In a study of 106 Japanese patients, the presentation was as follows: 41.5% had thoracic aorta lesions, 31.1% had abdominal aorta lesions, 22.6% had moderate to severe aortic regurgitation, 21.7% renal artery lesions, 8.5% had coronary lesions, 4.7% pulmonary artery lesions and 2.8% had loss of vision¹⁶. Japanese patients often present with "pulseless disease", with the majority of the stenotic lesions occurring in the ascending aorta, the aortic arch, and/or its branches (58%) and occasionally extending into the thoracic and abdominal aorta^{4,17}. On the other hand, in Korean patients, vasculitis generally occurs in the abdominal aorta (30%) involving renal arteries^{4,17,18}. Indian patients tend to present with hypertension, with a number of studies having noted the characteristic involvement of the abdominal aorta and the renal arteries in the majority of cases (71-92%)¹⁹⁻²¹. In an Indian observational study, patients with early TA were observed to have isolated abdominal and renal artery lesions at presentation, which over the course of 10-20 years progressed to involve the entire aorta and its branches⁴. Approximately 20-26% of Indian patients with TA have aneurysmal lesions of the abdominal aorta²², with the only case series of 30 patients with the aneurysmal form of TA being published in India in 1990²³. In the UK, a study of 97 patients revealed that the majority of patients (95%) had arterial stenosis or occlusions, as compared to the other 5% who had a discrete aneurysm²⁴. The supra-aortic vessels were involved more frequently, comprising 45.9% of affected segments, with the next most common site being the aorta (25.3%)²⁴. Examples of anatomic involvement on imaging scans are illustrated in **Figure 1-Figure 4**.

PRESENTATION

In Japanese patients, more common presentations include aortic regurgitation, ischaemic heart disease and visual disturbances, while amongst Korean and Indian patients the more frequent

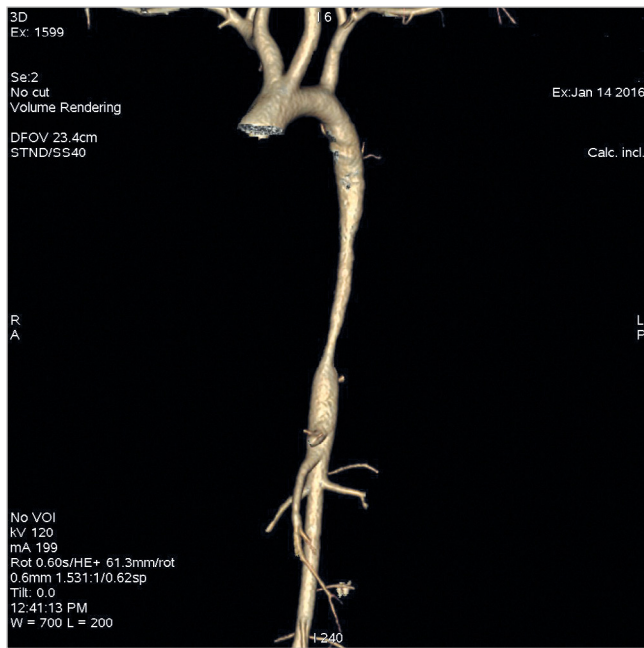


Figure 1. A 7-year-old female with stenosis of the descending thoracic aorta demonstrated on a CT aortogram.

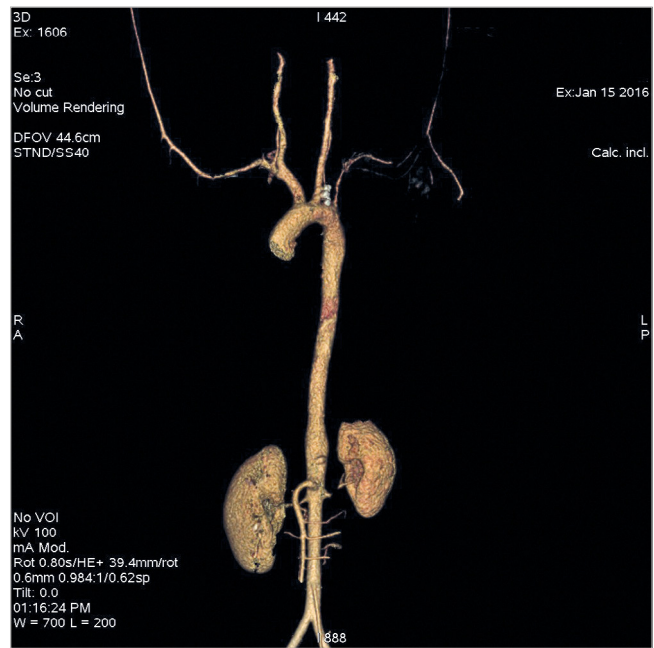


Figure 2. CT aortogram of a 12-year-old male showing stenosis of the left subclavian artery and left renal artery.

presentations were hypertension, headache, exertional dyspnoea, dizziness and malaise^{4,17,18}. In a study of 106 patients in India, hypertension was the most common mode of presentation (51.3%) and was detected in 82 patients (77.4%) at the time of presentation. Other presentations include vascular bruits which were heard in 72 patients (67.9%), while 13 (12.3%) patients were found to be in congestive heart failure²⁰. In Beijing, 530 patients were studied,

of whom 60% had hypertension, 57.5% had vascular bruits in the upper abdomen, 47.4% had carotid bruits, 37.2% had pulse deficit at the extremities and 24.7% had intermittent claudication²⁵. In essence, the affected lesions vary in different countries and therefore present differently.

The differences in clinical presentation based on geographical distribution are summarised in **Table 1**.

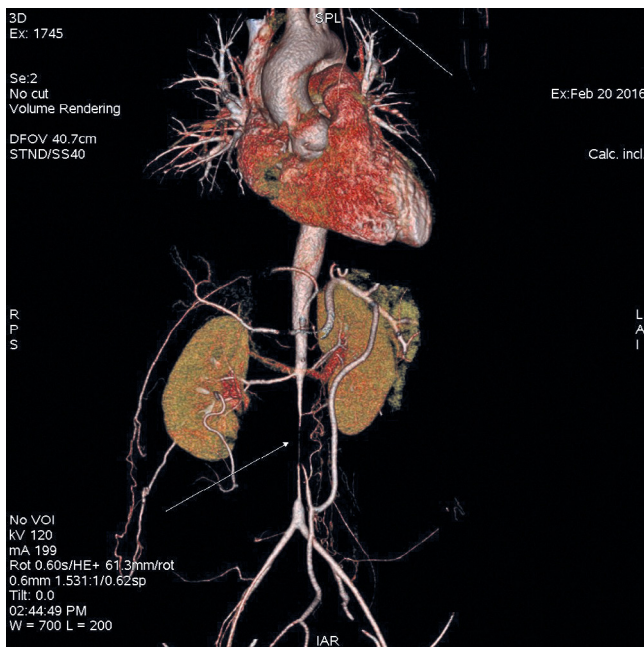


Figure 3. A 23-year-old female with stenosis of the descending abdominal aorta with collaterals from celiac to inferior mesenteric artery.

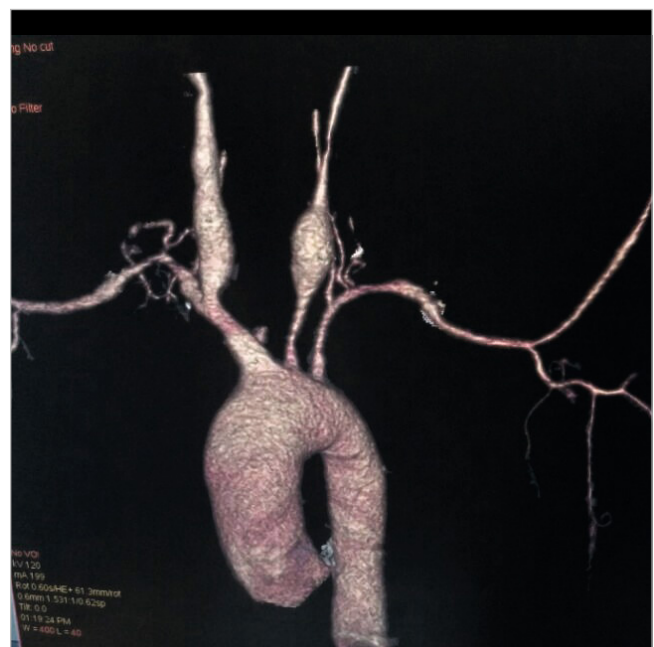


Figure 4. A CT aortogram showing bilateral common carotid artery aneurysms.

Table 1. Common presentation of Takayasu's arteritis.

| Country | Symptoms | Site of affected lesions |
|------------------------|---|---|
| Korea ¹⁷ | <ul style="list-style-type: none"> – Headache (60%) – Exertional dyspnoea (42%) – Dizziness (36%) – Malaise or weakness (34%) – Hypertension | <ul style="list-style-type: none"> – Abdominal aorta (46%) – Descending thoracic aorta (37%) – Ascending aorta (1%) – Aortic arch (2%) |
| Japan ^{16,23} | <ul style="list-style-type: none"> – Aortic regurgitation (22.6%) – Ischaemic heart disease (8.5%) – Visual disturbances/loss (2.8%) | <ul style="list-style-type: none"> – Thoracic aorta (41.5%) – Abdominal aorta (31.1%) – Moderate to severe aortic regurgitation (22.6%) – Renal artery lesions (21.7%) – Coronary lesions (8.5%) – Pulmonary artery lesions (4.7%) |
| India ¹⁹ | <ul style="list-style-type: none"> – Hypertension (51.3%) – Vascular bruit (67.9%) – Congestive heart failure (12.3%) | <ul style="list-style-type: none"> – Type I (branches of aortic arch) (6.6%) – Type II (aortic arch, its branches and descending thoracic aorta) (6.6%) – Type III (descending thoracic aorta and abdominal aorta) (3.8%) – Type IV (abdominal aorta only) (27.3%) – Type V (aortic arch, descending thoracic aorta and abdominal aorta) (55.7%) |
| China ²⁴ | <ul style="list-style-type: none"> – Hypertension (60%) – Vascular bruits upper abdomen (57.5%) – Carotid bruits (47.4%) – Pulse deficit (37.2%) – Intermittent claudication (24.7%) | <ul style="list-style-type: none"> – Type I (20.8%) – Type II (37.1%) – Type III (42.1%) – Type IV (52.3%) |

DIAGNOSIS

The first set of diagnostic criteria for TA was initially established by Ishikawa in 1988. This was then replaced by a new set of criteria by the American College of Rheumatology (ACR) in 1990²⁶. The current ACR classification consists of six criteria: (1) onset at age less than or equal to 40 years, (2) claudication of an extremity, (3) decreased brachial artery pulse, (4) greater than 10 mmHg difference in systolic blood pressure between arms, (5) a bruit over the subclavian arteries or the aorta, and (6) arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities. The presence of at least three of the six criteria was found to have demonstrated a sensitivity of 90.5% and a specificity of 97.8%²⁶.

A modification to the 1988 Ishikawa criteria by Sharma et al was validated and compared to the ACR 1990 criteria in a small Indian population (n=106) with a reported higher sensitivity (96% vs. 77.4%) and similar specificity²⁷. However, this has not been validated in other populations/studies; the ACR criteria remain the most widely used in studies and clinical practice^{14,28-31}.

The current “gold standard” investigation is digital subtraction angiography (DSA); however, it is invasive and only identifies late, structural changes in the vasculature³². Angiographic findings can be classified into six types, according to the vessels involved (**Figure 5**)^{33,34}. Additionally, involvement of the coronary and pulmonary arteries is indicated as C (+) or P (+), respectively. Type V has been documented as the most common type³⁵.

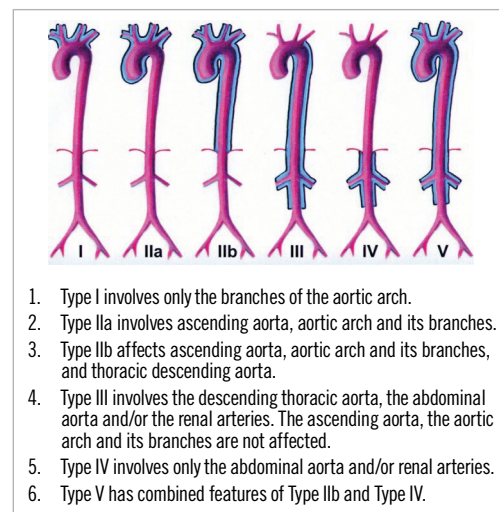


Figure 5. Angiographic types of Takayasu's arteritis.

Recent advances in non-invasive vascular imaging, on the other hand, have provided new insights into TA²⁶. Contrast-enhanced computed tomography angiography and magnetic resonance angiography are useful in demonstrating vascular anatomy, wall enhancement, oedema, as well as thickening, which might enable early disease detection while the luminal diameter is still preserved. 18F-fluorodeoxyglucose positron emission tomography has also been found to provide important additional information by highlighting areas of increased metabolic activity and is therefore useful to detect inflammation with a reported high sensitivity and specificity in TA, allowing diagnosis of early pre-stenotic disease^{36,37}. However, there are limitations with this technique, which include a lack of standardised technique for quantification of uptake, limited availability, and lack of reliable evidence for evaluation of disease activity³⁸. Histological diagnosis of TA includes granulomatous arteritis with infiltration of Langhans giant cells in the media with smooth muscle cell necrosis and destruction of the internal elastic membrane³⁹.

TREATMENT OPTIONS

Current treatment options include medical therapy, endovascular intervention and surgical vascular reconstruction. Briefly, the modality of treatment is largely dependent on the individual patient's clinical course and extent of disease activity. Patients who present during the active stage of the disease require corticosteroids and immunosuppressive agents to curb the systemic and vascular inflammatory response, whereas patients who have either

progressed into or present during the chronic phase of TA may require revascularisation, either by an endovascular or by an open approach, for haemodynamically significant arterial lesions⁴⁰.

MEDICAL TREATMENT

The administration of corticosteroids and other immunosuppressive agents has demonstrated positive anti-inflammatory effects in a majority of patients with TA¹. Although glucocorticoids have long been considered the mainstay of treatment for TA due to excellent initial response rates of 40-93%, sustained remission is maintained in only 28% of cases and up to 80% of patients experience steroid-related adverse effects^{1,5,28,41-43}. Immunosuppressive drugs such as cyclophosphamide, methotrexate and azathioprine are usually added due to glucocorticoid resistance, relapse upon reduction of glucocorticoid dose or serious side effects from steroid therapy¹. About 40% of all steroid-resistant patients respond to the addition of cytotoxic agents²⁸. Although remission can be achieved in the majority of patients with immunosuppression, over 90% have some form of relapse¹².

Biologic agents such as anti-TNF- α agents, anti-IL-6R, anti-CD20, anti-IL-12/23 p40, and the soluble CTLA4 receptor fusion protein have recently been used in patients with resistant TA, including those patients who fail to achieve remission despite glucocorticoid steroids and other immunosuppressive therapy. A recent meta-analysis in 2014, based on three small randomised controlled trials, showed that anti-TNF agents (infliximab, etanercept and adalimumab) are not effective in the ability to induce remission or reduce the amount of corticosteroids required⁴⁴. However, the same meta-analysis also observed that data from numerous case series suggested that tocilizumab and infliximab may be effective in the management of large vessel vasculitis and refractory TA⁴⁴, with 37-67% of patients achieving complete remission and 53% having a partial response⁴⁵⁻⁴⁷. Adverse events such as infections and hypersensitivity in approximately 20% of patients result in discontinuation of anti-TNF- α therapy⁴⁵.

INTERVENTION

TIMING

Intervention in TA is often challenging due to the complexity of the lesions and the high rates of restenosis. Approximately 20% of patients are resistant to any kind of medical treatment^{28,46}. This in turn leads to the need for endovascular or surgical interventions, which are usually recommended at a time of quiescent TA^{10,28,29}. This can be achieved by opting to revascularise patients during the chronic inactive phase or by administering preprocedural immunosuppression, which has been found to lower restenosis rates^{24,28,48,49}. Studies have demonstrated that both endovascular and open surgery during active TA were associated with a higher incidence of arterial complications as well as the need for repeat revascularisation^{10,28,29,50}. Therefore, assessment of disease activity plays an important role in determining the optimal timing for revascularisation. Clinical symptoms coupled with haemoglobin levels, erythrocyte sedimentation rate (ESR)

and C-reactive protein (CRP), as well as radiological imaging (e.g., CT angiography, magnetic resonance angiography, 18F-FDG positron emission tomography), can be used for assessment of disease activity^{28,36,51}.

INDICATIONS AND PATIENT SELECTION

Broadly speaking, the decision to intervene in TA has to be individualised based on the anatomic location of disease of each patient. For each lesion, i.e., renal artery stenosis, subclavian artery stenosis or aortic regurgitation, the decision to intervene is based on standard indications (**Table 2**)². Indications for intervention are generally the presence of haemodynamically significant lesions, such as hypertension caused by severe renal artery stenosis, severe limb claudication, progressive aneurysm enlargement, cerebrovascular ischaemia or critical stenosis of three or more cerebral vessels, coronary artery ischaemia, moderate to severe aortic regurgitation and severe aortic coarctation^{5,16,52}. For abdominal aneurysms, the indications are similar to those due to atherosclerosis and connective tissue disease. There are no other special situations that will alter the indication for surgery². Patients with two or more major complications of TA, defined as Ishikawa's prognostic criteria stage III, were noted to derive the most benefit from revascularisation as compared to those with less extensive disease^{52,53}.

Table 2. Intervention of Takayasu's arteritis based on organ involvement^{5,15,51}.

| Anatomy | Intervention | Indication for intervention |
|---|--|--|
| Aorta | 1) Open surgery 2) Percutaneous endovascular repair | – Progressive aneurysm enlargement – Moderate to severe aortic regurgitation – Severe aortic coarctation |
| Renal artery stenosis | 1) Percutaneous angioplasty 2) Open surgery/reconstruction | – Hypertension |
| Coronary artery stenosis | 1) Percutaneous intervention with drug-eluting stent and immunosuppressive steroids 2) CABG | – Coronary artery ischaemia |
| Carotid and subclavian artery occlusion | 1) Open surgery 2) Percutaneous angioplasty | – Severe limb claudication – Cerebrovascular ischaemia – Critical stenosis of 3 or more cerebral vessels |

ENDOVASCULAR VERSUS OPEN APPROACH

Currently there are no clear guidelines regarding the selection of endovascular versus open surgical intervention in TA patients with chronic inactive disease. The decision hinges on many factors including the anatomy of the lesion, local practices and expertise, and perioperative risk.

In general, a number of case control and cohort studies have reported lower restenosis rates for patients who underwent open

surgery as compared to an endovascular approach^{24,28,31,41,54,55}. A review of recent comparative studies published from 2007 to 2015 showed that 15-50% of patients who underwent surgery had recurrent disease requiring revision surgery after 5-20 years. For endovascular interventions, the restenosis rates ranged from 17-70% at 5-10 years. Conversely, a small US cohort study in 2009 found that treatment of late inactive stage TA lesions with either just angioplasty or angioplasty with stenting resulted in excellent to good clinical improvement at follow-up at 46.8 months⁵⁶. Symptom recurrence occurred in 31.4%, which was then successfully treated with repeat angioplasty and stenting⁵⁶. The contrasting, limited and retrospective evidence suggests that there may not be a “one size fits all” approach to revascularisation. Instead, each patient and lesion must be evaluated individually to determine the best mode of revascularisation.

In the modern era, survival rates for patients undergoing either open or endovascular revascularisation are generally good: 94.3% at 6.5 years and 73.5% at 20 years^{10,24,29,50,52}. According to Saadoun, the rates of early complications (<30 days) of surgical and endovascular procedures were similar in terms of restenosis, thrombosis and stroke²⁸. However, in terms of late complications (>30 days), endovascular procedures had slightly higher rates of restenosis at 64.5% compared to 46.1%, while surgical procedures had higher rates of thrombosis (15.4% versus 3.2%)²⁸. For surgically treated patients, it is important to identify a disease-free area of artery for the bypass graft anastomosis, to prevent the development of anastomotic strictures and/or the formation of pseudoaneurysms postoperatively⁵⁶. The high restenosis rates published are similar to those quoted in another recent 25-year retrospective cohort study (open surgery 44%, endovascular approach 66%, $p=0.33$)⁵⁴. This implies that, regardless of the approach, restenosis remains a frequent late complication and may necessitate repeat intervention.

RENAL ARTERY STENOSIS

The optimal approach for the treatment of Takayasu's arteritis-induced renal artery stenosis (TARAS) remains a topic for discussion, with evidence to support both endovascular and open approaches. Aortorenal bypass was shown in two earlier studies (2003-2004) to have five-year patency rates of 79% with a postoperative morbidity of 19% and 17%, respectively^{57,58}. More recently, primary angioplasty of TARAS has demonstrated procedural success of more than 90%, five-year patency of 67-91% and lower complication rates (5.7% in one study and 0% in another). Stenting is occasionally performed for ostial lesions, long-segment lesions, or incomplete dilatation of stenosis and dissection^{10,59-61}. Given the similar long-term outcomes of both approaches coupled with the reduced complication rate of endovascular techniques, angioplasty is currently favoured by most centres⁵⁰.

CORONARY ARTERY STENOSIS

Coronary stenosis in patients with TA tends to be ostial, involving the left main artery. A recent small retrospective analysis

suggests that percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) have similar long-term outcomes in patients with TA and stable disease. Patients with active TA who went for CABG had a lower incidence of major adverse cardiac events (MACE) as compared to PCI⁶². Use of periprocedural immunosuppression for three months prior to PCI has been found to maintain coronary stent patency for up to 10 years²⁴.

CAROTID AND SUBCLAVIAN ARTERY OCCLUSION

Common carotid and subclavian artery lesions in TA are often long, irregular and fibrotic. Surgical bypass has superior patency compared to endovascular intervention but with higher rates of major complications^{24,63}. Endovascular intervention is usually reserved for stenoses less than 5 cm, with initial success rates of up to 81% when combined with periprocedural immunosuppression⁶³⁻⁶⁵.

THORACIC AND ABDOMINAL AORTA

Historically, aneurysmal disease of the aorta in TA was treated with open surgery to varied outcomes⁶⁶⁻⁶⁸. In contemporary practice, it is now commonly treated with standard techniques and devices such as aortic stent grafts^{69,70}.

PROGNOSIS

A literature review revealed the overall survival at 15 years after diagnosis of TA to be 82.9%⁵³. Aortic regurgitation, retinopathy, aneurysm and secondary hypertension are associated with poorer prognosis, the presence of two or more of which led to higher five-year (69.9%) and 10-year (36.7%) mortality rates^{71,72}. Common causes of death include congestive cardiac failure, renal failure, cerebrovascular accident, and pulmonary infections.

Conclusion

Takayasu's arteritis is a chronic non-specific granulomatous vasculitis affecting the aorta and its main branches. Its presentation is different in different ethnicities and countries. Management includes medical therapy with immunosuppressive therapy during the acute phase. Surgical bypass/reconstruction or endovascular therapy may be required for haemodynamically significant or symptomatic disease during the late phase. Careful long-term follow-up is essential due to the risk of disease activation or flare-up, requiring appropriate evaluation of the diseased vessels⁵⁶.

Impact on daily practice

Endovascular interventions are recommended at a time of quiescent TA, which can be achieved by timing them during the chronic inactive phase or by administering preprocedural immunosuppression. Limited data exist but suggest that surgery results in lower restenosis rates than endovascular intervention. Primary angioplasty for TARAS is currently favoured by most centres, due to procedural success rates of more than 90% and lower complications as compared to the open approach.

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Permission for the use of the image labelled **Figure 5** was obtained from RadioGraphics.

Conflict of interest statement

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Safety and feasibility of interventional left atrial appendage closure without contrast agent



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KEYWORDS

- atrial fibrillation
- imaging modalities
- left atrial appendage
- prior stroke or transient ischaemic attack
- renal insufficiency
- transoesophageal echocardiogram

Abstract

Aims: Interventional left atrial appendage closure (LAAC) is routinely performed under both echocardiographic and angiographic guiding. However, adverse outcomes, e.g., kidney injury and cerebral embolism, might be associated with injections of contrast agent into the LAA. Therefore, this prospective registry investigated the safety and feasibility of LAAC without the support of angiographic images as the default approach.

Methods and results: This single-centre registry included a total of 46 non-selected, consecutive patients. In the first 25 patients (54%), LAAC with the Amulet device was performed routinely with LAA angiography prior to implantation and after release of the device. The following 21 patients (46%) were treated without the use of contrast agent. The combination of successful implantation and lack of procedural complications was regarded as the primary endpoint. Procedure time, number of recapture manoeuvres, change of device size, compression, leakage, dose area product and late thrombosis on the device were investigated as secondary endpoints. Besides the longer fluoroscopy time and duration of the procedure in the group using angiography, no significant differences could be found. Major complications occurred equally often in both cohorts.

Conclusions: Interventional LAAC with the Amulet device can be performed safely without the use of contrast agent. This approach might help to enhance the use of LAAC in patients at high risk of contrast-induced nephropathy and procedural stroke.

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Abbreviations

| | |
|-------------|-----------------------------------|
| AF | atrial fibrillation |
| CKD | chronic kidney disease |
| CT | computed tomography |
| LAA | left atrial appendage |
| LAAC | left atrial appendage closure |
| NOAC | novel oral anticoagulants |
| OAC | oral anticoagulation |
| LCx | left circumflex coronary artery |
| TOE | transoesophageal echocardiography |
| TSP | transseptal puncture |

Introduction

Atrial fibrillation is the underlying cause of 15-20% of all strokes, with more than 90% of these resulting from thromboembolic events originating in the left atrial appendage (LAA)¹. Oral anticoagulation (OAC) has been shown to be very effective in preventing these thromboembolic events²⁻⁴. However, a significant number of patients at risk for embolic stroke are not treated properly with OAC for various reasons including poor compliance or high risk of bleeding events^{5,6}. Two large randomised controlled trials (PROTECT AF, PREVAIL) and data from several registries have shown that left atrial appendage closure (LAAC) is an equivalent, effective and safe concept in terms of stroke prevention in atrial fibrillation⁷⁻¹³. The results of a recent international questionnaire displayed a high level of confidence in LAAC amongst interventional cardiologists surveyed. The majority believed the procedure to be as effective as OAC in terms of stroke prevention and safer in terms of bleeding risk¹⁴.

In daily clinical practice, the majority of patients treated with LAAC have a relative or absolute contraindication to OAC, such as previous major bleeding or a high bleeding risk¹³. Another important subgroup is patients with chronic kidney disease (CKD) who are unsuitable for the novel oral anticoagulants (NOAC) and at the same time carry an elevated risk of stroke¹⁵ and bleeding events^{16,17}. This situation leads to a clinical dilemma and makes LAAC a viable option for stroke prevention in this particular subgroup. However, the use of contrast agent for angiography and/or cardiac computed tomography (CT) prior to or during LAAC poses the risk of contrast-induced nephropathy¹⁸, which might hinder the referral of these patients for LAAC and thereby leave them with a high risk of thromboembolic or bleeding events. For this special subgroup of patients, it is desirable to avoid the use of contrast agent during LAAC, as well as to abandon the CT scan prior to the procedure.

In this study we investigated the hypothesis that LAAC without angiography of the LAA and CT imaging is feasible and safe.

Methods

PATIENT POPULATION

The analysed data originate from a single-centre cohort study containing patients who underwent percutaneous LAAC, performed using the AMPLATZER™ Amulet™ Left Atrial Appendage

Occluder (St. Jude Medical, St. Paul, MN, USA) between December 2014 and January 2016. Procedure and device were approved, clinically indicated and followed the Declaration of Helsinki guidelines. Patients gave their written consent. Data evaluation was authorised by the ethics committee (Ethik-Kommission der Ärztekammer Hamburg, Bearb.-Nr: WF-32/16).

Clinical, procedural and outcome variables were collected for 46 patients. Indications for LAAC were at the implanting physician's discretion and followed the current European Society of Cardiology (ESC) and local institutional guidelines¹⁹⁻²¹, including absolute or relative contraindications to OAC or excessive risk of both bleeding and thromboembolic events.

In this study, 25 consecutive patients were treated with the use of angiography compared to 21 consecutive patients who were treated afterwards without the use of contrast agent. The change of imaging strategy from dual mode to single mode was chosen arbitrarily after an internal review of the study protocol in April 2015.

The primary endpoint was the combination of successful implantation and the lack of procedural complications (mortality, stroke/TIA/peripheral embolism, systemic embolism, pericardial effusion/tamponade, bleeding, access-related complications, or any device-related complication). Secondary endpoints were procedure time, number of recapture manoeuvres, change of device size, compression, leakage, dose area product, late thrombosis on the device and device embolism in the first three months.

CHARACTERISTICS OF THE OCCLUSION DEVICE

We focused on the AMPLATZER Amulet Left Atrial Appendage Occluder because it appeared to be a safely implantable and less traumatic device for our pilot study. It is a transcatheter self-expanding device with two flexible components, the proximal disc and the distal lobe, connected by a central waist. This device is made out of nitinol mesh with Dacron patches sewn into the lobe and disc. It is available in eight sizes (16, 18, 20, 22, 25, 28, 31 or 34 mm corpus diameter; 7.5 or 10 mm length). The diameter of the proximal disc is 6 to 7 mm larger than the lobe diameter. Depending on the device size, the Amulet lobe has 12, 16 or 20 stabilising wires to anchor in the LAA. It is installed to a delivery catheter and can be recaptured after positioning. The delivery catheter tip is blunt. The catheter also allows injection of contrast agent into the LAA and proximal to the device in order to facilitate accurate placement and angiographic assessment of leakage²².

PROCEDURE

All procedures were performed under conscious sedation by two operators with two- and three-dimensional transoesophageal echocardiography (TOE) (iE33 and EPIQ 7 ultrasound system; Philips Healthcare, Andover, MA, USA) and in 25 cases additionally with angiographic guidance (**Figure 1**). CT data were not collected in either group. After transseptal puncture (TSP) under TOE guidance, the patients received intravenous heparin in order to maintain an activated clotting time >250 seconds.

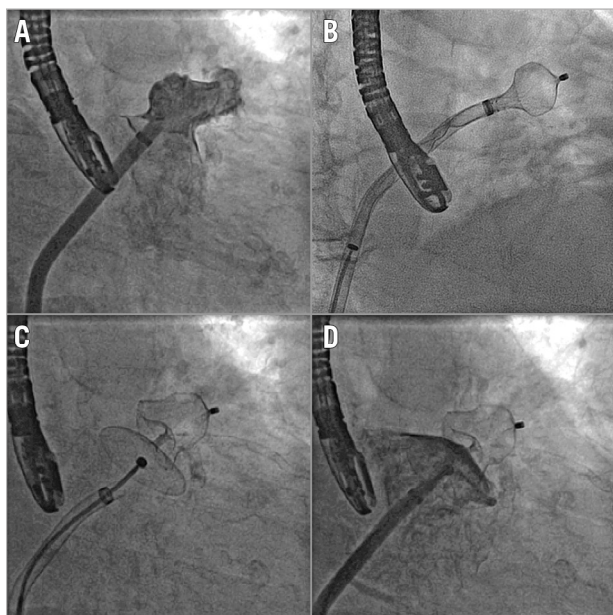


Figure 1. Fluoroscopic and angiographic imaging. A) Contrast agent application for the presentation of LAA morphology. B) Positioning the partly extended Amulet device in the landing zone. C) Full expansion of the device. D) Injection of contrast agent shows effective LAA occlusion. LAA: left atrial appendage

As recommended in the expert consensus approach described by Tzikas et al²³, the sheath was introduced into the LAA under echocardiographic and fluoroscopic guidance. In the first 25 cases contrast medium was injected through the sheath, which was positioned at the level of the LAA ostium and angiographic pictures were

recorded typically in a right anterior oblique (RAO) 30°/cranial 20° and an RAO 30°/caudal 20° view. Fluoroscopy was used in all cases.

In TOE the LAA landing zone was evaluated in multiple planes (mainly 0°, 45°, 90°, 135°) 10 mm distal to the left circumflex coronary artery (LCx), as this usually predicts the actual landing zone best suited for the Amulet device. Maximum and minimum diameters were recorded, measured edge to edge. The device size was chosen to be 3 to 5 mm larger than the mean diameter of the LAA landing zone. Additional angiographic measurements in the first cohort were comparable with the TOE measurements and did not influence the selection of device size.

A stable implantation was achieved when: a) the compression of the device lobe was sufficient, b) the axis of the device lobe was in line with the axis of the LAA neck, c) the disc was concavely shaped and affixed to the atrial wall, d) separation between the device lobe and disc was visible, e) two thirds of the device lobe was positioned distal to the LCx in the LAA, and f) the disc met manual stability criteria (pull and tug) (**Figure 2**). In the angiographic group, contrast agent was injected through the sheath to confirm the correct device positioning and the effective LAA occlusion. After meeting these criteria, the device was released (**Figure 3**). Standard post-procedural treatment included dual platelet inhibition (aspirin and clopidogrel) until control TOE after three months. Other treatment strategies were determined individually based on a higher risk of embolism.

FOLLOW-UP

All patients were scheduled for follow-up TOE and assessment of clinical endpoints three months after implantation. In the absence of device-related thrombi or peri-device leakages, patients were switched to aspirin monotherapy.

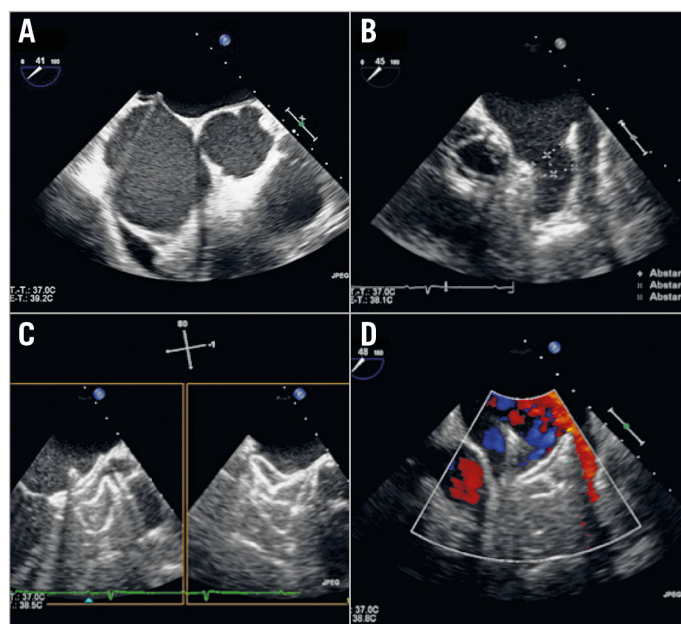


Figure 2. Transoesophageal imaging. A) Puncture needle tenting the interatrial septum in the fossa ovalis. B) Measuring landing zone diameter 10 mm distal to the LCx. C) Biplane view of implanted Amulet device. D) Colour Doppler signal showing missing flow in the LAA. LAA: left atrial appendage; LCx: left circumflex coronary artery

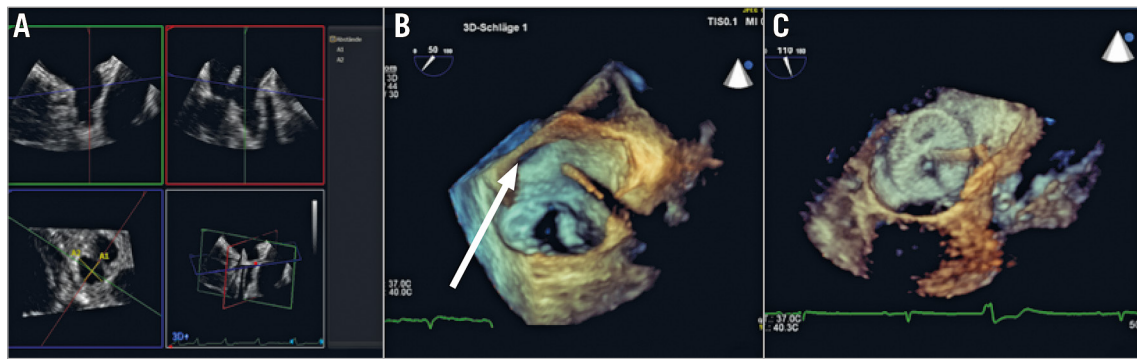


Figure 3. 3D transoesophageal imaging. A) Measurements of the landing zone diameter. B) Sheath aimed perpendicular to the LAA ostium (white arrow) after transseptal puncture. C) Successfully implanted Amulet device before release from the delivery catheter. LAA: left atrial appendage

DATA ANALYSIS

Statistical analysis was conducted using SigmaPlot 11.0 (Systat Software, Inc., San Jose, CA, USA). The results were expressed as mean±standard deviation (SD) for normally distributed data. Event rates were displayed as percentages. Continuous variables that were not normally distributed were expressed as medians. Comparisons between groups were performed using unpaired t-tests or Mann-Whitney rank-sum tests for continuous variables, and χ^2 or Fisher's exact tests for categorical variables. Results were defined to be statistically significant at a p-value <0.05.

Results

A total of 46 patients with non-valvular atrial fibrillation, $\text{CHA}_2\text{DS}_2\text{-VASc}$ score ≥ 2 and relative or absolute contraindications to OAC therapy who were treated with the Amulet device between December 2014 and January 2016 were included in the registry. The baseline characteristics are displayed in **Table 1**. Apart from age, there was no significant difference in the two analysed groups.

The device was successfully implanted in all patients (**Table 2**). The diameter of the LAA landing zone did not vary between the groups and median device size was 25 mm for both groups. The amount of contrast agent (Imeron® 350; Bracco Imaging S.p.A., Milan, Italy) used in the angiography cohort was 76 (± 50) ml. The procedure time was measured from TSP to the end of the procedure and showed a significant difference

Table 1. Baseline characteristics (n=46).

| | | LAAC with contrast agent (n=25) | LAAC without contrast agent (n=21) | Significance (p-value) |
|---|----------------|---------------------------------|------------------------------------|------------------------|
| Age, years | | 74.0±7.3 (median: 77) | 79.0±3.4 (median: 79) | 0.009 |
| Sex | Female | 8 (32.0%) | 5 (23.8%) | 0.278 |
| Atrial fibrillation | Paroxysmal | 10 (40.0%) | 9 (42.9%) | 0.536 |
| | Persistent | 10 (40.0%) | 5 (23.8%) | |
| | Permanent | 5 (20.0%) | 7 (33.3%) | |
| Sinus rhythm (at time of implantation) | | 13 (52.0%) | 13 (61.9%) | 0.513 |
| $\text{CHA}_2\text{DS}_2\text{-VASc}$ score | | 4 (median) | 5 (median) | 0.441 |
| Prior stroke (incl. TIA/ICB) | | 8 (32.0%) | 6 (28.6%) | |
| HAS-BLED score | | 4 (median) | 4 (median) | 0.588 |
| Indication | Prior bleeding | 13 (52.0%) | 9 (42.9%) | 0.549 |
| | High risk | 12 (48.0%) | 12 (57.1%) | 0.991 |

ICB: intracranial bleeding; LAAC: left atrial appendage closure; TIA: transient ischaemic attack

between groups (37.6±16.6 min vs. 27.6±9.2 min; $p=0.044$). In addition, fluoroscopy time was significantly longer in the first cohort (12.3±6.1 vs. 7.9±2.9 min; $p=0.018$). The dose area product did not vary between the cohorts (3,504±2,661 cGy/cm² vs. 2,338±2,009 cGy/cm²) (**Figure 4**).

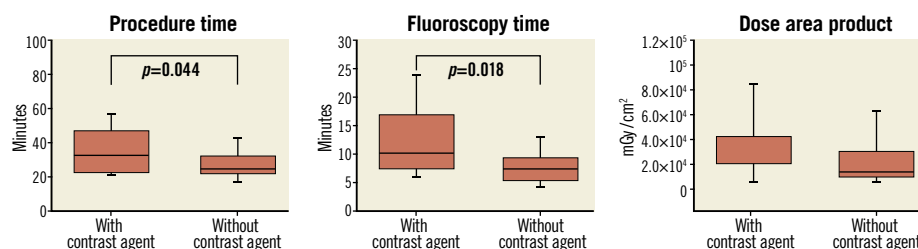


Figure 4. Comparison of procedure time, fluoroscopy time and dose area product between the groups with and without using contrast agent.

Table 2. Procedure details (n=46).

| | LAAC with contrast agent (n=25) | LAAC without contrast agent (n=21) | Significance (p-value) |
|--|---------------------------------|------------------------------------|------------------------|
| Size of device (mm) | 23.7±4.3 (median: 25) | 25.5±4.0 (median: 25) | 0.142 |
| Landing zone diameter* (mm) | 20.1±4.1 | 21.0±5.0 | 0.570 |
| Compression (%) | 17.0 | 17.6 | 0.718 |
| Dose of heparin (IU) | 9,166.7 ±2,823.3 | 9,000.0 ±2,052.0 | 0.674 |
| Successful implantation (n) | 25 (100.0%) | 21 (100.0%) | |
| Recapture (n) | 14 (56.0%) | 6 (28.6%) | 0.066 |
| Change of device size (n) | 5 (20.0%) | 2 (9.5%) | 0.339 |
| Procedure time** (min) | 37.6±16.6 | 27.7±9.2 | 0.044 |
| Amount of contrast agent (Imeron 350) (ml) | 76.2±49.7 | 0 | <0.001 |
| Fluoroscopy time (min) | 12.3±6.1 | 7.9±2.9 | 0.018 |
| Dose area product (cGy/cm ²) | 3,503.5 ±2,660.5 | 2,337.2 ±2,008.8 | 0.081 |
| Complications (n) | Total | 2 (8.0%) | 2 (9.3%) |
| | Mortality | 0 | 0 |
| | Stroke/TIA/peripheral embolism | 0 | 0 |
| | Coronary air embolism | 1 | 0 |
| | Systemic embolism | 0 | 0 |
| | Pericardial effusion/tamponade | 0 | 1 |
| | Bleeding | 1 | 1 |
| | Device-related complications | 0 | 0 |
| Discharge medication | DAPT | 23 | 19 |
| | Warfarin | 1 | 1 |
| | NOAC | 1 | 1 |

*Landing zone diameter was measured in 4 planes (0°, 45°, 90°, 135°) and mean value was calculated. **Procedure time was measured in transoesophageal echocardiography from transseptal puncture to the end of the procedure. DAPT: dual antiplatelet therapy; LAAC: left atrial appendage closure; NOAC: novel oral anticoagulants; TIA: transient ischaemic attack

In the angiography group, recapturing of the device was necessary in 14 patients (56%), in the other group in six patients (28%). Change of device size was necessary in five (20%) versus two (9%) patients.

With respect to the primary outcome, no significant difference between the two cohorts could be found. Implantation was successful in all patients and procedural complications occurred equally often, in two patients in each group (8.0 vs. 9.3%; p=0.874).

In the contrast agent cohort, one complication was an air embolism into the right coronary artery, which led to temporary

atrioventricular block III° and was managed by single-shot injection of epinephrine (0.4 mg) and atropine (1 mg). Another patient developed a relevant haematoma at the puncture site (BARC type 2).

In the group without contrast agent, one patient had a procedural pericardial tamponade which was successfully managed by pericardiocentesis. There was no repositioning of the device during the procedure. Furthermore, one patient developed post-procedural haematemesis (BARC type 3a), most likely caused by a laceration trauma from the TOE probe which was positioned in mid-oesophagus during the complete procedure. In this case, gastrointestinal bleeding was also the indication for LAAC. Endoscopy showed long-segment oesophageal ulcerations. After a fasting period, high-dose proton pump inhibitor therapy and transfusion of three packed red blood cells, healing was achieved.

The majority of patients were discharged on dual platelet inhibition (aspirin and clopidogrel). One patient in each group was still treated with warfarin and one patient in each group received NOAC because of excessive risk of embolism. Follow-up data, including TOE imaging at three months after the procedure, were available for 38 out of 46 patients (83%) and are presented in **Table 3**. Two patients in the angiography group showed cardiovascular events such as bleeding under dual platelet inhibition as did one patient in the group not using contrast agent. Neither stroke nor device embolism was documented in either cohort. Late thrombus formation on the device was documented for one patient from each group. Both patients received oral anticoagulation for at least 12 weeks. A remaining insignificant gap (<5 mm) was documented in four patients in the angiography group and in three patients in the contrast-free group. Here the medication was continued longer with aspirin and clopidogrel. All other patients were switched to aspirin monotherapy indefinitely.

Table 3. Follow-up data (n=38).

| | LAAC with contrast agent (n=21) | LAAC without contrast agent (n=17) |
|-------------------|---------------------------------|------------------------------------|
| Lost to follow-up | 4 | 4 |
| Thrombus | 1 | 1 |
| Device embolism | 0 | 0 |
| Gap | 4 | 3 |
| Stroke/TIA | 0 | 0 |
| Bleeding | 2 | 1 |

DAPT: dual antiplatelet therapy; LAAC: left atrial appendage closure; NOAC: novel oral anticoagulants; TIA: transient ischaemic attack

Discussion

This observational pilot study demonstrates that the additional use of contrast agent might not be obligatory in LAA occlusion. In our cohort, with 21 patients, the procedure was safe and feasible using fluoroscopic and echocardiographic guidance only. Furthermore, our objective is to address the simplification of LAAC by encouraging implanting physicians not only to

consider contrast-free implantation in certain patients but also to forego preprocedural CT imaging.

Several studies have found evidence that echocardiography in addition to angiography is a suitable imaging procedure for percutaneous LAAC²⁴⁻²⁶. Furthermore, it has been shown that LAAC in general is a safe procedure with an acceptable incidence of periprocedural complications. Despite the lack of randomised trials, registries have shown that Amulet devices have a favourable early outcome²⁷⁻²⁹.

Our data displayed a total complication rate of 8.7% (periprocedural and post-procedural) without a significant difference between the investigated groups. The only complication described, which might have resulted from imaging quality, was the pericardial tamponade. There is a risk of LAA injury while performing LAA angiography due to the sheath. However, this complication occurred in the group without angiographic guidance and showed no statistical significance.

A device-related complication, thrombus formation, is a well-described incident after LAAC with the Amulet device. Two patients (5.3%) out of our 38 follow-up patients revealed this adverse event, which is in line with prior published experiences from large-scale series^{30,31}. As both patients had a successful device implantation with good positioning of the plate, the imaging modalities during the procedure did not have any influence on this complication. The thrombus dissolved completely in both cases after OAC treatment. Device embolism^{32,33} did not occur in either group.

From a general perspective, a lack of increase in complications or other clinically relevant events might have been caused by the learning curve of the operators refining this implantation technique. As operators get more expertise, recapturing and changing the device size becomes less frequent, potentially lowering complication rates. However, the overall learning curve was rather flat because the operators had implanted over 100 devices before starting this study.

LAAC can dramatically lower the rate of thromboembolic events or major bleedings, which is especially important for patients with chronic kidney disease, who have a much higher risk at baseline. While a study by Kefer and al¹² did not show any significant difference in the procedural safety of LAAC (using the AMPLATZER™ Cardiac Plug; St. Jude Medical) for patients with or without prior renal impairment, it is likely that patients with critical renal function were not taken into account for the procedure. A contrast-free implantation approach might help more patients to be considered for this form of embolic protection.

In our opinion, LAAC without additional angiographic guidance should be performed for all patients who have relevant or absolute contraindications to contrast agent use and have sufficient echocardiographic imaging quality. However, angiographic assessment of LAA size and anatomy is still the gold standard and should be part of the standard approach in all suitable patients. In patients with complicated LAA anatomy, i.e., multiple lobes or poor echocardiographic imaging quality, angiography is still necessary and helpful.

Limitations

The main limitation of this study is the small number of patients which results in a low statistical power. However, this investigation was able to demonstrate that the contrast-free approach may enrich the opportunities of implantation techniques available to the implanting physicians treating patients with chronic kidney disease. Thus, it should only be performed by experienced operators.

As the main priority of this study was to demonstrate feasibility of this new technique, future studies with a greater patient collective and strict inspection of renal function parameters in a randomised fashion need to prove the benefit of our approach on kidney function.

A distinct advantage of angiography-free guidance is the absence of nephrotoxic effects associated with contrast agent. In addition, omitting injections into the LAA might reduce cerebral embolism based on spontaneous echo contrast, sludge and thrombus formation in the LAA³⁴. The study of Rillig et al shows that the number of LAA angiographies during LAAC is associated with the incidence and number of acute brain lesions³⁵. Our series was too small to draw conclusions on clinical endpoints such as periprocedural stroke. Therefore, it remains hypothetical whether neurocognitive deficits could be reduced by angiography-free guidance.

Conclusions

This observational pilot study demonstrates the safety and feasibility of interventional LAAC without the support of angiographic imaging of the LAA. However, future research with larger population groups is needed to underscore these findings and increase the statistical power.

Impact on daily practice

Patients with chronic kidney disease are frequently found in routine clinical practice. As these patients are often unsuitable for NOAC therapy but have an elevated risk of stroke and bleeding events, LAAC is an alternative. Because of relative or absolute contraindications to contrast agent, we suggest performing LAAC only with fluoroscopic and echocardiographic guidance.

Conflict of interest statement

F. Meincke and A. Ghanem received honoraria as proctors from St. Jude Medical. The other authors have no conflicts of interest to declare.

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Concurrent transcatheter transfemoral tricuspid valve-in-valve and aortic valve implantation using a 3D printed model for pre-OT planning



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KEYWORDS

- aortic stenosis
- elderly
- prior cardiovascular surgery
- TAVI
- tricuspid disease
- valve-in-valve

Abstract

Re-operation of a tricuspid bioprosthesis carries high morbidity and mortality, especially when carried out with other concomitant valvular heart surgery. Concurrent transcatheter valve implantation has evolved as an alternative option. Here we report on a 77-year-old lady who suffered from symptomatic severe recurrent stenosis of a tricuspid bioprosthesis (Sorin Pericarbon More, 27) and moderate to severe aortic stenosis (AS) who was declined for redo open heart surgery as it was deemed very high risk. We used a 3D customised printed right heart model for pre-OT rehearsal. Percutaneous V-in-V TVR using a 26 mm Edwards SAPIEN 3 was performed under general anaesthesia via the right femoral vein and showed a satisfactory result in one single attempt. We also evaluated the necessity of aortic valve intervention in detail before and after V-in-V TVR. After confirmation of severe AS, a 26 mm Medtronic CoreValve Evolut R was deployed in the non-calcified rheumatic aortic valve without any predilatation or post-dilatation via the right femoral artery. No significant gradient or leakage was seen. This case shows the feasibility and safety of concurrent transfemoral V-in-V TVR and TAVI. Rehearsal using a 3D printed model helped to increase the accuracy and success rate of the procedure. The transcatheter approach allows detailed haemodynamic assessment after each valvular intervention in the case of multiple valve interventions.

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Abbreviations

| | |
|---------------|---|
| AVA | aortic valve area |
| IVC | inferior vena cava |
| PA | pulmonary artery |
| TAVI | transcatheter aortic valve implantation |
| TVR | tricuspid valve replacement |
| V-in-V | valve-in-valve |

Introduction

Redo tricuspid valve replacement carries high morbidity and mortality. Transcatheter valve-in-valve (V-in-V) transcatheter valve replacement (TVR) has proved to be an alternative for high-risk patients. With the limited number of cases, a three-dimensional (3D) customised printed model can be used to plan and rehearse the procedure to try to increase its accuracy.

Methods

Here we report the case of a 77-year-old lady with chronic rheumatic heart disease who had undergone open heart surgery four

times. She had a closed mitral valvotomy in 1973, a mechanical mitral replacement (CM27) in 1988, TVR (Pericarbon More, 27; Sorin Group [now LivaNova], Milan, Italy) in 2007 and surgery the next day for excision of subvalvular chordae of the TVR because of chordal obstruction. A ventricular pacing ventricular sensing inhibition response and rate-adaptive (VVIR) pacemaker was implanted at the coronary sinus in 2007 for her slow atrial fibrillation. A transthoracic echocardiogram in 2011 showed severe stenosis and regurgitation of the tricuspid bioprosthesis. However, redo open heart surgery was declined by the surgeons because of very high surgical risk.

This year, she presented with decreased exercise tolerance and bilateral lower limb oedema with a subsequent transthoracic echocardiogram showing severe stenosis (mean gradient 10 mmHg) and regurgitation of the tricuspid bioprosthetic valve (**Figure 1A, Figure 1B**), moderate to severe aortic stenosis (AS) (mean gradient: 27 mmHg, AVA: 0.82 cm², AVA index: 0.63 cm²/m²) (**Figure 1C, Figure 1D**) and satisfactory mitral valve replacement (MVR) function without any leakage. Left ventricular

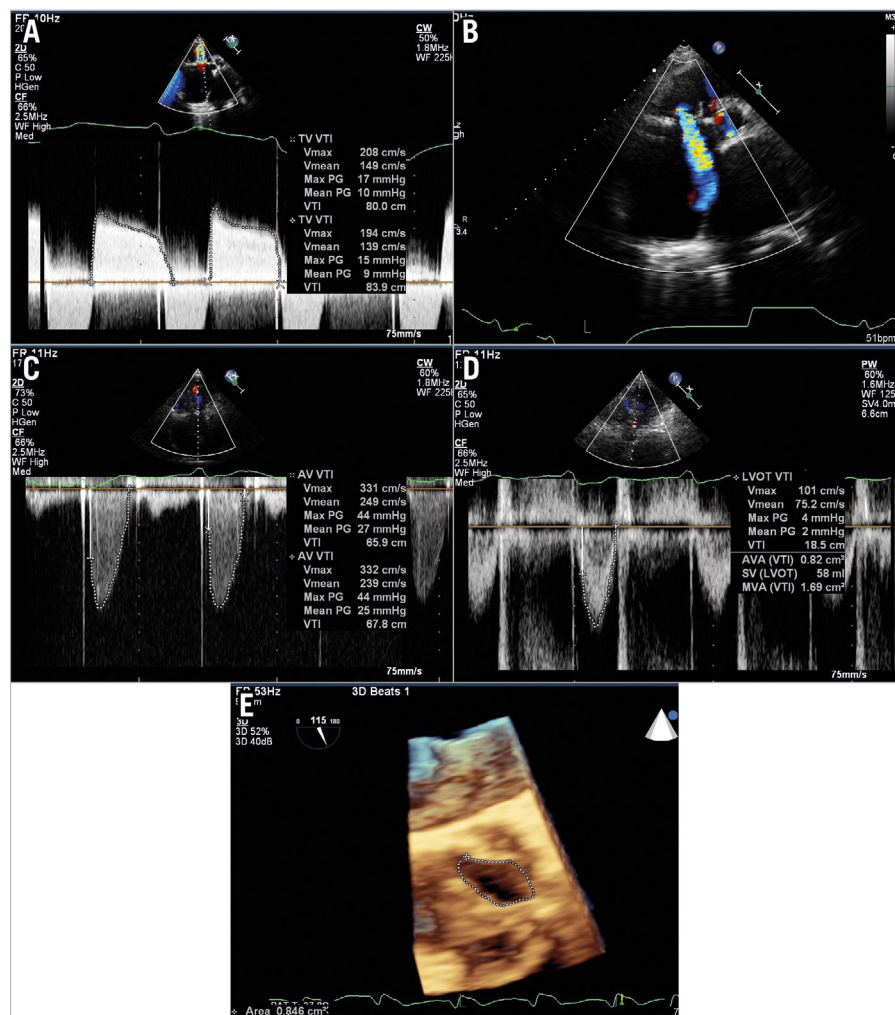


Figure 1. Baseline echocardiographic assessments. A) & B) Severe stenosis and regurgitation in tricuspid bioprosthesis. C) & D) Moderate aortic stenosis by Doppler echocardiogram. E) Planimetry of aortic valve area by 3D TEE.

function was satisfactory with an ejection fraction (EF) of 65%, as was right ventricular function. A transoesophageal echocardiogram showed rheumatic AS with doming of leaflets in systole. There was a fused commissure between the non-coronary and right coronary cusps. The planimetry of the aortic area was around 0.7 to 0.85 cm² (**Figure 1E**).

The patient was deemed to be inoperable for redo open heart surgery after discussion in the Heart Team and therefore transcatheter tricuspid V-in-V implantation ±TAVI was planned.

A computed tomography (CT) scan showed a trileaflet aortic valve and the perimeter of the aortic annulus was 64.3 mm, 22.8×17.9 mm in diameter without much calcium. The tricuspid valve bioprosthesis *in situ* had an area of 447 mm². The size of the V-in-V device could be chosen easily using the CT measurement. However, the approach and placement of the supporting wire to obtain the best coaxial plane can be difficult to judge by CT alone. A wire could be placed in the pulmonary artery or in the right ventricle if the right ventricle has enough depth. Therefore, a tailor-made 3D model of the patient's right heart was made in order to

rehearse the V-in-V procedure and to try to find the preferred wire position in order to gain a better coaxial plane between the transcatheter device and the TVR (**Figure 2**).

A transfemoral venous approach with a supporting wire in the right ventricle instead of the pulmonary artery seemed to be the preferred approach in order to obtain a better coaxial plane for V-in-V TVR implantation, taking into account the dilated right atrium and the angle between the inferior vena cava (IVC) and the right atrium. This might not fully mimic the situation in the real heart as the model was not a beating heart. However, it gave us a rough idea concerning the procedure.

Because severe AS could not be confirmed by the echocardiogram alone and there was uncertainty of change in the aortic gradient after V-in-V TVR, pre-procedure cardiac catheterisation was performed for comparison after V-in-V TVR. Cardiac catheterisation showed a mean gradient across the aortic valve of 31 mmHg, AVA 0.62 cm², AVA index 0.47 cm²/m², cardiac output of 3.41 L/min, while the mean diastolic gradient across the TVR was 8.60 mmHg and the TVR area was 0.52 cm² (**Figure 3A**).

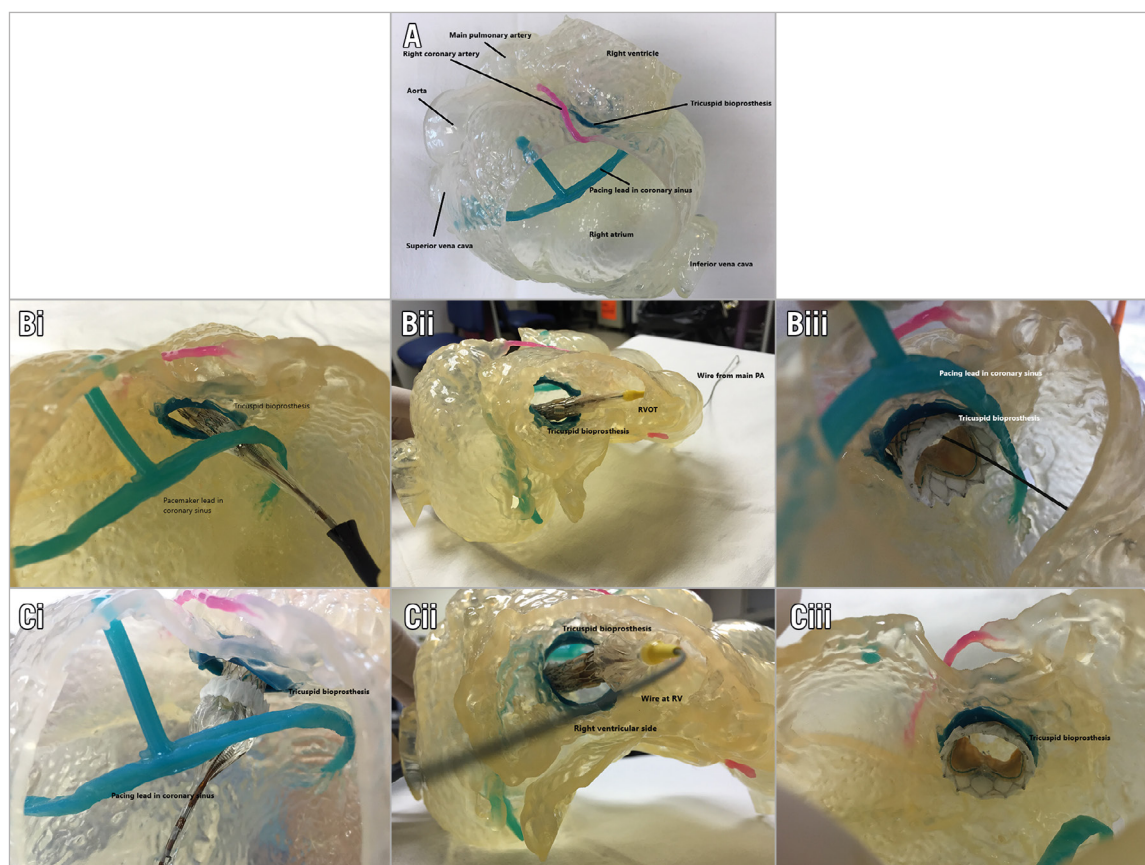


Figure 2. Rehearsal with the 3D right heart model. A) Patient's 3D right heart model showing different parts of the right heart including the tricuspid bioprosthesis and pacemaker lead. B) (i) Rehearsal: tilting (not full coaxial) of the SAPIEN 3 device if the wire is placed at the pulmonary artery (PA) and accessed from the inferior vena cava (view from the right atrium). (ii) Orientation of SAPIEN 3 device with wire at PA (view from the right ventricle). (iii) Tilting and a little gap between the SAPIEN 3 device and the bioprosthesis after deployment with wire at PA (view from the right atrium). C) (i) Rehearsal: more coaxial of the SAPIEN 3 device with the wire placed at right ventricle and accessed from inferior vena cava (view from the right atrium). (ii) Orientation of SAPIEN 3 device with the wire in right ventricle (view from the right ventricle). (iii) No tilting or gap between SAPIEN 3 and the bioprosthesis after deployment with wire placed at right ventricle (view from the right atrium).

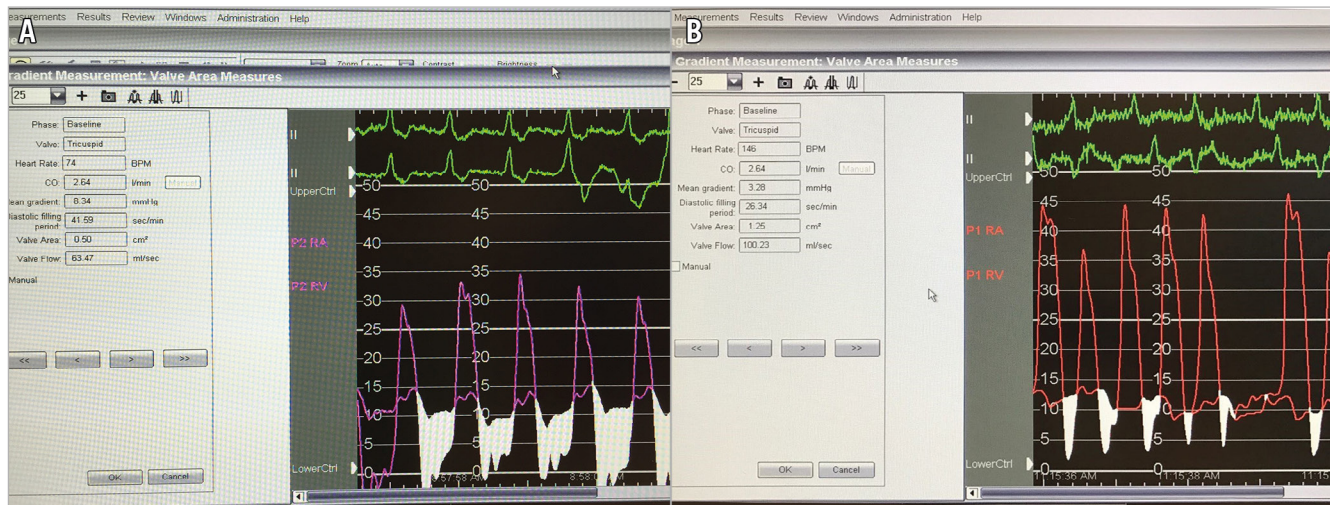


Figure 3. Haemodynamics of tricuspid valve, pre- and post-V-in-V TVR. A) Pre-V-in-V tricuspid valve replacement haemodynamic. B) Post-V-in-V tricuspid valve replacement haemodynamic.

Results

A V-in-V TVR was performed under general anaesthesia and transoesophageal echocardiographic guidance immediately after cardiac catheterisation. The TVR was crossed with a multipurpose catheter and exchanged for an extra-stiff wire in the main pulmonary artery via the right femoral vein. Predilatation with an Edwards 20 mm×4 cm balloon was carried out. Based on the area of 447 mm² on CT and the Pericarbon More 27 having an inner diameter of 23 mm, a 26 mm SAPIEN 3 device (Edwards Lifesciences, Irvine, CA, USA) was chosen. The SAPIEN 3 finally passed through the stenotic TVR but with a poor coaxial plane. Based on the result in the 3D model, the best alignment parallel to the axis of the TVR could be obtained immediately after pulling the wire to the right ventricle. The 26 mm SAPIEN 3 device was deployed uneventfully without rapid pacing (**Figure 4**) and no immediate regurgitation was seen after the deployment. Catheterisation showed that the mean diastolic gradient across the transcatheter valve (TV) was 2.41 mmHg with a TV area of 1.20 cm² (**Figure 3B**).

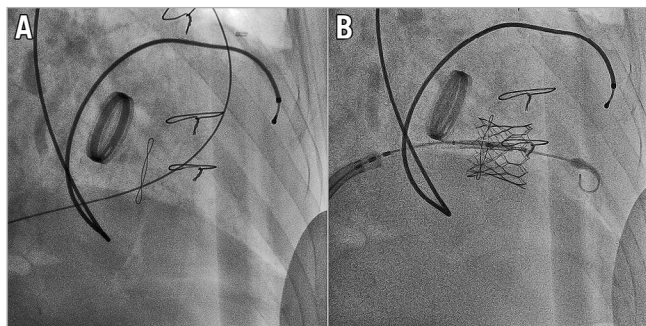


Figure 4. V-in-V TVR. A) & B) Cine images showing pre- and post-V-in-V tricuspid valve replacement using a 26 mm SAPIEN 3 device.

Re-evaluation of the aortic stenosis showed that the mean gradient had increased from 31 mmHg to 46.36 mmHg, with an AVA of 0.54 cm², and an AVA index of 0.41 cm²/m².

Concurrent TAVI was performed via the right femoral artery with confirmation of severe AS. A 3D model was not developed for TAVI even with the presence of MVR in this case, as in the CT double oblique multiplanar reconstruction (MPR) view the distance from the aortic annulus to the MVR was 11.3 mm. It was much longer than 7 mm, which has been shown to be an independent risk factor for embolisation¹. A 26 mm CoreValve® Evolut™ R (Medtronic, Minneapolis, MN, USA) was deployed directly at the aortic annulus as usual (**Figure 5**) without any pre or post balloon dilatation. There was no significant gradient or leakage across the TAVI device (**Figure 6**). The patient was discharged on post-procedure day five.

A follow-up transthoracic echocardiogram at one month showed no significant leakage or gradient across both TAVI and V-in-V TVR. The patient's functional class improved from New York Heart Association functional Class III to II.

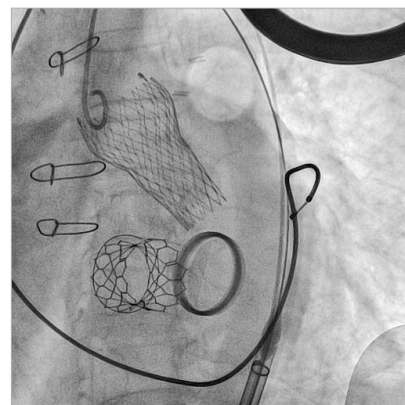


Figure 5. Deployment of a 26 mm Evolut R at the aortic valve.

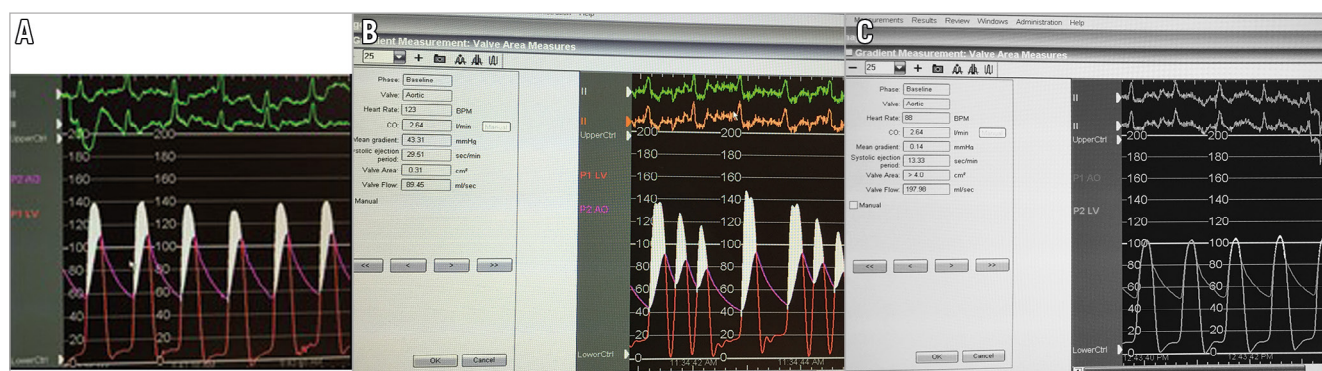


Figure 6. Pre- and post-TAVI haemodynamics. A) Before valve-in-valve tricuspid valve replacement. B) Post V-in-V tricuspid valve replacement. C) Post TAVI.

Discussion

Transcatheter valve implantation does provide a new option to patients who have had no surgical options in the past, such as our patient. This case showed the safety and feasibility of concurrent transfemoral tricuspid V-in-V implantation and TAVI. We used both the latest-generation balloon-expandable and self-expanding TAVI devices to treat different pathologies. We used the SAPIEN 3 for V-in-V TVR because the balloon-expandable devices (SAPIEN or Melody™ valve [Medtronic]) have the most evidence in the setting of V-in-V TVR². With relatively little calcium at the aortic annulus in our case, we used a self-expanding TAVI device, the Evolut R, to decrease the chance of device embolisation³.

The transcatheter approach in our patient had several advantages. Firstly, the procedure is feasible and relatively safe. Data from a valve-in-valve registry showed an ~99% success rate and few serious complications for V-in-V TVR². Secondly, we had the chance to assess the aortic valve after V-in-V TVR implantation in order to decide on the necessity of TAVI. Thirdly, recovery time was short in our patient even with two valves being treated concurrently. Detailed and accurate preprocedural planning and imaging by using a multislice CT scan with 3D reconstruction and a 3D printed model for pre-OT rehearsal are suggested to be beneficial in order to achieve good results with few complications.

Limitations

The 3D printed model was not a beating heart and the nature of the material was not exactly the same as heart tissue. However, it gave us a rough idea and the possibility of practising before the real procedure.

Conclusion

Concurrent transcatheter multiple valve implantation is possible with good outcome and allows faster recovery and a shorter hospitalisation time. Different devices fit different anatomies according to different factors such as the valve involved, bioprosthesis,

size and calcification. A 3D printed model seems to be useful to increase the accuracy of the procedure.

Impact on daily practice

Multiple transcatheter valve implantations are safe and have good outcome.

Conflict of interest statement

A. Yeung has received research grant support from Edwards and Medtronic, and is also a scientific advisor for Medtronic. The other authors have no conflicts of interest to declare.

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