AsiaIntervention
www.asiaintervention.org
Volume 1 - Number 2 - September 2015 - ISSN: 2426-3958

CORONARY INTERVENTIONS

EDITORIALS

HOW SHOULD I TREAT?

WILL THIS TRIAL CHANGE MY PRACTICE?

EDITORIAL

WILL THIS TRIAL CHANGE MY PRACTICE? | *Proceedings of* asia PCR Singapore Live

CORONARY INTERVENTIONS

HOW SHOULD I TREAT?

Your daily practice companion

Discover the revamped EuroIntervention iPad edition!

Enjoy the following features:

- Quick and intuitive navigation: browse journal articles, figures, tables, multimedia links and supplementary content
- Fully integrated application
- Rich and valuable, up-to-date content
- Automatically downloadable issues and articles when online

EIJ EuroIntervention

iOS

PCR Innovation in education at work

Aims and scope

AsiaIntervention Journal is an international, English language, peer-reviewed journal whose aim is to create a forum of high quality research and education in the field of percutaneous and surgical cardiovascular interventions.
It is released twice, in paper and electronic formats. AsiaIntervention will apply for indexation in Science Citation Index® (ISI), SciVerse Scopus, MEDLINE®/PubMed®.

Advertising information
Orders and enquiries can be sent to Europa Digital & Publishing.

Orders, claims, and journal enquiries
Please contact Europa Digital & Publishing.

Photocopying
Single copies of single articles may be made for personal use as allowed by national copyright laws. Permission from the publisher and the payment of a fee is required for all other photocopying.

Derivative works
Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission from the publisher is required for resale or distribution outside the institution.
For all other derivative works permission should be sought from the publisher.

Electronic storage or usage
Permission from the publisher is required to store or use electronically any material contained in this journal, including any article or part of an article. Please contact Europa Digital & Publishing.

Notice
No responsibility is assumed by the publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material.
Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made of it by its manufacturer.

Disclaimer
The publishers and editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the publisher and editors, neither does the publication of advertisements constitute any endorsement by the publisher and editors of the products advertised.

Europa Digital & Publishing
19, allées Jean-Jaurès – BP 61508
31015 Toulouse cedex 6 – France
Fax: +33 5 61 42 00 09
asiaintervention@asiaintervention.org

Author's instructions

All articles should be submitted to submission@asiaintervention.org

A full version of the instructions can be found and downloaded on the website: www.asiaintervention.org

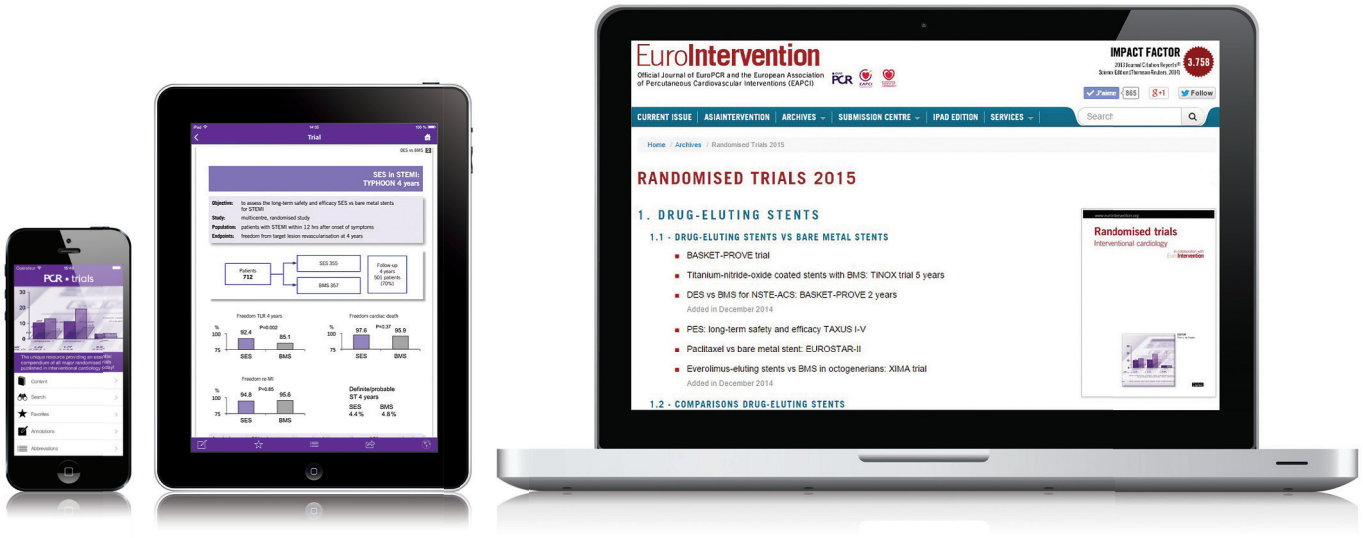
AsiaIntervention will consider submissions for possible publication in the following formats:

– Original research papers (clinical and pre-clinical/experimental)
– Expert reviews
– Letters to the Editor
– Special reports
– How should I treat
– Image in cardiology

All submissions must be accompanied by a cover letter.

Your daily practice companion

NEW! Discover the updated app
21 new clinical trials available



PCR trials

Free app!

Available on the App Store

www.eurointervention.org

The PCR trials free iOS app and website gather 295 trials extracted from publication over the 2010-2015 period in:

- The New England Journal of Medicine
- The Lancet
- The Journal of the American Medical Association
- Circulation
- The Journal of the American College of Cardiology
- European Heart Journal
- Annals Internal Medicine
- Circulation: Cardiovascular Interventions
- JACC: Cardiovascular Interventions
- EuroIntervention

Made available thanks to an unrestricted educational grant from Boston Scientific
Advancing science for life™

PCR Innovation in education at work

AsiaIntervention Journal

ASIAINTERVENTION
Publication : 2 numéros par an
Volume 1 - N°2 - septembre 2015

Directeur de la publication :
Marc Doncieux

Responsable éditorial :
Paul Cummins
p.cummins@eurointervention.org

Assistantes éditoriales :
Sylvie Lhoste
slhoste@eurointervention.org
Wendel van der Sluis
wvandersluis@eurointervention.org

Coordination éditoriale :
Véronique Deltort
Sheldon Heitner
Isabelle Uzielli
Sonia Morcuende

AsiaIntervention.org
Ronnie Lassiaille
Gregori Despeaux
Coralie Massonnié
Davy Bonnafous
Yann Szevo

Direction artistique :
Siobhan Royer-Hardy

Graphisme et mise en page :
Groupe Composer : 2, impasse du Ramier des Catalans
CS 38503
31685 Toulouse Cedex 6 - France

Editeur :
Frédéric Doncieux

Gérant : Marc Doncieux.
Principal actionnaire : Europa Organisation.
ISSN : 2426-3958
Dépôt légal à parution

AsiaIntervention est édité par la Société Europa Digital & Publishing, S.A.R.L. au capital de 8 000 euros, siège social : 19, allées Jean-Jaurès, 31000 Toulouse, France ; RCS Toulouse 411 134 489, APE 5814 Z.

11TH AICT

ASIAN INTERVENTIONAL CARDIOVASCULAR THERAPEUTICS

THE OFFICIAL CONGRESS OF APSIC

NOVEMBER 13-14, 2015

Pan Pacific Sonargaon Hotel
Dhaka, Bangladesh

WWW.AICT-CONGRESS.COM

ASIAN INTERVENTIONAL CARDIOVASCULAR THERAPEUTICS (AICT)

THE OFFICIAL CONGRESS OF THE ASIAN PACIFIC SOCIETY OF INTERVENTIONAL CARDIOLOGY

AsiaIntervention 2015;1:89-90

Perspectives on cardiovascular interventions in Asia

Runlin Gao*, *Chief Editor*

Fu Wai Hospital, Department of Cardiology, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Beijing, China

Asia accounts for over 60% of the world population. Alongside its tremendous economic development, the Asian region has experienced the most rapid expansion in interventional cardiology worldwide: approximately 1.2 million percutaneous coronary interventions (PCI) performed in 2014; broad use and good immediate and long-term outcomes of percutaneous treatments for congenital atrial or ventricular septal defect and patent ductus arteriosus (PDA); the introduction of novel techniques and devices, such as transcatheter aortic valve replacement (TAVR), MitraClip (Abbott Vascular, Santa Clara, CA, USA) implantation, left appendage occlusion, and the Parachute® device (CardioKinetix Inc., Menlo Park, CA, USA) to isolate the malfunctioning left ventricular portion in ischaemic heart failure, among others.

Research and development (R&D) of interventional devices has also been unfolding at an unprecedented rate in Asia. Beyond the long-standing R&D centres in Japan for angiography devices such as catheters, guidewires, balloons, stents, drug-eluting stents (DES), and microcatheters (notably those used to treat chronic total occlusion [CTO]), recently, in China and India, we have witnessed the active development of drug-eluting stents (DES), biodegradable polymer DES, fully biodegradable scaffolds and TAVR devices. Biodegradable sirolimus-eluting scaffolds developed in China are undergoing clinical trials, and a safe and effective self-expandable TAVR device manufactured in China is awaiting approval from the Chinese Food and Drug Administration (CFDA).

The expansion in interventional procedures has also fuelled significant clinical and basic research, as is evidenced by the many high-quality papers originating from the Asian region which have been published in world-renowned journals. Several CTO techniques[1] masterminded by Japanese scholars have been adopted worldwide, and Korea is a global leader in PCI of left main (LM) coronary artery disease[2,3].

Years of research have provided insight into differential features of cardiovascular disease in Asia. For instance, as compared to Caucasians, Asians have a significantly smaller coronary artery diameter[4]; symptomatic South Asians appear to have more aggressive and diffuse arterial calcification despite similar conventional risks for coronary artery disease[5]; Chinese patients with degenerative aortic valve stenosis presenting for TAVR have a higher frequency of bicuspid valve morphology, and high aortic valve calcium burden, even in tricuspid disease[6]; and East Asian patients have a similar or even lower rate of ischaemic events after PCI, despite a higher level of platelet reactivity during dual antiplatelet therapy, the so-called "East Asian paradox"[7]. Furthermore, despite its worldwide distribution, aortoarteritis (Takayasu arteritis) is most commonly known to occur in Asians[8,9].

The particularities of cardiovascular diseases in Asia have promoted very active and promising research on the underlying differential mechanisms and treatment strategies, which are not only of local and regional but also of global relevance. The massive and

*Corresponding author: Department of Cardiology, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Fu Wai Hospital, Beijing 100037, China. E-mail: gaorunlin@citmd.com

DOI: 10.4244/AsiaInterv_V1I2A15

increasing cardiovascular disease burden in Asia also poses formidable research, clinical and socioeconomic challenges. In China, for instance, cardiovascular disease is the leading cause of death, accounting for 41% of mortality[10]. The burden of cardiovascular diseases in Asia can be multifaceted, as is exemplified by valvular disease, the increasing prevalence of which reflects that of a degenerative aetiology with the aging of the population in addition to the persisting background of a rheumatic aetiology in some countries. The heavy cardiovascular disease burden often renders healthcare resources insufficient in many parts of Asia, warranting cost-effective therapy particularly tailored to Asian patients. Guidelines or expert consensus which meet the needs and characteristics of Asians should be established, and academic exchanges and collaboration are essential to address these challenges more effectively.

The Asian Pacific Society of Interventional Cardiology (APSIC) continues to play an important role in fostering academic collaborations throughout the region[11]. AsiaIntervention, a new journal particularly focused on scientific contributions from the Asia region, has been launched officially and is successfully running with the assistance of the Editorial Office of EuroIntervention, under the guidance of Professor Patrick Serruys, the Senior Consulting Editor to the Chief Editors. Two issues will be published in 2015 and four are planned for 2016. AsiaIntervention aims to contribute further to the development of interventional cardiology in Asia by being a helpful friend to Asian cardiovascular interventionalists and by providing a unique publication venue and a much needed platform for academic exchanges within Asia and between Asia and other parts of the world. Through this and other means, the rapid expansion into a glorious future for interventional cardiology in Asia will continue unabated.

Conflict of interest statement

The author has no conflict of interest to declare in relation to this editorial.

References

1. Inohara T, Kohsaka S, Miyata H, Ueda I, Hayashida K, Maekawa Y, Kawamura A, Numasawa Y, Suzuki M, Noma S, Nishi Y, Fukuda K. Real-World Use and Appropriateness of Coronary Interventions for Chronic Total Occlusion (from a Japanese Multicenter Registry). *Am J Cardiol.* 2015;116:858-64.

2. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Chung CH, Lee JW, Lim DS, Rha SW, Lee SG, Gwon HC, Kim HS, Chae IH, Jang Y, Jeong MH, Tahk SJ, Seung KB. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med.* 2011;364:1718-27.

3. Park DW, Seung KB, Kim YH, Lee JY, Kim WJ, Kang SJ, Lee SW, Lee CW, Park SW, Yun SC, Gwon HC, Jeong MH, Jang YS, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, Park SJ. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. *J Am Coll Cardiol.* 2010;56:117-24.

4. Dhawan JL, Bray CL. Are Asian coronary arteries smaller than Caucasian? A study on angiographic coronary artery size estimation during life. *Int J Cardiol.* 1995;49:267-9.

5. Koulaouzidis G, Nicoll R, Charisopoulou D, McArthur T, Jenkins PJ, Henein MY. Aggressive and diffuse coronary calcification in South Asian angina patients compared to Caucasians with similar risk factors. *Int J Cardiol.* 2013;167:2472-6.

6. Jilaihawi HL, Wu Y, Yang Y, Xu L, Chen M, Wang J, Kong X, Zhang R, Wang M, Lv B, Wang W, Xu B, Makkar RR, Sievert H, Gao R. Morphological characteristics of severe aortic stenosis in China: imaging corelab observations from the first Chinese transcatheter aortic valve trial. *Catheter Cardiovasc Interv.* 2015;85:752-61.

7. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC Jr. World Heart Federation expert consensus statement on antiplatelet therapy in east asian patients with ACS or undergoing PCI. *Glob Heart.* 2014;9:457-67.

8. Koide K. Takayasu arteritis in Japan. *Heart Vessels Suppl.* 1992;7:48-54.

9. Liu LS, Zheng DY. Aortoarteritis: a report of 480 cases. *J Hum Hypertens.* 1990;4:135-7.

10. Hu SS, Kong LZ, Gao RL, Zhu ML, Wang W, Wang YJ, Wu ZS, Chen WW, Liu MB; Editorial Board. Outline of the report on cardiovascular disease in China, 2010. *Biomed Environ Sci.* 2012;25:251-6.

11. Tan HC. The role of the Asian-Pacific Society of Interventional Cardiology (APSIC) in the future of interventional cardiology. *AsiaIntervention.* 2015;1:10-1.

AsiaIntervention 2015;1:91-92

Biodegradable or durable polymer: more data required

Andrew T. L. Ong*, MBBS, PhD, FRACP

Department of Cardiology, Westmead Hospital, Westmead, NSW 2145, Australia

In this issue of AsiaIntervention, Wan Azman Wan Ahmad reports on the final five-year results of the BEACON II clinical registry, a 497-patient real-world, all-comers registry conducted at 12 Asia Pacific sites[1]. This single-arm study followed up patients in whom BioMatrix (Biosensors Europe SA, Morges, Switzerland) Biolimus A9-eluting stent(s) were implanted. Biolimus A9 is an analogue to sirolimus, and is released from a biodegradable polymer, polylactic acid (PLA), applied to the abluminal surface of the stent.

Article, see page 102

This trial was predominantly conducted in Asia with nine sites, with the remaining three sites located in the Pacific. Historically, most drug-eluting stent trials were US-centric and/or Eurocentric, mirroring the headquarters of the drug-eluting stent companies. Companies, for regulatory purposes or otherwise, have recognised that Asian patients may be different from Caucasian patients: therefore, information regarding their response to drug-eluting stents may provide new insights[2]. To date, company-sponsored stent trials in Asia have generally been registries. This is the second contemporary report to be published in AsiaIntervention, after the RESOLUTE ASIA Registry[2]. As the specialist interventional cardiology journal of the region, it is a privilege for both the authors and the journal to be able to publish trials pertinent to the audience and the patients in this region.

Remarkably for a registry, clinical follow-up was available for 94% of the population at five years. The most striking finding in this registry is the low definite stent thrombosis rate of 0.8% at one year, and a cumulative incidence of 1.2% at five years, with an incidence of 0.4% from years one to five[1].

The authors emphasise the biodegradable polymeric system as being the principal reason for the low observed rate of very late stent thrombosis. As we move into the second decade of drug-eluting stents, the use of biodegradable polymers in drug-eluting stent systems has become a popular choice over durable polymers **(Table 1)**. This move was an industry response to the clinical and pathological findings of the first generation of drug-eluting stents, in which a significant inflammatory response was associated with the use of durable polymers[3]. It is worth noting that human post-mortem studies of second-generation systems utilising durable polymers demonstrate a lack of the inflammatory response seen with earlier stents[4].

The largest trial utilising the BioMatrix stent was the LEADERS trial. The five-year results demonstrated a lower incidence of definite stent thrombosis when compared to the durable polymer-coated sirolimus-eluting stent (2.6% vs. 4.5%, respectively, p=0.06)[5]. When a landmark analysis was performed at one year, there was a significant reduction in late stent thrombosis (0.66% vs. 2.5%, respectively, p=0.003). A meta-analysis of biodegradable versus durable polymers also suggested that there was a benefit of the former in the reduction of late stent thrombosis[6].

One must interpret the results with the utmost caution, as the devices compared were completely different. It is well understood that the efficacy of a particular device is a triangular synergy among the platform (the stent), a carrier (usually a polymer), and an agent (a drug)[7]. As such, any valid comparison would have to differ in only

**Corresponding author: Department of Cardiology, Westmead Hospital, Westmead, NSW, 2145, Australia. E-mail: AndrewTLOng@gmail.com*

DOI: 10.4244/AsiaIntery_V1I2A16

Table 1. List of drug-eluting stents from the major manufacturers.

Biodegradable polymer	Durable polymer
BioMatrix (Biolimus A9™**)	Promus PREMIER™¶/Element™¶ (everolimus)
SYNERGY™¶ (everolimus)	Resolute Onyx™§/Integrity™§ (zotarolimus)
Orsiro¶¶ (sirolimus)	XIENCE Xpedition®* (everolimus)
Nobori®§§ (Biolimus A9)	
Ultimaster®§§ (sirolimus)	
Absorb*/Absorb GT1* (everolimus)	

*Abbott Vascular, Santa Clara, CA, USA; **Biosensors Europe SA, Morges, Switzerland; ¶Boston Scientific Corp., Marlborough, MA, USA; ¶¶Biotronik, Bülach, Switzerland; §Medtronic, Minneapolis, MN, USA; §§Terumo Corp., Tokyo, Japan

the carrier. To date, the largest randomised trial to compare the efficacy of a biodegradable versus durable polymer utilising the same drug (everolimus) has been the EVOLVE II trial, in which 1,648 patients were randomised to receive either the SYNERGY everolimus-eluting biodegradable polymer stent or the PROMUS Element Plus everolimus-eluting durable polymer stent (both Boston Scientific Corporation, Marlborough, MA, USA). This study is scheduled to report results up to five years. However, to date, only 12-month results have been reported. These demonstrated no difference in outcomes: in particular, the incidence of definite stent thrombosis at one year was 0.4% vs. 0.6%, respectively, p=0.5[8].

The interventional community awaits the long-term results of this trial, with the same company providing both stents, as it will provide the scientific validity to demonstrate the benefit, if any, of biodegradable polymers over second-generation durable polymers. Until then, in the absence of any other trials where the difference is only the polymer, one should only comment on the safety and efficacy of the entire device (drug, polymer and stent) over another, and not of its individual components.

Conflict of interest statement

The author has no conflicts of interest to declare.

References

1. Ahmad WA, Koh TH, Santoso T, Tresukosol D, Soerianata S, Wilkins GT, Nair D, Walters DL, Jayasinghe R, Ong TK, Low AF, Ghapar AK, Abidin IZ. Long-term outcomes with Biolimus A9-eluting stents in real-world, all-comers Asia Pacific patients. Final 5-year report of the BEACON (Biolimus Eluting A9 Coronary Stent Obviating Luminal Narrowing) II Clinical Registry. *AsiaIntervention.* 2015;1:102-8.

2. Zambahari R, Lee MK, Hiremath S. Resolute zotarolimus-eluting coronary stent implantation in Asian patients with multivessel disease and long lesions: clinical outcomes in RESOLUTE Asia. *AsiaIntervention.* 2015;1:18-25.

3. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation.* 2004;109:701-5.

4. Otsuka F, Vorpahl M, Nakano M, Foerst J, Newell JB, Sakakura K, Kutys R, Ladich E, Finn AV, Kolodgie FD, Virmani R. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. *Circulation.* 2014;129:211-23.

5. Serruys PW, Farooq V, Kalesan B, de Vries T, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, Rademaker-Havinga T, van Es GA, Meier B, Jüni P, Windecker S. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. *JACC Cardiovasc Interv.* 2013;6:777-89.

6. Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Jüni P, Schömig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J.* 2012;33:1214-22.

7. Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. *N Engl J Med.* 2006;354:483-95.

8. Kereiakes DJ, Meredith IT, Windecker S, Lee Jobe R, Mehta SR, Sarembock IJ, Feldman RL, Stein B, Dubois C, Grady T, Saito S, Kimura T, Christen T, Allocco DJ, Dawkins KD. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II Randomized Trial. *Circ Cardiovasc Interv.* 2015 April 8. [Epub ahead of print].

AsiaIntervention 2015;1:93-95

Reperfusion for all: reimagining STEMI care in low and middle income countries

Thomas Alexander[1]*, MD, DM, FACC; Brahmajee K. Nallamothu[2], MD, MPH, FAHA, FACC

1. Kovai Medical Centre and Hospital, Coimbatore, India; 2. University of Michigan, Cardiovascular Center SPC, Ann Arbor, MI, USA

The development and use of reperfusion therapy in ST-elevation myocardial infarction (STEMI) has been one of the great achievements of modern medicine in the United States of America and Western Europe. In the 1960s, one-year mortality rates after STEMI approached 30% in these countries. However, their numbers are dramatically different today: under ideal circumstances, reperfusion therapy – in combination with cardiac care units and other evidence-based treatments – has now lowered one-year mortality rates after STEMI to well under 10% in clinical trials. The goal of the last two decades in these countries has been to translate these outcomes under "ideal circumstances" into "real-world" practice.

Article, see page 109

The article by Dharma et al[1] in this issue of AsiaIntervention turns the spotlight on STEMI systems of care in this process, focusing on the importance of delivering 24/7 reperfusion therapy. Most importantly, this retrospective analysis using the Jakarta Acute Coronary Syndrome (JAC) registry shows what is possible when adequate facilities and staffing exist within a regional STEMI network. Not only were outstanding outcomes achieved in STEMI patients at this large centre in Indonesia, with the one-year mortality rate of approximately 10% seen in the United States of America and Western Europe, but also the similarity of acute and one-year results between STEMI patients admitted during regular hours versus off-duty hours demonstrates that high performance is achievable even in challenging situations. However, as rightly emphasised by the authors, this has been achieved in an island of excellence where the catheterisation laboratory staff and "on-duty" cardiologists stay within the hospital during "off-duty" hours.

This is a luxury seldom available in most countries across Asia and perhaps the world. It is a testament to the dedication of this institution, these physicians and other healthcare providers.

What about the rest of the world which may practise in a more resource-constrained environment where PCI is not always readily available? How can the benefits of reperfusion therapy be extended to their STEMI patients, beyond the walls of these islands of excellence? These questions have implications not only for us but also for the National Cardiovascular Center in Jakarta and other large centres in Asia which have begun reporting outstanding outcomes. Of the 5,237 patients within the JAC registry during this period, for instance, only 1,126 patients were included in the analysis since the vast majority (78%) of the patients did not receive reperfusion due to late presentation. This raises the larger question facing STEMI systems of care today, particularly in low and middle income countries (LMIC): how do we extend reperfusion therapy when primary PCI is not an option. To tackle this issue requires considerable thought and urgent action.

While there are no accurate estimates of STEMI in LMIC, it is possible that there could be upwards of three to four million cases per year. The reduction of system delay in the developed countries has led to a significant drop in mortality in recent years; however, a further reduction below 60 minutes may have more limited mortality benefit[2]. Detailed analysis of this has resulted in more effort being made to reduce the "non-system" delays associated with STEMI patients arriving too late for reperfusion therapy as being the way to improve outcomes further and reduce the total ischaemia time.

At first, it might seem that the challenge for most STEMI systems of care in LMIC in Asia and Africa is first to grasp the "low-hanging fruit" of addressing system delays within hospitals and then quickly to move on to developing pre-hospital systems. However, with the knowledge we have currently, it may make sense to take a different approach. We advocate that it may be prudent for these countries to address the issues of "non-system" and "system" delays

**Corresponding author: Kovai Medical Centre and Hospital, PB 3209, Avanashi Road, Coimbatore, 641014, India. E-mail: tomalex41@gmail.com*

DOI: 10.4244/AsiaIntery_V1I2A17

simultaneously, while attempting to launch a STEMI system of care. Paradoxically, the lack of any system in many of these countries could help in developing a composite approach by preventing old biases and deeply seated special interests in the status quo. In addition, a deeper inspection of the available resources in many of these regions shows that most larger countries already have the building blocks of a system that could take into account their limited resources, both in terms of infrastructure and manpower.

To develop a STEMI system of care in LMIC, for example, it is important to understand first that primary PCI as the sole mode of reperfusion is not feasible. The CREATE registry from India[3], a prospective registry study of 12,405 STEMI patients from 89 centres from 10 regions and 50 cities in India over a four-year period ending in 2005, showed that 58.5% received thrombolytic therapy and only 8% primary PCI. The China PEACE-Retrospective AMI Study[4], which again was based on hospital data, analysed 13,815 patients treated for STEMI at 162 hospitals. Greater use of primary PCI in patients eligible for revascularisation was shown (from 10.2% in 2001 to 27.6% in 2011); however, the percentage of patients who underwent no reperfusion remained low and stagnant at around 55%. We feel the situation in other LMIC is likely to be similar and will remain unchanged if primary PCI becomes the ultimate goal.

In developing a STEMI system of care in LMIC, the STEMI INDIA Model[5] stands as a stark alternative. STEMI INDIA utilised current evidence on the utility of the pharmacoinvasive strategy, including recent data from the STREAM (STrategic Reperfusion Early After Myocardial infarction) trial[6] and STEP-PAMI trial[7] in India showing that the pharmacoinvasive strategy compared well with primary PCI when delays with primary PCI were anticipated. Based on this evidence and the success of the Kovai Erode Pilot STEMI Study[8], STEMI INDIA proposes that STEMI management in India adopts the dual strategy of combining fibrinolysis with routine early PCI to develop a coherent framework for developing a STEMI system of care in LMIC.

The architecture of this system is based on a hub and spoke model, with each hub hospital connected to multiple spoke hospitals and the unit being called a STEMI cluster. Examples of this exist and, in fact, this appears to be what has already taken place in Jakarta through the National Cardiovascular Center. The other important component of these types of programme is the use of technology to link centres. For example, STEMI INDIA has developed a multifunctional STEMI device[9] which not only records ECG, but also serves as a low-cost monitoring and data entry device. Thus, a 12-lead ECG can be done at the point of first contact – home, ambulance or hospital – and transmitted in real time from the device to a handheld device with the "on-call" cardiologist in the hub hospital for confirmation and early initiation of STEMI treatment. Addressing areas of delay before arrival into the system and within the system can be attempted simultaneously. Shown below are the various areas of non-system and system delays that we have identified in the STEMI INDIA system of care, and our attempts to address them **(Figure 1)**.

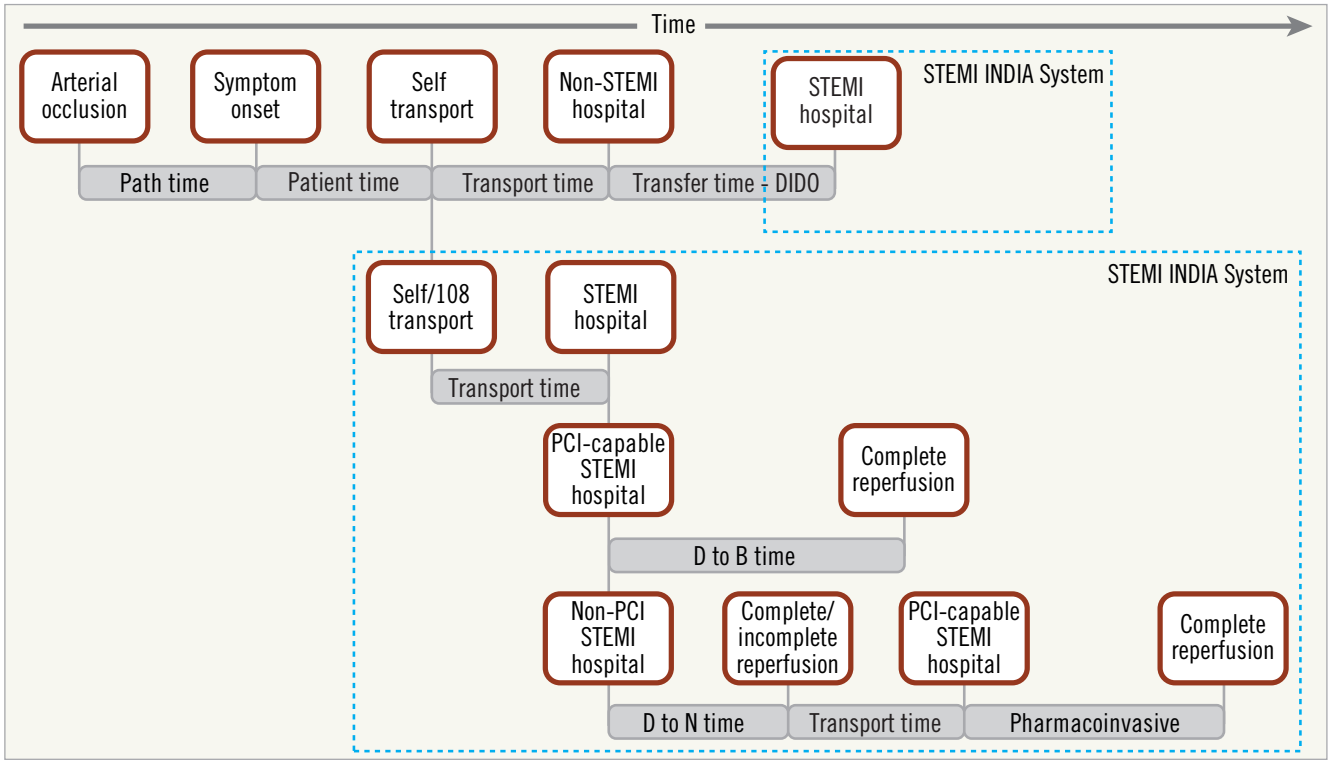


Figure 1. *Non-system and system delays identified in the STEMI INDIA system of care. D to B: door to balloon; D to N: door to needle; DIDO: door in-door out*

Some of the non-system delays can be overcome by public education, using pre-hospital ECG as in the STEMI INDIA project, and accrediting and publicising "STEMI hospitals". This will ensure that patients do not lose time when they are admitted to "non-STEMI" hospitals and then have to be transferred to another hospital for STEMI management (beyond PCI services).

Pre-hospital fibrinolysis has been shown to be very effective and shows a significant increase in rates of aborted MI[10]. Traditionally, this term has been used to indicate fibrinolysis within the ambulance, as practised in many STEMI systems of care in Europe[11]. STEMI INDIA has broadened the definition of "pre-hospital fibrinolysis" and coined a new phrase – pre-coronary care unit fibrinolysis (Pre-CCU Lysis). This will encompass any facility that does not have a coronary care unit and historically has not provided fibrinolysis in STEMI patients, such as primary or rural health centres, or, in certain locations, designated private clinics. These facilities would have trained doctors with third-generation fibrinolytics. They would also have "STEMI devices" capable of recording ECG and transmitting the ECG to "STEMI centres" for confirmation of the diagnosis before initiating fibrinolysis and monitoring patients until they are transported to a CCU.

Dharma et al are to be congratulated on showing the world what is possible within the walls of a modern Asian centre dedicated to providing high-quality performance in primary PCI. In an environment of resource constraints with a burgeoning population of patients in LMIC with coronary artery disease and STEMI, however, we need to move beyond these "islands of excellence"' to ensure that, through innovation, we can deliver reperfusion for all.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Dharma S, Sukmawan R, Siswanto BB, Andriantoro H, Dakota I, Sunil V, Rao S. One-year mortality of primary angioplasty for acute myocardial infarction during regular working hours versus off-hours. *AsiaIntervention.* 2015;1:109-15

2. Flynn A, Moscucci M, Share D, Smith D, LaLonde T, Changezi H, Riba A, Gurm HS. Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Arch Intern Med.* 2010;170:1842-9.

3. Xavier D, Pais P, Devereaux PJ, Xie C, Prabhakaran D, Reddy KS, Gupta R, Joshi P, Kerkar P, Thanikachalam S, Haridas KK, Jaison TM, Naik S, Maity AK, Yusuf S; CREATE registry investigators. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. *Lancet.* 2008;371:1435-42.

4. Li J, Li X, Wang Q, Hu S, Wang Y, Masoudi FA, Spertus JA, Krumholz HM, Jiang L; China PEACE Collaborative Group. ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): a retrospective analysis of hospital data. *Lancet.* 2015;385:441-51.

5. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Rosell Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanas J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberghe K, Bogaerts K, Van de Werf F; STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med.* 2013;368:1379-87.

6. Victor SM, Subban V, Alexander T, Bahuleyan CG, Srinivas A, Selvamani S, Mullasari AS. A prospective, observational, multicentre study comparing tenecteplase facilitated PCI versus primary PCI in Indian patients with STEMI (STEPP–AMI). *Open Heart.* 2014;1:e000133.

7. Alexander T, Mullasari A, Narula J. Developing a STEMI system of care for low- and middle-income countries: the STEMI-India model. *Glob Heart*. 2014;9:419-23.

8. Alexander T, Mehta S, Mullasari A, Nallamothu BK. Systems of care for ST-elevation myocardial infarction in India. *Heart.* 2012;98:15-7.

9. Alexander T, Victor SM, Mullasari AS, Veerasekar G, Subramaniam K, Nallamothu BK; TN-STEMI Programme Investigators. Protocol for a prospective, controlled study of assertive and timely reperfusion for patients with ST-segment elevation myocardial infarction in Tamil Nadu: the TN-STEMI programme. *BMJ Open.* 2013;3:e003850.

10. Lamfers EJ, Schut A, Hertzberger DP, Hooghoudt TE, Stolwijk PW, Boersma E, Simoons ML, Verheugt FW. Prehospital versus hospital fibrinolytic therapy using automated versus cardiologist electrocardiographic diagnosis of myocardial infarction: abortion of myocardial infarction and unjustified fibrinolytic therapy. *Am Heart J.* 2004;147:509-15.

11. Hanssen M, Cottin Y, Khalife K, Hammer L, Goldstein P, Puymirat E, Mulak G, Drouet E, Pace B, Schultz E, Bataille V, Ferrières J, Simon T, Danchin N; FAST-MI 2010 Investigators. French Registry on Acute ST-elevation and non ST-elevation Myocardial Infarction 2010. FAST-MI 2010. *Heart.* 2012;98:699-705.

AsiaIntervention 2015;1:96-98

Remote ischaemic preconditioning: essential part of the "Great Game" to reduce myocardial injury after PCI

Fabrizio D'Ascenzo*, MD; Francesca Giordana, MD; Claudio Moretti, MD

Division of Cardiology, University of Turin, Turin, Italy

"Go up the hill and ask. Here begins the Great Game" - Kim, Kipling, 1901

We read with great interest the paper of Kumar et al[1] published in the present edition of AsiaIntervention, as this is the first randomised clinical trial demonstrating the benefit of remote ischaemic preconditioning (RIPC) on the reduction of periprocedural myocardial infarction (PMI) after a percutaneous coronary intervention (PCI) in Indian patients.

Two main considerations may arise from the present work: 1) RIPC is not affected by ethnicity; 2) the benefit offered in patients undergoing PCI for stable angina seems consistent with data already reported in the literature.

Some animal studies that date back to almost twenty years ago have already postulated the beneficial effect of a "brief ischaemia", both in the heart and in the non-cardiac tissues[2,3]. Recently, some steps towards clarifying the mechanism responsible for remote ischaemic preconditioning have been taken[4-6]. The signals seem to be transferred to the peripheral target organs through different pathways, involving both the somato-sensory and the autonomous nervous systems[4]. Both of them might carry the central inputs to the downstream extracellular specific receptors, and then, by intracellular signal transduction molecules, may cause changes in mitochondrial function[4,5], as shown in **Figure 1**. Adenosine, bradykinin, and calcitonin gene-related peptide are probably important mediators in the afferent loop of this reflex[2,3,6,7]; however, the exact nature of the signal transduction from the remote tissue to the target organs remains to be fully clarified.

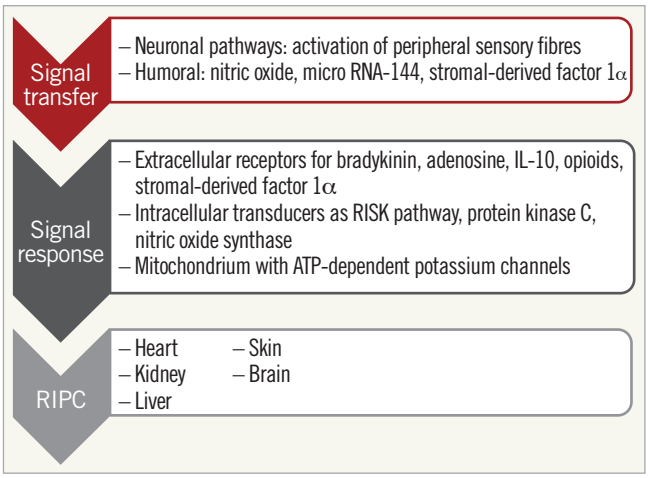


Figure 1. *RIPC exerts its function through different pathways.*

The impact of these experimental models in clinical practice has been largely debated. A meta-analysis of randomised controlled trials (RCTs) of patients undergoing coronary surgical revascularisation showed a reduced release of troponin after the intervention in those treated with RIPC, especially in the presence of multivessel coronary disease[8]. Interestingly, among the nine selected trials, one[9] focused on Asian patients, showing consistent benefit of RIPC in terms of myocardial protection.

**Corresponding author: Division of Cardiology, Città della Salute e della Scienza Hospital, University of Turin, Corso Bramante 88-90, 10126 Turin, Italy. E-mail: fabrizio.dascenzo@gmail.com*

DOI: 10.4244/AsiaIntery_V1I2A18

Similarly, another meta-analysis has shown a reduction in terms of PMIs for patients treated with PCI[10], despite heterogeneity of definition[11]. In that paper, two RCTs enrolling Asian patients were included, one from Egypt and the other from Iran[12,13]. These trials showed conflicting results, but when pooling them together with the present study a significant reduction of PMIs was shown (OR 0.29 [0.16-0.53]) **(Figure 2)**.

Moreover, this paper opens new horizons for future research. Kumar et al[1] have found a trend towards a lower incidence of TIMI flow <3 during the procedure in the RIPC group, postulating a positive effect of the remote preconditioning in the setting of acute coronary syndrome, as shown in the work of Bøtker et al[14]. Certainly, in this clinical context the inflammatory response to the plaque rupture and the individual stress response to the event are significant confounding factors that might influence the clinical response to RIPC. However, it is precisely these patients, who lack collateral circulation systems, who could benefit more from remote preconditioning.

Finally, like Kipling's Kim, now is the time to leave the research laboratories and to go on up the hill in the interventional cathlabs to "ask" patients if RIPC may exert positive effects after interventional procedures.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Kumar S, Krishna A, Kapoor A, Tewari S, Garg N, Kumar Goel P. Role of remote ischaemic preconditioning on myocardial injury in stable patients undergoing percutaneous coronary intervention: a randomised case-control study. *AsiaIntervention.* 2015;1:116-23.

2. Gho BC, Schoemaker RG, van den Doel MA, Duncker DJ, Verdouw PD. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation.* 1996;94:2193-200.

3. Pell TJ, Baxter GF, Yellon DM, Drew GM. Renal ischemia preconditions myocardium: role of adenosine receptors and ATP-sensitive potassium channels. *Am J Physiol.* 1998;275:H1542-7.

4. Heusch G, Bøtker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. *J Am Coll Cardiol.* 2015;65:177-95.

5. Heusch G. Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. *Circ Res.* 2015;116:674-99.

6. Leung CH, Wang L, Nielsen JM, Tropak MB, Fu YY, Kato H, Callahan J, Redington AN, Caldarone CA. Remote cardioprotection by transfer of coronary effluent from ischemic preconditioned rabbit heart preserves mitochondrial integrity and function via adenosine receptor activation. *Cardiovasc Drugs Ther.* 2014;28:7-17.

7. Jensen RV, Stottrup NB, Kristiansen SB, Bøtker HE. Release of a humoral circulating cardioprotective factor by remote ischemic

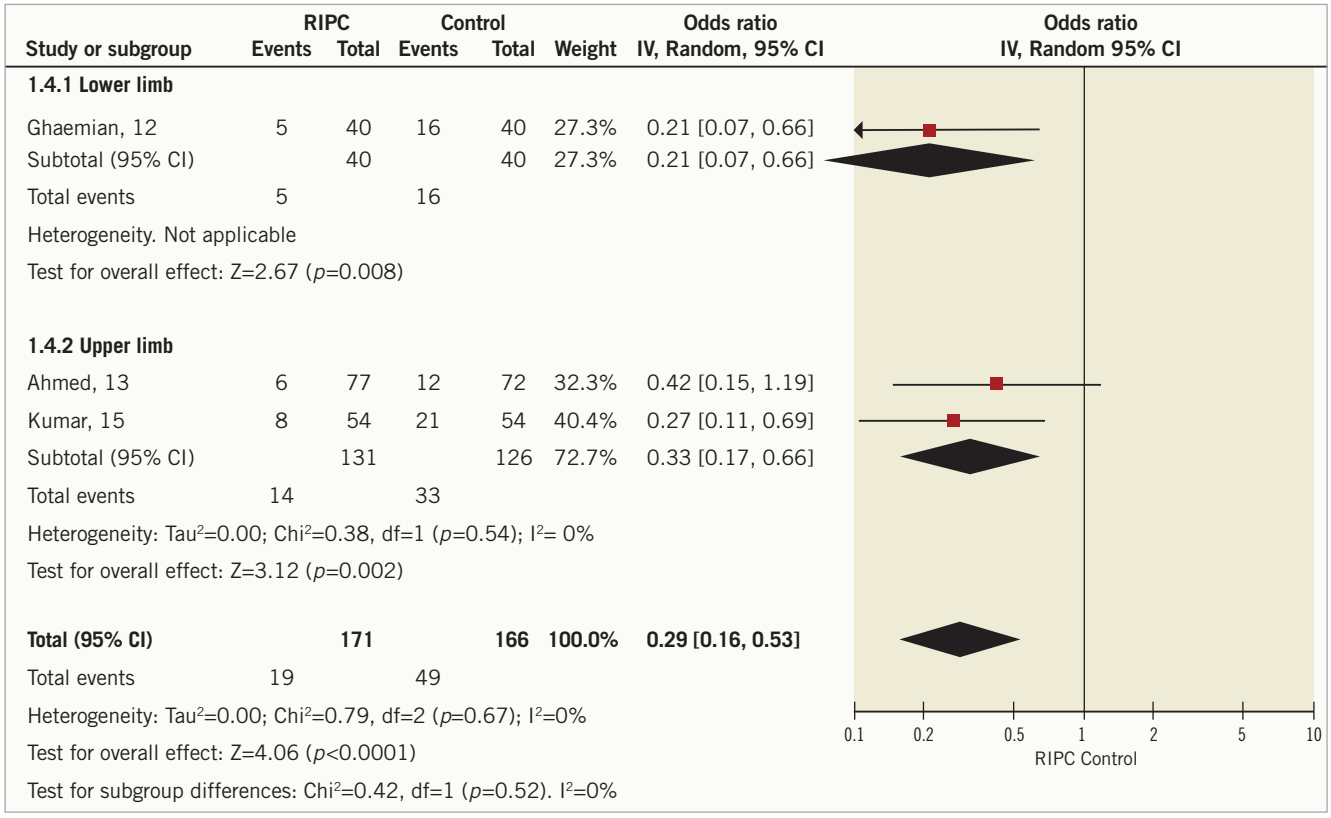


Figure 2. *Benefit of RIPC in Asian patients to reduce periprocedural myocardial infarctions.*

preconditioning is dependent on preserved neural pathways in diabetic patients. *Basic Res Cardiol.* 2012;107:285.

8. D'Ascenzo F, Cavallero E, Moretti C, Omedè P, Sciuto F, Rahman IA, Bonser RS, Yunseok J, Wagner R, Freiberger T, Kunst G, Marber MS, Thielmann M, Ji B, Amr YM, Modena MG, Zoccai GB, Sheiban I, Gaita F. Remote ischaemic preconditioning in coronary artery bypass surgery: a meta-analysis. *Heart.* 2012;98:1267-71.

9. Hong DM, Mint JJ, Kim JH, Sohn IS, Lim TW, Lim YJ, Bahk JH, Jeon Y. The effect of remote ischaemic preconditioning on myocardial injury in patients undergoing off-pump coronary artery bypass graft surgery. *Anaesth Intensive Care.* 2010;38:924-9.

10. D'Ascenzo F, Moretti C, Omedè P, Cerrato E, Cavallero E, Er F, Presutti DG, Colombo F, Crimi G, Conrotto F, Dinicolantonio JJ, Chen S, Prasad A, Biondi Zoccai G, Gaita F. Cardiac remote ischaemic preconditioning reduces periprocedural myocardial infarction for patients undergoing percutaneous coronary interventions: a meta-analysis of randomised clinical trials. *EuroIntervention.* 2014;9:1463-71.

11. Gili S, D'Ascenzo F, Moretti C, Cerrato E, Cavallero E, Er F, Presutti DG, Colombo F, Crimi G, Conrotto F, Dinicolantonio JJ, Chen S, Prasad A, Biondi Zoccai G, Gaita F. Impact on prognosis of periprocedural myocardial infarction after percutaneous coronary intervention. *J Interv Cardiol.* 2014;27:482-90.

12. Ahmed RM, Mohamed EH, Ashraf M, Maithili S, Nabil F, Rami R, Mohamed TI. Effect of remote ischemic preconditioning on serum troponin T level following elective percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2013;82:E647-53.

13. Ghaemian A, Nouraei SM, Abdollahian F, Naghshvar F, Giussani DA, Nouraei SA. Remote ischemic preconditioning in percutaneous coronary revascularization: a double-blind randomized controlled clinical trial. *Asian Cardiovasc Thorac Ann.* 2012;20:548-54.

14. Bøtker HE, Kharbanda R, Schmidt MR, Bottcher M, Kaltoft AK, Terkelsen CJ, Munk K, Andersen NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen SD, Thuesen L, Nielsen SS, Rehling M, Sørensen HT, Redington AN, Nielsen TT. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet.* 2010;375:727-34.

AsiaIntervention 2015;11:99-101 published online ahead of print May 2015

Will the DAPT trial (long-term dual antiplatelet treatment after stent implantation) change my practice?

Chee Tang Chin[1,2], MBChB, MRCP(UK); Davide Capodanno[3], MD, PhD; Philip Urban[4], MD; Alan Ching Yuen Yeung[5], MD; Azeem Latib[6], MD; Sunarya Soerianata[7], MD; Hyeon-Cheol Gwon[8], MD; William Wijns[9]*, MD; Andrew Ong[10], MD, PhD

1. National Heart Centre Singapore, Singapore; 2. Duke-NUS Graduate Medical School, Singapore; 3. Ferrarotto Hospital, University of Catania, Catania, Italy; 4. Hôpital de La Tour Meyrin, Geneva, Switzerland; 5. Stanford University, Stanford, CA, USA; 6. San Raffaele Scientific Institute, Milan, Italy; 7. National Cardiovascular Center, Harapan Kita Hospital, Jakarta, Indonesia; 8. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; 9. Cardiovascular Research Center, Aalst, Belgium; 10. Westmead Hospital, Sydney, Australia

Introduction

Dual antiplatelet therapy (DAPT) combining aspirin with an adenosine diphosphate receptor inhibitor has significantly reduced the incidence of ischaemic events, including stent thrombosis, after percutaneous coronary intervention, and is thus strongly recommended by international practice guidelines[1,2]. However, less clear has been the optimal duration for which DAPT should be recommended, especially in the context of a drug-eluting stent (DES) implantation, where previous reports have implicated an association with increased late stent thrombosis events after DAPT has been stopped. In addition, this issue is further influenced by the exposure of the patient to an increased risk of bleeding while on DAPT.

The DAPT study was therefore designed to evaluate the benefits and risks of continuing a patient on DAPT beyond 12 months after coronary stenting[3]. This study was distinct from prior studies in that it was powered to detect a difference in stent thrombosis rates, and was composed of five individual studies with similar protocols involving eight different devices and pharmaceutical companies.

Briefly, the DAPT study was an international, multicentre, prospective, blinded, placebo-controlled study that included 9,961 patients who had successfully completed 12 months of DAPT after coronary stenting without a significant ischaemic or bleeding event, and who were then randomly assigned to either continuing on DAPT for a further 18 months, or stopping DAPT and continuing on aspirin alone[4]. The two co-primary efficacy endpoints were stent thrombosis and major adverse cardiovascular and cerebrovascular events (MACCE) (a composite of death, myocardial infarction, or stroke) during the period from 12 to 30 months. The primary safety endpoint was moderate or severe bleeding. Patients who were randomised to continuing DAPT after the initial 12 months, as compared with patients who discontinued DAPT, had reduced rates of stent thrombosis (0.4% vs. 1.4%; hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.17 to 0.48; p<0.001) and MACCE (4.3% vs. 5.9%; HR 0.71, 95% CI: 0.59 to 0.85; p<0.001). The rate of myocardial infarction (MI) was also reduced with prolonged DAPT (2.1% vs. 4.1%; HR 0.47; p<0.001). However, both the rates of death from any cause (2.0% vs. 1.5%; HR 1.36, 95% CI: 1.00 to 1.85; p=0.05) and moderate or severe bleeding (2.5% vs. 1.6%, p=0.001) were higher in the prolonged DAPT group as compared to the group where DAPT was stopped at 12 months **(Figure 1)**.

This important and potentially practice-changing study was discussed in the first ever "Will this trial change my practice?" session at AsiaPCR 2015. The objectives of this new session format were succinctly outlined by W. Wijns, who explained to the audience the

*Corresponding author: Cardiovascular Center Aalst, Moorselbaan 164, B-9300 Aalst, Belgium.
E-mail: William.Wijns@olvz-aalst.be

DOI: 10.4244/AIJY15M05_01

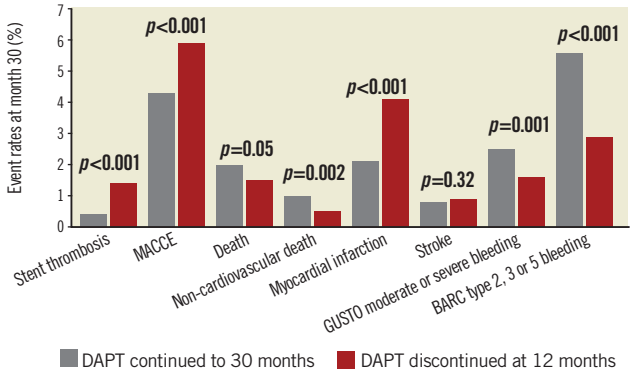


Figure 1. *Clinical event rates in the two randomisation groups at month 30 (%). Stent thrombosis, MACCE and myocardial infarction are significantly lower with DAPT continued to 30 months, while bleeding, as well as non-cardiovascular death is increased.*

need to achieve a detailed understanding of the results of a particular published trial that may impact on their clinical practice, the importance of being able to evaluate the relevance of new results for the treatment of their patients, and the importance of being able to share current and future practice with colleagues from around the world. The expert panel at the session comprised colleagues from Asia, Australia, North America, and Europe and was therefore in a unique position to provide a global appraisal of the study and its relevance to an international audience.

W. Wijns proceeded to put into context the relevance of the study to daily clinical practice by presenting a case study of an actual patient from the DAPT study. He then polled the audience to determine practice patterns with regard to DAPT duration before the results of the DAPT study were known. The following three choices were presented to the audience: 1) stop DAPT no later than one year; 2) continue DAPT beyond one year whenever possible; or 3) decide on a case-by-case basis. Only a small minority of the audience stated their preference for stopping DAPT no later than one year. This differed significantly from the panel, as most of the panel members indicated their preference for option 1 (stop no later than one year). The majority of the audience supported either option 2 or option 3, about 50% each.

With the clinical context firmly established, A. Ong presented a concise summary of the rationale for DAPT post coronary stenting and the evolution in practice patterns over time prior to the publication of the DAPT study. A meta-analysis by Bulluck and colleagues demonstrated firstly the lack of studies examining a DAPT duration of 12 versus 24+ months, and, secondly, showed that, although there was no advantage in terms of reducing mortality, MI, or stent thrombosis, a prolonged DAPT duration of at least 24 months was associated with more bleeding incidents than a DAPT duration of 12 months[5]. However, because only two small studies were included in this analysis, the results were more likely to be hypothesis-generating rather than definitive, hence emphasising the importance and relevance of the DAPT study.

This was therefore the context for D. Capodanno's in-depth review of the DAPT study design, results and interpretation. He showed that, although the study was an international multicentre effort, the majority of sites were from the USA. There were no sites from Asia in the study. He then highlighted the study protocol and its impact on the final study population. Because the DAPT study was attempting to answer the question of the effect of prolonging DAPT beyond 12 months, by design it was necessary to enrol and randomise patients who were event-free for the first 12 months on DAPT after coronary stenting. As such, from the initial 22,866 patients who were enrolled after the index DES stenting procedure, only 9,961 were finally randomised. Patients were not randomised for a variety of reasons, including having had a clinical event, but a significant number were also not randomised because of non-adherence, withdrawal of consent, or loss to follow-up. From the published data of events during the 12 months post coronary stenting (i.e., before randomisation), the DAPT study population could be characterised as a low-risk population, with respect to both ischaemic and bleeding risks.

The event curves for the two arms in the DAPT study were shown and discussed in detail. Two observations were highlighted. 1) The event curves diverged early on, but also appeared to converge in the observational period after DAPT had been stopped in the prolonged DAPT arm, thus suggesting a possible "rebound" phenomenon. 2) More than half (55%) of the MI events were not related to stent thrombosis and thus by implication occurred at a non-stented site.

In the DAPT study, more than one third of patients had a "first-generation" paclitaxel or sirolimus-eluting stent placed. Although subgroup analysis showed a significant interaction between stent type and MACCE, there was no significant interaction with stent thrombosis. In fact, generally there was a consistent treatment effect in most subgroups favouring prolonging DAPT for reducing stent thrombosis and MACCE, especially MI. The issue of all-cause mortality which showed a numerical excess (mainly from trauma, bleeding, or cancer-related deaths) in the prolonged DAPT arm was presented. The issue of cancer-related deaths was further defined by the DAPT study investigators who performed a *post hoc* analysis and reported more cancers at baseline in the prolonged DAPT arm. Furthermore, they also published a meta-analysis of DAPT vs. aspirin studies and reported no mortality benefit favouring either management strategy[6].

D. Capodanno summed up his review by stating that, although there was a significant reduction in stent thrombosis, MACCE, and MI with prolonged DAPT, this was at the expense of more bleeding events. In addition, the benefit in MI appeared to be not solely confined to the stented segment. There appeared to be a rebound phenomenon or withdrawal of protection after DAPT was discontinued at 30 months, with the event curves approaching each other. Finally, he emphasised that these results would apply to low-risk patients who have tolerated one year of DAPT after stent placement with no ischaemic or bleeding events.

The audience asked whether the study results could be generalised to an Asian population, bearing in mind that there were no

Asian sites in the study, that Asian patients may have a different bleeding profile compared to Western patients, and that "first-generation" DES had long been discontinued in Asia. In response, H.C. Gwon echoed these concerns by stating that bleeding had been well established as being associated with mortality and adverse outcomes, and that with newer-generation DES the risk of ischaemic events was much less and hence the risk-benefit ratio might not be in favour of prolonging DAPT duration. P. Urban shared his concern with regard to bleeding, especially in the context of the DAPT study which, he pointed out, showed an excess of deaths in the treatment arm which had more bleeding events. Other issues raised included the potentially diverging effects in subgroups such as the elderly (>75 yrs), or non-diabetics. P. Urban and D. Capodanno emphasised that, although these were interesting observations, they were ultimately only hypothesis-generating and should not inform treatment decisions.

The session concluded with the final clinical outcome of the initial case study from the trial. A. Ong summarised the session by stating again that overall the DAPT study had not shown any mortality benefit with regard to prolonging DAPT beyond 12 months as compared to stopping at 12 months. Although there was benefit in reducing stent thrombosis and MI, this was at the expense of bleeding, including nuisance bleeding, which may impact on quality of life.

To close the session, the panel members emphasised that, as with all important studies, data from the DAPT study would continue to inform clinical practice beyond the results included in the main manuscript. Of particular interest and importance would be further data and analyses with regard to patient presentation (acute coronary syndromes versus stable coronary artery disease), predictors of increased bleeding risk, and also factors associated with recurrent MI, be they related to the index stenting procedure or at another coronary site.

So, will the DAPT trial results change practice in the Asia-Pacific region?

A repeat poll of the audience indicated that the results of the DAPT study would not change their current clinical practice patterns. As to the colleagues participating in the discussion, the vast majority were already continuing DAPT beyond one year or at least considering it on a case-by-case basis. The DAPT trial now brings evidence in support of this practice.

As to the panel members, nearly all remained reluctant to continue DAPT beyond one year in all patients in the absence of mortality benefit. Following the release of the DAPT trial results, however, they will more often consider continuation of DAPT on a case-by-case basis for treatment of patients with high ischaemic and low bleeding risks.

Acknowledgements

We are indebted to A. Banning, N. Bowers and A.H. Gershlick for kindly providing the clinical case history for discussion during the session.

Conflict of interest statement

C.T. Chin has received an honorarium from AstraZeneca and has ongoing research collaborations with Eli Lilly and Daiichi Sankyo. P. Urban is a consultant for Biosensors, and has received honoraria from Abbott Vascular and Edwards Lifesciences, and institutional grant/research support from Boston Scientific. W. Wijns has received institutional research grants from Boston Scientific, Cordis J&J, Medtronic, Terumo and AstraZeneca. The other authors have no conflicts of interest to declare.

References

1. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation.* 2011; 124:e574-651.

2. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention.* 2015;10: 1024-94.

3. Mauri L, Kereiakes DJ, Normand SL, Wiviott SD, Cohen DJ, Holmes DR, Bangalore S, Cutlip DE, Pencina M, Massaro JM. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. *Am Heart J.* 2010;160: 1035-41.

4. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med.* 2014;371:2155-66.

5. Bulluck H, Kwok CS, Ryding AD, Loke YK. Safety of short-term dual antiplatelet therapy after drug-eluting stents: An updated meta-analysis with direct and adjusted indirect comparison of randomized control trials. *Int J Cardiol.* 2015;181:331-9.

6. Elmariah S, Mauri L, Doros G, Galper BZ, O'Neill KE, Steg PG, Kereiakes DJ, Yeh RW. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. *Lancet.* 2015;385:792-8.

AsiaIntervention 2015;1:102-108

Long-term outcomes with Biolimus A9-eluting stents in real-world, all-comers Asia Pacific patients. Final 5-year report of the BEACON (Biolimus Eluting A9 Coronary Stent Obviating Luminal Narrowing) II clinical registry

Wan Azman Wan Ahmad[1]*, MD; Koh Tian Hai[2], MD; Teguh Santoso[3], MD, PhD; Damras Tresukosol[4], MD, PhD; Sunarya Soerianata[5], MD; Gerard Wilkins[6], MD; Dinesh Nair[7], MD; Darren L. Walters[8], MD; Rohan Jayasinghe[9], MD, PhD; Ong Tiong Kiam[10], MD; Adrian F. Low[11], MD; Abdul Kahar Ghapar[12], MD; Imran Zainal Abidin[1], MD; on behalf of the BEACON II investigators

1. University of Malaya Medical Centre, Kuala Lumpur, Malaysia; 2. National Heart Centre Singapore, Singapore; 3. Medistra Hospital, Jakarta, Indonesia; 4. Siriraj Hospital, Bangkok, Thailand; 5. Harapan Kita Hospital, Harapan Kita, Indonesia; 6. Dunedin Hospital, Dunedin, New Zealand; 7. Tan Tock Seng Hospital, Singapore; 8. The Prince Charles Hospital, Chermside, QLD, Australia; 9. Gold Coast Hospital, Southport, QLD, Australia; 10. Sarawak General Hospital, Sarawak, Malaysia; 11. National University Hospital, Singapore; 12. Serdang Hospital, Selangor, Malaysia

W.A. Wan Ahmad and Koh Tian Hai contributed equally to this manuscript.

KEYWORDS

- biodegradable polymer
- drug-eluting stent
- major adverse cardiac events
- stent thrombosis

Abstract

Aims: To evaluate and report the final five-year clinical outcomes of treatment with BioMatrix DES in a real-world, all-comers population of Asian Pacific patients.

Methods and results: BEACON II is a prospective observational registry at 12 sites with 497 patients enrolled in six Asia Pacific countries. The primary endpoint was a composite of cardiac death, myocardial infarction (Q and non-Q-wave) or target lesion revascularisation at 12 months. Secondary endpoints included extending the primary endpoint to five years and rates of stent thrombosis. Analysis was performed according to the intention-to-treat principle. Patients in the BEACON II registry were relatively young with a mean age of 59.8 years and a high prevalence of diabetes mellitus (32.5%). In spite of many complex lesion subsets, acute procedural success was achieved in 98% of patients. At five years, the hierarchical major adverse cardiac events (MACE) rate was 11.2%, the cumulative incidence of cardiac death 4.4%, myocardial infarction 4.5%, and target lesion revascularisation 3.8%, respectively. Although this was an all-comers population excluding the enrolment of patients with left main disease, the five-year definite stent thrombosis cumulative incidence was low (1.2%), and definite very late stent thrombosis (VLST) events were rare (0.4%). There were no VLST in native coronary arteries; indeed, VLST was limited to saphenous vein grafts (SVGs).

Conclusions: The low hierarchical MACE incidence and the absence of VLST in native coronary arteries suggest an excellent safety profile up to five years for the BioMatrix stent when used in routine clinical practice in an Asian Pacific population.

**Corresponding author: Department of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.*
E-mail: wanazman@ummc.edu.my

DOI: 10.4244/AsiaInterv_V1I2A20

Introduction

The efficacy of drug-eluting stents (DES) over bare metal stents (BMS) has been demonstrated in large randomised clinical trials leading to their widespread use in clinical practice[1,2]. However, major concerns regarding the long-term safety of the first-generation DES include the increased risk of late stent thrombosis (LST), very late stent thrombosis (VLST)[3-6], and the need for prolonged dual antiplatelet therapy (DAPT) with its inherent risk of bleeding. Although the cause of LST/VLST is probably multifactorial, the durable polymer surface coating of DES may play a role. The durable polymer carrier can cause persistent inflammatory response which leads to poor healing due to delayed re-endothelialisation, positive remodelling with late acquired malapposition and the risk of LST/VLST[7-10]. Other concerns with durable polymer are the ongoing inflammatory response which may induce the "late catch-up" phenomenon[11,12] and an acceleration of neoatherosclerosis which may also trigger a subsequent risk of late device failure (stenosis and thrombosis)[13].

Second-generation DES are designed to improve the safety and efficacy profile of earlier-generation stents. One of these innovations has been the development of biodegradable polymer which is often abluminally coated. This ensures the polymer is applied in the minimum amount necessary for its function and is then removed over time, theoretically limiting the delay in arterial healing.

The BioMatrix™ drug-eluting coronary stent system (Biosensors Europe SA, Morges, Switzerland) comprises the active pharmaceutical ingredient Biolimus A9™ (BA9) (Biosensors) which is a proprietary, semi-synthetic analogue that is chemically related to both sirolimus and everolimus. It is highly lipophilic and rapidly absorbed in tissues. BA9 is encapsulated in the biodegradable polymer, polylactic acid (PLA), to bind the drug mechanically to the primer of the stent surface and also regulate drug release from the stent to the surrounding tissue. The coating mixture is applied solely to the abluminal surface of a flexible 316L stainless steel stent. The PLA coating was previously demonstrated in an *in vivo* study to convert fully to lactic acid after six to nine months; thereafter, the stent has a profile like a BMS.

Editorial, see page 91

The objective of this registry was to assess the clinical outcomes in patients receiving the BioMatrix biodegradable polymer DES during treatment of real-world, all-comer patients.

Methods

This was a prospective, multinational multicentre observational, patient data registry conducted in 12 centres in six Asia Pacific countries: Singapore (3), Thailand (1), Indonesia (2), Australia (2), New Zealand (1), and Malaysia (3).

The patient population consisted of men and non-pregnant women who were at least 18 years old, with a diagnosis of stable angina, unstable angina or silent ischaemia, including one or more *de novo* or restenotic lesions (>50%) in a native coronary artery or saphenous vein graft (SVG). Angiographic lesion requirements included a reference vessel diameter visually estimated to be ≥2.5 mm and ≤4.0 mm, while there was no limit to the lesion length or the number of treated lesions or vessels. There was also no limit to disease/lesion morphology.

Patients were excluded when antiplatelet and/or anticoagulation therapy was contraindicated. Patients with known hypersensitivity to stainless steel, contrast agents, sirolimus or biolimus were excluded. Patients considered for non-registry DES implant during a procedure or having a lesion located in a protected/unprotected left main coronary artery were also excluded.

This study received approval from the local ethics committee at each site, as well as approval of an informed consent text specific to the registry.

ENDPOINTS AND FOLLOW-UP DEFINITION

The primary endpoint per protocol was the cumulative number and rate of major adverse cardiac events (MACE), defined as a composite of cardiac death, myocardial infarction (MI), and target lesion revascularisation (TLR) at 12 months post procedure. The definition of cardiac death included any death due to an immediate cardiac cause (e.g., myocardial infarction, low-output failure, fatal arrhythmia), procedure-related deaths including those related to concomitant treatment, unwitnessed death and death of unknown cause, where cardiac causes could not be excluded. Myocardial infarction was defined using the electrocardiographic criteria of the Minnesota Code or as an elevation of CK levels to more than two times normal with positive levels of CK MB or troponin I or T. TLR was defined as any repeat percutaneous coronary intervention of the target lesion or bypass surgery of the target vessel. These are clinically driven revascularisations in which the patient had a positive functional study, ischaemic ECG changes at rest in a distribution consistent with the target vessel, or ischaemic symptoms, and an in-lesion diameter stenosis >50% by quantitative coronary angiography (QCA). Revascularisation with an in-lesion diameter stenosis >70% (by QCA) in the absence of the above-mentioned ischaemic signs or symptoms was also considered clinically driven. In the absence of QCA data, the clinical need for revascularisation would be adjudicated using the presence or absence of ischaemic signs and symptoms. QCA assessment was not mandatory and up to the discretion of the investigator.

The secondary endpoints were: ischaemia-driven target lesion failure (TLF), a composite of cardiac death, target vessel MI (Q- and non-Q-wave) and ischaemia-driven TLR at 12 months; the rates of definite stent thrombosis up to five years according to the Academic Research Consortium (ARC) definition[14]; and MACE at 30 days, 90 days, six months, and two to five years annually.

Clinical follow-up visits were performed at one month, and telephone follow-ups at three months, six months, and one to five years annually. The Kaplan-Meier method was used to calculate time-to-event in the patient population. Data were captured using an Electronic Data Capture (EDC) system in compliance with the FDA requirement.

Event adjudication was performed by an independent clinical events committee (CEC) composed of cardiologists not involved in the study.

STATISTICAL ANALYSIS

There were no *a priori* statistical considerations for deriving the sample size of this registry. The primary analysis sample was based on the principle of intention-to-treat (ITT). All patients who met the registry entry criteria and signed the written informed consent were counted in the primary analysis. The enrolment period for each participating site was about six months.

Survival analyses were carried out using the time to the first event. Cumulative incidence rates were estimated using the Kaplan-Meier method. Kaplan-Meier estimates can be interpreted as the proportions of patients with a given clinical outcome. In the survival analyses, the number of patients with the event of interest was reported together with the number at risk. The number of patients at risk at time t is the number of patients who may experience the event of interest at t.

Results

BEACON II patients had a high prevalence of cardiovascular risk factors: 32.5% had diabetes, and 46.2% had a history of smoking, while 62.1% had hypertension, 74.4% had hypercholesterolaemia and 29% had a family history of coronary artery disease (CAD). A large percentage of patients (38.6%) had a history of myocardial infarction **(Table 1)**. The follow-up rate for each time point is specified accordingly: 98.6% at 30 days, 98.4% at three months, 97.8% at six months, 97.2% at one year, 97.6% at two years, 93.6% at three years, 94.2% at four years and 93.8% at five years.

In total, 742 lesions were treated. Sixty-three percent of the patients had one lesion treated, 27% two lesions, and 10% more than two lesions. ACC/AHA lesion classification was 10.1% type A, 32.3% type B1, 28.3% type B2, and 29.2% type C. Lesion distribution among the three primary epicardial arteries was 46% left anterior descending (LAD), 31.3% right coronary artery (RCA), 21.6% left circumflex coronary artery (LCX), and 1.2% saphenous vein graft (SVG). Most lesions (94.5%) were *de novo* lesions; only 5.5% were restenotic lesions. Relatively small vessel diameter lesions, that is with a diameter smaller than 2.75 mm, accounted for 33.7% of the lesions. Other complex lesions included long lesions (>20 mm; 31.4%) and those with moderate to severe calcification (23.9%) **(Table 2)**.

Table 1. Patient demographics.

Parameter		Number of patients (n=497)
Male, n (%)		399 (80.3)
Age, mean±SD		59.8±10.75
Diabetes mellitus, n (%)		156 (32.5)
Hypertension, n (%)		306 (62.15)
Hypercholesterolaemia, n (%)		338 (74.45)
Smoking, n (%)		215 (46.25)
Family history of CAD, n (%)		126 (29)
Previous MI, n (%)		184 (38.65)
Previous PCI, n (%)		54 (27.55)
Previous CABG, n (%)		27 (5.55)
Current angina status	Asymptomatic, n (%)	78 (15.7)
	Stable angina, n (%)	268 (53.9)
	Unstable angina, n (%)	151 (30.4)
LVEF %, mean±SD		52.43±14.07
LVEF <30%, n (%)		18 (6.84)

Data are mean (SD) or number (%). CABG: coronary artery bypass graft; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 2. Lesion characteristics.

Parameter	Number of lesions (n=742)
Target lesion coronary artery, n (%)	701 (94.5)
Bifurcation lesion (side branch >2 mm), n (%)	101 (13.6)
with moderate/severe calcification, n (%)	32 (4.3)
Moderate/severe calcification, n (%)	177 (23.9)
Lesions >20 mm, n (%)	232 (31.4)
Reference vessel diameter <2.75 mm, n (%)	250 (33.7)
Total occlusion, n (%)	69 (9.3)
De novo lesions, n (%)	701 (94.5)
Restenotic lesions, n (%)	41 (5.5)

Device success, defined as achievement of less than 30% residual in-segment percent diameter stenosis and either TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure using the assigned device only, was achieved in 98.8% of patients. Lesion success, defined as achievement of less than 30% residual in-segment percent diameter stenosis and either TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure, was achieved in 98.9% of patients. Procedure success, defined as achievement of less than 30% residual in-segment percent diameter stenosis and either TIMI flow 3 or a consistent TIMI flow 2 before and after the procedure with the assigned stent and without the occurrence of death, MI or repeat revascularisation of the target vessel during the hospital stay, was achieved in 98% of patients **(Table 3)**.

Table 3. Procedure characteristics.

Parameter	Number of lesions (n=742)
Lesions per patient, mean±SD	1.49±0.74
Stents per patient, mean±SD	1.73±0.96
Stents per lesion, mean±SD	1.16±0.47
Lesion length (mm), mean±SD	18.7±9.7
Total stent length per lesion (mm), mean±SD	22.6±10.9
Stent length (mm), mean±SD	19.2±6
Glycoprotein IIb/IIIa inhibitor use, n (%)	81 (10.9)
Lesion success, n (%)	734 (98.9)
Device success, n (%)	733 (98.8)
Procedure success, n (%)	727 (98)

Outcomes for clinical events are reported using Kaplan-Meier estimates. The number of events are given in parentheses. Hierarchical MACE rates at one and five years were 4.3% (21) and 10.9% (52), respectively **(Figure 1)**. For five years the cumulative incidence of all death was 8.5% (41). The cumulative incidence of cardiac death was 4.4% (21), with about half of the total deaths occurring during the first year **(Figure 2)**. The cumulative incidence of MI at five years was 4.5% (21), of which 3.6% (17) and 1% (5) were non-Q-wave and Q-wave MI, respectively, with a Q-wave MI plateau at 1% **(Figure 3)**. The TLR rate at five-year follow-up was 3.8% (18). Most of the TLR occurred during the first two years, with a tendency to plateau after two years. Interestingly, for TVR and non-TLR TVR, the rates increased linearly **(Figure 4)**. Target lesion failure (TLF), defined as a composite of cardiac death that could not be clearly attributed to a non-target vessel, target vessel MI or TLR, had a cumulative incidence of 8.2% (39) at five-year follow-up **(Figure 5)**. The five-year definite stent thrombosis (ST) cumulative incidence was only 1.2% (6). Most of the ST occurred during the first year (0.8%), and after two years it plateaued at 0.4% **(Figure 6)**.

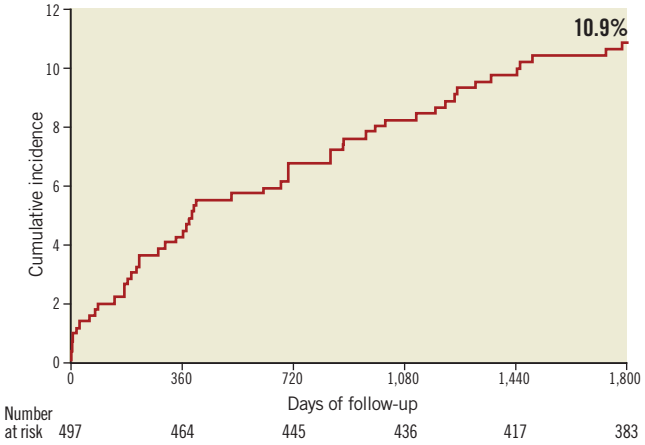


Figure 1. *Hierarchical MACE. Cumulative incidence rate at 5 years.*

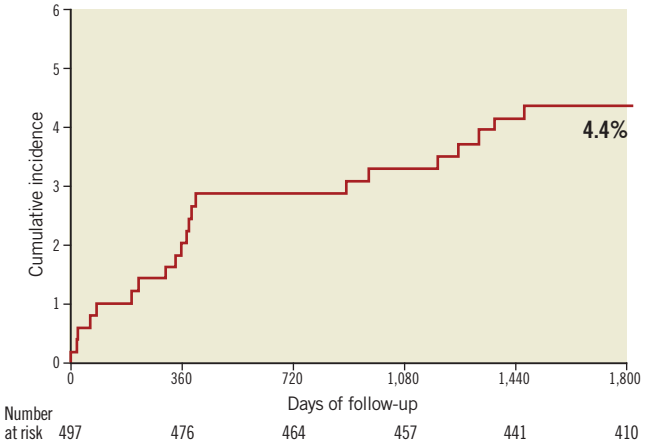


Figure 2. *Cardiac death. Cumulative incidence rate at 5 years.*

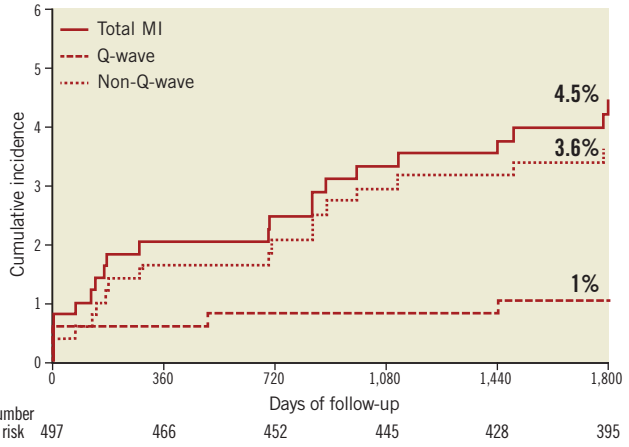


Figure 3. *Myocardial infarction, stratified by Q-wave and non-Q-wave MI. Cumulative incidence rate at 5 years. MI: myocardial infarction*

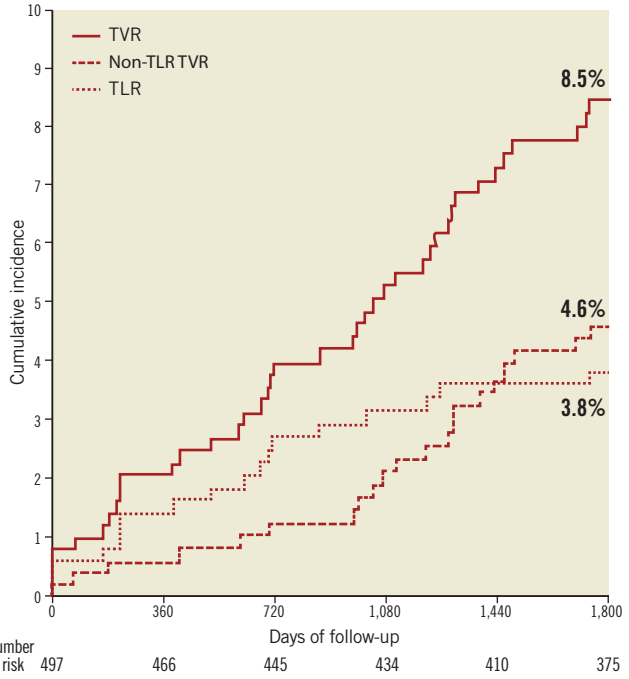


Figure 4. *Revascularisation stratified by TVR, TLR only and non-TLR TVR only. Cumulative incidence rate at 5 years. TVR: target vessel revascularisation*

Discussion

The final five-year follow-up results of the LEADERS trial using a similar Biolimus A9-eluting stent have been published[15-19]. The results showed that a biodegradable polymer-based Biolimus A9-eluting stent (BES) was non-inferior to a durable polymer sirolimus-eluting stent (SES). Compared with a durable polymer SES, the biodegradable polymer-based BES was linked to a significant reduction in very late (>1 year) ST and associated composite clinical endpoints. The safety benefit of the biodegradable polymer-based BES appeared to occur in more complex CAD and was secondary to a reduction in MI and repeat revascularisation.

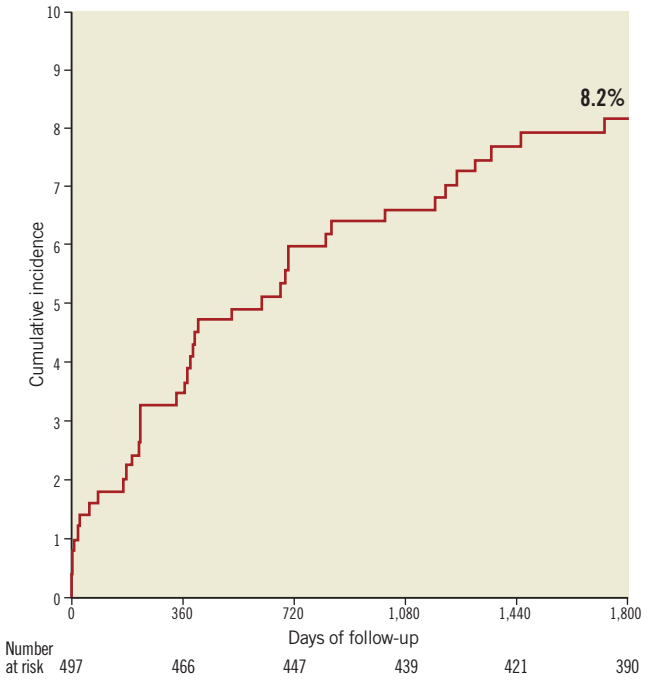


Figure 5. *Target lesion failure. Cumulative incidence rate at 5 years.*

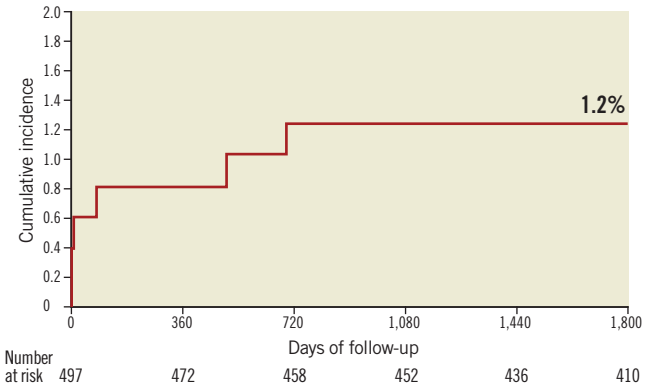


Figure 6. *Definite ST. Cumulative incidence rate at 5 years. ST: stent thrombosis*

Patient demographics and characteristics differed across LEADERS and BEACON II. Asian patients undergoing percutaneous coronary intervention (PCI) were usually much younger with a high prevalence of CV risk factors[20]. BEACON II patients, as compared to LEADERS patients, were younger (59.8 vs. 64.6), had a higher prevalence of diabetes (32.5% vs. 26.0%) and hypercholesterolaemia (74.4% vs. 65.3%) and a higher rate of multivessel disease (58.1% vs. 24.4%). In LEADERS[15], the MACE rate at nine months was 9.1%, while in BEACON II the rate at one year was 4.9%.

Patient compliance with DAPT and follow-up rates were similar at five years. Follow-up was available in 96% of patients in the BES arm of the LEADERS trial and in 94% of patients in BEACON II at five years. The final five-year report of the LEADERS trial[19] demonstrated that there was a significant interaction between treatment effect and time (zero to one year, and one to five years, p-value for interaction=0.022). Specifically, there was a significantly lower risk of definite ST for the biodegradable polymer BES compared with the durable polymer SES, from years one to five (RR: 0.26 [95% CI: 0.10 to 0.68]; p=0.003), whereas, at year zero to one year, the incidence of definite ST was similar between the two groups. Similar findings were noted in BEACON II for ST: there was a significant interaction between treatment effect and time (zero to one year, and one to five years, p-value for interaction=0.043). The Kaplan-Meier cumulative incidence percentage at zero to one year, and from one to five years was 0.8% and 0.4%, respectively.

A favourable advantage of the biodegradable polymer BES stent seems to occur after one year, in particular the rare incidence of VLST. Both LEADERS and BEACON II showed similar low very late event rates for BES, in particular very late definite stent thrombosis from one to five years.

Another biodegradable polymer BES is the Nobori® (Terumo Corporation, Tokyo, Japan). The only difference between the BioMatrix and the Nobori stent is the slight modification in stent design, the delivery catheter and the coating method. The use of the Nobori stent results in better endothelial recovery, with normal coronary vasodilatation in the adjacent stent segment after implantation, contrasting with the paradoxical vasoconstriction seen with first-generation DES[21]. A recently pooled analysis based on individual patient data from the ISAR-TEST 3, ISAR-TEST 4 and LEADERS trials[22] showed that biodegradable DES (BioMatrix Flex™, n=857; and biodegradable polymer SES, n=1,501) improved safety and efficacy compared with durable polymer SES during long-term follow-up to four years. In this meta-analysis, the efficacy endpoint of interest was TLR and the safety endpoint of interest was definite ST. At four years, the risk of TLR was significantly lower with biodegradable polymer DES vs. durable polymer SES (hazard ratio [HR] 0.82, 95% CI: 0.68-0.98, p=0.0029). In addition, the risk of ST was also significantly reduced with biodegradable polymer DES vs. durable polymer SES (HR 0.56, 95% CI: 0.35-0.90, p=0.015), driven by a lower risk of VLST (HR 0.22, 95% CI: 0.08-0.61, p=0.004). The incidence of MI between one and four years was lower with biodegradable polymer DES vs. durable polymer SES (HR 0.59, 95% CI: 0.73-0.95, p=0.031). In the COMPARE II and NEXT trials, biodegradable polymer BES have been shown to be as safe and efficacious as the current standard of a thin-strut everolimus-eluting stent with a durable biocompatible polymer at one-year follow-up[23,24]. Longer-term follow-up will show whether the beneficial effect of the biodegradable polymer BES on late stent thrombosis also applies when compared to newer-generation DES.

The concept of polymer-free stents and bioresorbable vascular scaffolds looks very interesting. Preclinical studies support their use, but robust clinical data are still lacking. Until then, biodegradable polymer BES/DES will have a major role to play in our daily PCI practice.

Limitations

Several limitations should be underlined. First of all, this is a single-group, non-randomised design, which has some degree of selection bias. Data analysis is hence descriptive in nature and inferior to a randomised trial as no direct comparison can be made versus a control group. Secondly, the results reported here may have been affected by the type of bias inherent in all registries, namely the selective inclusion of lower-risk patients, together with less exhaustive monitoring than that applied in randomised controlled trials, potentially contributing to an overall under-reporting of events. Additionally, the SYNTAX score was not common practice at all study sites at the time of the study and was not calculated for all patients as part of the screening process. Patients with left main disease were excluded during the enrolment period in 2008 as the choice of treatment then was CABG. This was before the ACCF/AHA/SCAI guidelines for left main PCI were established in 2011. Last but not least, our sample size was small and was not calculated to determine predictive factors for MACE, revascularisation and stent thrombosis outcome.

Conclusions

The BEACON II registry confirms the findings of the LEADERS trial and other trials involving biodegradable polymer BES. Indeed, the BioMatrix stent has a good safety profile up to five years when used in routine clinical practice in an Asian Pacific population. There appears to be a significant interaction between treatment effect and time zero to one year and from one to five years. After one year, the rate of definite ST (VLST) was very low and was maintained up to five years.

Impact on daily practice

In daily clinical practice we often encounter complex lesions and Asian patients in particular have a high prevalence of diabetes mellitus. The findings from the BEACON II registry, which indicate a good safety profile in the BioMatrix drug-eluting stent, at least up to five years, give us great reassurance in using this stent in our routine clinical practice.

Acknowledgements

This study was supported by Biosensors International Group, Singapore.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R; RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-80.

2. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME; TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med.* 2004;350:221-31.

3. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schömig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Jüni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet.* 2007;370:937-48.

4. Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med.* 2006;119:1056-61.

5. Jensen LO, Tilsted HH, Thayssen P, Kaltoft A, Maeng M, Lassen JF, Hansen KN, Madsen M, Ravkilde J, Johnsen SP, Sorensen HT, Thuesen L. Paclitaxel and sirolimus eluting stents versus bare metal stents: long-term risk of stent thrombosis and other outcomes. From the Western Denmark Heart Registry. *EuroIntervention.* 2010;5:898-905.

6. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol.* 2006;48:193-202.

7. Finn AV, Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R. Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler Thromb Vasc Biol.* 2007;27:1500-10.

8. Finn AV, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation.* 2007;115:2435-41.

9. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, Kimura T, Briguori C, Sabate M, Kim HS, De Waha A, Kedhi E, Smits PC, Kaiser C, Sardella G, Marullo A, Kirtane AJ, Leon MB, Stone GW. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet.* 2012;379:1393-402.

10. Cemenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation.* 2007;115:1440-55; discussion 1455.

11. Raber L, Wohlwend L, Wigger M, Togni M, Wandel S, Wenaweser P, Cook S, Moschovitis A, Vogel R, Kalesan B, Seiler C, Eberli F, Luscher TF, Meier B, Jüni P, Windecker S. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial. *Circulation.* 2011;123:2819-28.

12. Raber L, Baumgartner S, Garcia HM, Kalesan B, Justiz J, Pilgrim T, Moschovitis A, Khattab AA, Buellesfeld L, Wenaweser P,

Meier B, Serruys P, Jüni P, Windecker S. Long-term vascular healing in response to sirolimus-eluting and paclitaxel-eluting stents: an optical coherence tomography study. *JACC Cardiovasc Interv.* 2012;5:946-57.

13. Park SJ, Kang SJ, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a final common pathway of late stent failure. *J Am Coll Cardiol.* 2012;59:2051-7.

14. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115: 2344-51.

15. Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, Di Mario C, Davies S, Van Geuns RJ, Eerdmans P, van Es GA, Meier B, Jüni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet.* 2008;372:1163-73.

16. Klauss V, Serruys PW, Pilgrim T, Buszman P, Linke A, Ischinger T, Eberli F, Corti R, Wijns W, Morice MC, Di Mario C, van Geuns RJ, van Es GA, Kalesan B, Wenaweser P, Jüni P, Windecker S. 2-year clinical follow-up from the randomized comparison of biolimus-eluting stents with biodegradable polymer and sirolimus-eluting stents with durable polymer in routine clinical practice. *JACC Cardiovasc Interv.* 2011;4:887-95.

17. Wykrzykowska J, Serruys P, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, Di Mario C, Van Geuns RJ, Van Es GA, Juni P, Windecker S. The three year follow-up of the randomized "all-comers" trial of a biodegradable polymer biolimus-eluting stent versus permanent polymer sirolimus-eluting stent (LEADERS). *EuroIntervention.* 2011;7:789-95.

18. Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, van Es GA, Meier B, Windecker S, Jüni P. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet.* 2011;378:1940-8.

19. Serruys PW, Farooq V, Kalesan B, De Vries, Buszman P, Linke A, Ischinger T, Klauss V, Eberli F, Wijns W, Morice MC, Di Mario C, Corti R, Antoni D, Sohn HY, Eerdmans P, Rademaker-Havinga T, van Es GA, Meier B, Jüni P, Windecker S. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted from a Durable Versus ERodable Stent Coating) randomized, noninferiority trial. *JACC Cardiovasc Interv.* 2013;6:777-89.

20. Ahmad WA, Ali RM, Khanom M, Han CK, Bang LH, Yip AF, Ghazi AM, Ismail O, Zambahari R, Hian SK. The journey of Malaysian NCVD-PCI (National Cardiovascular Disease Database-Percutaneous Coronary Intervention) registry: a summary of three years report. *Int J Cardiol.* 2013;165:161-4.

21. Hamilos M, Ostojic M, Beleslin B, Sagic D, Mangovski L, Stojkovic S, Nedeljkovic M, Orlic D, Milosavlijevic B, Topic D, Karanovic N, Wijns W; NOBORI CORE Investigators. Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. *J Am Coll Cardiol.* 2008;51:2123-9.

22. Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, Jüni P, Schömig A, Windecker S, Kastrati A. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. *Eur Heart J.* 2012;33:1214-22.

23. Smits PC, Hofma S, Togni M, Vázquez N, Valdés M, Voudris V, Slagboom T, Goy JJ, Vuillomenet A, Serra A, Nouche RT, den Heijer P, van der Ent M. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. *Lancet.* 2013;381:651-60.

24. Natsuaki M, Kozuma K, Morimoto T, Kadota K, Muramatsu T, Nakagawa Y, Akasaka T, Igarashi K, Tanabe K, Morino Y, Ishikawa T, Nishikawa H, Awata M, Abe M, Okada H, Takatsu Y, Ogata N, Kimura K, Urasawa K, Tarutani Y, Shiode N, Kimura T; NEXT Investigators. Biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent: a randomized, controlled, noninferiority trial. *J Am Coll Cardiol.* 2013;62:181-90.

AsiaIntervention 2015;1:109-115

One-year mortality of primary angioplasty for acute myocardial infarction during regular working hours versus off-hours

Surya Dharma[1]*, MD, PhD, FIHA, FICA, FAPSIC, FESC, FSCAI; Renan Sukmawan[1], MD, PhD, FIHA; Bambang Budi Siswanto[1], MD, PhD, FIHA, FAsCC, FAPSC, FESC, FACC, FSCAI; Hananto Andriantoro[1], MD, PhD, FIHA, FICA; Iwan Dakota[1], MD, PhD, FIHA, FICA, FESC, FSCAI; Sunil V. Rao[2], MD, FSCAI

1. Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, National Cardiovascular Center Harapan Kita, Jakarta, Indonesia; 2. Duke University Medical Center, Durham VA Medical Center, Durham, NC, USA

KEYWORDS

- long-term mortality
- off-hours
- regular hours
- STEMI care

Abstract

Aims: We aimed to evaluate the relationship between timing of admission and long-term mortality of ST-elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (PPCI) in a tertiary care academic teaching hospital.

Methods and results: A total of 1,126 STEMI patients admitted during off-hours (week nights, weekends, holidays) and regular hours treated with PPCI between 2008-2013 were analysed. Descriptive analysis and multivariable survival analysis were used to estimate the relationship between treatment during off-hours versus regular hours and the incidence of all-cause mortality during hospitalisation and at one-year follow-up. There was a similar proportion of patients achieving door-to-device time ≤90 minutes (45.3% vs. 48%) among STEMI patients admitted during off-hours (n=857) as compared with regular hours (n=269). Aspirin and clopidogrel use within 24 hours approached 97% and 98% of patients admitted in off-hours and regular hours, respectively. Achievement of post-PPCI Thrombolysis In Myocardial Infarction flow grade 3 approached 93% and 91% in off-hours and regular hours admission, respectively (p=0.18). In-hospital mortality was similar in patients admitted during off-hours and those admitted during regular hours (5.1% vs. 5.9%; adjusted hazard ratio 0.81; 95% CI: 0.43-1.54). One-year mortality was also similar (10.5% vs. 13%; adjusted hazard ratio 0.73; 95% CI: 0.46-1.12).

Conclusions: STEMI patients who were admitted during off-hours to an academic hospital and treated with PPCI had similar survival at one year as compared with those who were admitted during regular hours. Study registration: Clinicaltrials.gov NCT02319473

**Corresponding author: Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, National Cardiovascular Center Harapan Kita, Jl S Parman Kav 87, Slipi, Jakarta Barat, 11420, Indonesia. E-mail: drsuryadharma@yahoo.com*

DOI: 10.4244/AsiaInterv_V1I2A21

Introduction

Randomised clinical trials have shown the superiority of primary percutaneous coronary intervention (PPCI) over fibrinolysis therapy in terms of better event-free survival and clinical outcomes in patients with acute ST-elevation myocardial infarction (STEMI)[1]. However, there has been concern as to whether STEMI patients who are admitted during off-hours (week nights, weekends, and holidays) to undergo PPCI might have higher mortality than patients admitted during regular "office" hours. The mortality difference is thought to be due to the variations in door-to-device (DTD) time, door-to-ECG time, awareness of the alarm centre staff, physician performance, and the numbers of staff in the catheterisation laboratory and intensive cardiovascular care unit. On the other hand, the establishment of a STEMI network may narrow these disparities, resulting in similar outcomes regardless of the time of the patient's presentation.

Editorial, see page 93

While prior studies have shown contradictory outcomes in STEMI patients who underwent PPCI during off-hours versus regular office hours[2-14], most of the studies did not evaluate the long-term outcomes[3,4,6,8,9,11-14]. Moreover, many of these studies included several centres, and results from hospitals with poor STEMI processes may offset those from leading centres (i.e., "regression to the mean"). In this context, data from a single centre may provide value by providing an example of "best practices" for PPCI if outcomes are similar between off-hours and on-hours patients. We evaluated the relationship between timing of admission of STEMI patients (off-hours versus regular hours) and long-term mortality of STEMI patients treated with PPCI in a tertiary care academic teaching hospital.

Methods

PATIENT POPULATION

Data were derived from a local registry (Jakarta Acute Coronary Syndrome [JAC] registry) in the National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. The hospital is a tertiary referral and teaching hospital, serving approximately 11 million inhabitants. The hospital provides a 24/7 PPCI service and performs approximately 2,000 PCIs annually with 13 interventional cardiologists. Since 2008, all consecutive patients with acute coronary syndrome (ACS), including STEMI patients who presented within 12 hours of symptom onset and underwent PPCI in the hospital, were recorded in the database. Using the JAC registry database, we examined the characteristics of STEMI patients admitted during off-hours versus regular hours and treated with PPCI. The Jakarta Cardiovascular Care Unit Network System was developed in 2010 to provide rapid and optimal reperfusion therapy for STEMI within a regional network of 156 hospitals and 44 primary healthcare centres. The STEMI network is coordinated by the emergency department (ED) staff of our hospital and manned 24/7[15-17]. Currently, the JAC registry is the main data source for measuring the performance of the STEMI network, and this study is part of the analysis of the performance measures.

Hospital admission time (off-hours and regular hours) was the primary basis for classification used in the study cohort. Off-hours arrival time was defined as week nights (Monday to Thursday: 4 pm to 7.30 am, and Friday: 4.30 pm to 7.30 am), weekends, and holidays. Regular hours arrival was defined as weekdays/regular office hours (Monday to Thursday: 7.30 am to 4 pm, and Friday: 7.30 am to 4.30 pm).

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 leads[18]. This study has been approved by the local institutional review board committee.

STUDY SAMPLE

Between 1st January 2008 and 29th December 2013, the JAC registry database contained 15,252 ACS patients, of whom 5,237 were STEMI patients. Of these, 1,126 patients underwent PPCI and were included in the analysis. The majority of STEMI patients did not receive reperfusion therapy, mainly due to late presentation of the patient[15-17]. Patient distribution is displayed in **Figure 1**. Patients with a repeated PPCI procedure were included in the study since hospital admission time is the primary basis of the analysis.

MANAGEMENT PROTOCOL

The management of STEMI was in accordance with the European Society of Cardiology (ESC) guidelines[18]. All patients were pretreated with 160-320 mg acetylsalicylic acid and 600 mg clopidogrel orally before PPCI, followed by daily administration of 75 mg clopidogrel for six to 12 months after discharge and 80-100 mg acetylsalicylic acid indefinitely. Before PPCI, all patients received an intravenous bolus of unfractionated heparin in the catheterisation laboratory (50 IU/kg if receiving glycoprotein IIb/IIIa inhibitor [GPI] or 100 IU/kg if not receiving GPI). The use of GPI was left to the discretion of the interventional cardiologist in charge.

Vascular access site choice for PPCI was according to operator preference, and PPCI was performed based on standard techniques. In our institution, stenting only in the infarct-related coronary artery (IRA) was adopted. Technical considerations, such as direct stenting or balloon predilation were left to the operator's discretion. Manual thrombus aspiration was recommended as part of the local protocol[19].

Angiographic measurement of coronary flow using the Thrombolysis In Myocardial Infarction (TIMI) flow classification was applied to evaluate the microvascular perfusion in all patients following PPCI[20].

DATA COLLECTION AND FOLLOW-UP

Data elements consisting of demographic, clinical, procedural, angiographic and follow-up variables were collected from the JAC registry electronic database. Data quality is maintained through point-of-entry and monthly data quality checks by the principal investigator of the JAC registry (SD). In-hospital and one-year mortality were obtained from the medical records, phone calls, and/or family interviews by dedicated research staff using a standardised questionnaire.

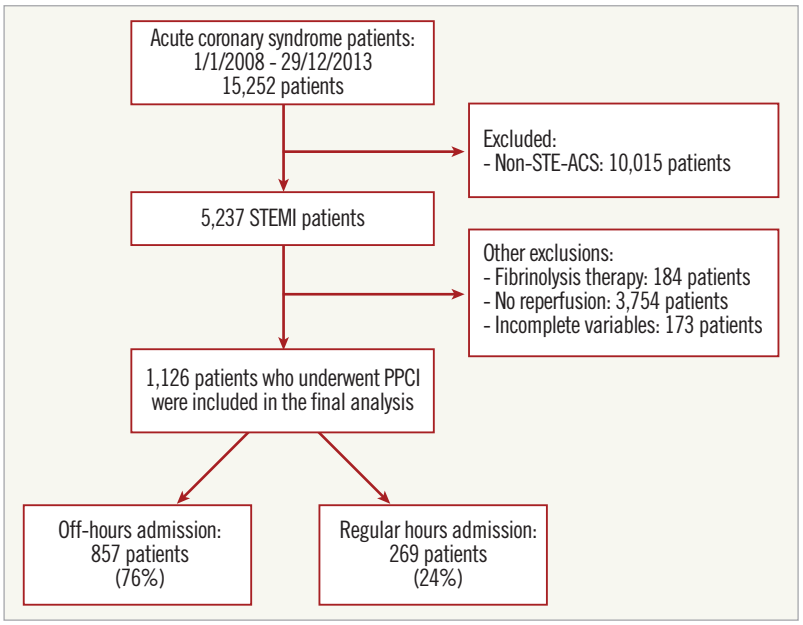


Figure 1. *Patient distribution. PPCI: primary percutaneous coronary intervention; STE-ACS: ST-elevation acute coronary syndrome; STEMI: ST-elevation myocardial infarction*

STUDY OUTCOME AND DEFINITION

The primary outcome of the study was all-cause mortality, assessed at one-year follow-up. The secondary outcomes included in-hospital mortality, proportion of patients achieving door-to-device (DTD) time ≤90 minutes, dual antiplatelet use within 24 hours and achievement of post-PPCI TIMI flow grade 3. Door-to-device time was defined as the time from patient arrival at the emergency department to the introduction of the first device, either a thrombus aspiration catheter or a balloon catheter into the IRA. Thrombolysis In Myocardial Infarction flow grade 3 was defined as a patent epicardial artery with normal flow[20].

STATISTICAL METHODS

We grouped patients according to time of admission (off-hours or regular hours). Baseline demographic, medical history, and procedural data were compared between the two groups. Data are expressed as mean±standard deviation for normally distributed continuous variables. For skewed distribution, data are expressed as median and range. Continuous variables were compared with the Student's t-test or Mann-Whitney U test and the chi-square test or Fisher's exact test was used to compare categorical variables as appropriate. Cox proportional hazard regression models were used to examine the association between treatment during off-hours versus regular hours and the incidence of all-cause mortality during hospitalisation and at one-year follow-up.

The incidence of death over time was studied with the use of the Kaplan-Meier method, and a log-rank test was applied to evaluate differences between the two groups (admission during off-hours versus regular hours). Hazard ratios (HR) (95% confidence intervals) for in-hospital and one-year mortality by off-hours and regular hours are presented, where the reference is off-hours. Several baseline clinical and procedural characteristics which are listed in **Table 1** were considered as potential confounders for the in-hospital and one-year mortality; therefore, the relevant variables were used to adjust the HRs including sex, diabetes mellitus, anterior MI, Killip class, TIMI risk score, symptom onset, thrombus aspiration and post-PPCI TIMI flow grade. The analysis was repeated in several important subgroups, including the relevant variables described.

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).

Results

STUDY SAMPLE

Out of 1,126 patients presenting with STEMI who underwent PPCI in our institution, 857 (76%) presented during off-hours **(Figure 1)**.

CLINICAL CHARACTERISTICS

The majority of STEMI patients in both groups were referred from other hospitals and presented to the ED of our hospital within two to six hours after symptom onset. Aspirin and clopidogrel use within 24 hours approached 97% and 98% of patients admitted in off-hours and regular hours, respectively. Discharge treatment was similar in both groups. In general, the patient clinical characteristics were similar between off-hours and regular hours admission **(Table 1)**.

PROCEDURAL AND ANGIOGRAPHIC CHARACTERISTICS

The proportions of patients receiving DTD in ≤90 minutes and final achievement of TIMI 3 flow after PPCI were similar between the two groups. However, the use of manual thrombus aspiration during PPCI

Table 1. Clinical characteristics of STEMI patients based on timing of presentation.

		Off-hours (n=857)	Regular hours (n=269)	*p*-value
Age, years		55.44±9.73	56.4±9.94	0.15
Male gender, n (%)		753 (87%)	224 (83%)	0.052
Source of referral, n (%)	Walk-in/Ambulance	250 (29.1%)	74 (27.5%)	0.59
	Inter-hospital	580 (67.6%)	171 (63.5%)	0.21
Anterior wall MI, n (%)		484 (56.5%)	152 (56%)	0.99
Blood pressure, mmHg	Systolic BP	131 (56-220)	130 (18-240)	0.77
	Diastolic BP	80 (33-153)	77 (43-131)	0.16
Heart rate, bpm		78 (16-166)	76 (20-142)	0.23
Risk stratification, n (%)	Killip class 1	623 (72.7%)	207 (76.9%)	0.167
	Killip class 2-4	234 (27.3%)	62 (23%)	
	TIMI score >4	310 (36.2%)	88 (32.7%)	0.30
Risk factor, n (%)	Hypertension	472 (55%)	154 (57.2%)	0.53
	Diabetes mellitus	256 (29.8%)	74 (27.5%)	0.45
	Dyslipidaemia	385 (44.9%)	130 (48.3%)	0.33
	Smoker	570 (66.5%)	163 (60.6%)	0.07
	Family history	189 (22%)	57 (21.2%)	0.76
Onset of infarction, hours	2-6 hrs	463 (54%)	150 (55.7%)	0.61
	6-12 hrs	310 (36.2%)	80 (29.7%)	0.053
Antiplatelet within the first 24 hrs, n (%)	Aspirin	836 (97%)	264 (98%)	0.57
	Clopidogrel	829 (97%)	263 (98%)	0.38
Medication at discharge, n (%)	Aspirin	788 (92%)	249 (92%)	0.74
	Clopidogrel	786 (91%)	246 (91%)	0.89
	ACE inhibitor	656 (76%)	190 (71%)	0.12
	Statin	789 (92%)	240 (89%)	0.14
	Beta-blocker	646 (75%)	185 (69%)	0.08
Length of stay, days		5.86±4.63	6.45±4.91	0.07

BP: blood pressure; MI: myocardial infarction; PPCI: primary percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

was more common in the off-hours than the regular hours patients (off-hours 49.6% vs. regular hours 41.6%, p=0.009) **(Table 2)**.

MORTALITY

Survival data were complete for all patients. The cumulative incidence of all-cause mortality during the hospitalisation period was similar in STEMI patients admitted during off-hours versus regular hours (5.1% vs. 5.9%). Similarly, no statistically significant differences were found in all-cause mortality at one year (10.5% vs. 13.0%). The log-rank test of the one-year cumulative survival between the two groups was 0.21 **(Figure 2)**. Multivariable adjustment for confounders of the relation between admission timing (off-hours) showed no significant association between off-hours presentation and early or later mortality (adjusted HR for in-hospital mortality 0.81, 95% CI: 0.43-1.54; adjusted HR for one-year mortality 0.73, 95% CI: 0.46-1.12) **(Table 3)**.

Table 2. Procedural characteristics.

		Off-hours (n=857)	Regular hours (n=269)	*p*-value
Door-to-device, minutes		114±89.32	111±66.65	0.58
Door-to-device ≤90 minutes, n (%)		388 (45.3%)	129 (48%)	0.44
Manual thrombus aspiration, n (%)		425 (49.6%)	112 (41.6%)	0.009
Post-PPCI TIMI 3 flow, n (%)		801 (93%)	245 (91%)	0.18
Use of GPI, n (%)		574 (67%)	172 (64%)	0.35
Culprit vessel, n (%)	LAD	394 (46%)	117 (43.5%)	0.45
	LCX	37 (4.3%)	15 (5.6%)	0.38
	RCA	288 (33.6%)	89 (33.1%)	0.47

GPI: glycoprotein IIb/IIIa inhibitor; LAD: left anterior descending artery; LCX: left circumflex artery; PPCI: primary percutaneous coronary intervention; RCA: right coronary artery; TIMI: Thrombolysis In Myocardial Infarction

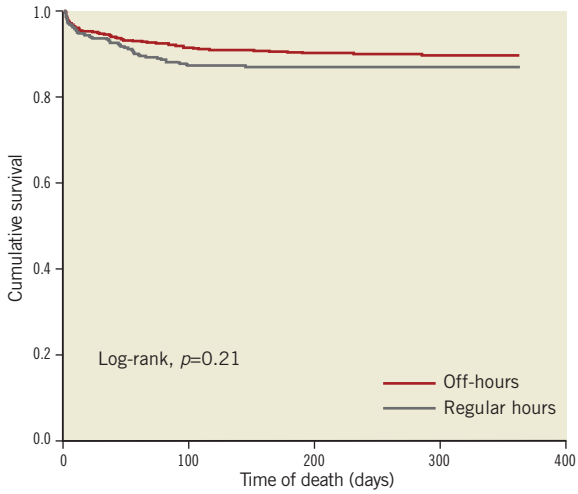


Figure 2. *The one-year cumulative survival between off-hours and regular hours admission.*

Table 3. Primary outcomes according to timing of admission.

		In-hospital			1-year		
		Number of events, n (%)	Crude HR and 95% CI	Adjusted HR and 95% CI	Number of events, n (%)	Crude HR and 95% CI	Adjusted HR and 95% CI
Death	Off-hours	44 (5.1%)	0.86 (0.48–1.52)	0.81 (0.43–1.54)	90 (10.5%)	0.77 (0.52–1.15)	0.73 (0.46–1.12)
	Regular hours	16 (5.9%)	1	1	35 (13%)	1	1

CI: confidence interval; HR: hazard ratio

SUBGROUP ANALYSIS

In the subgroup analysis involving several relevant clinical and procedural variables, we found a consistent result with respect to the similar mortality at one year between the two admission times across all subgroups **(Figure 3)**.

Discussion

In this long-term follow-up study involving 1,126 patients with STEMI undergoing PPCI at an academic hospital, we found that admission during off-hours was not associated with an increased risk of short or long-term mortality. The results are consistent in the relevant subgroups. These data suggest that, at centres with well-established STEMI processes, outcomes are not compromised even when patients present during times when full hospital operations are not available.

Prior studies have demonstrated that the disparity in quality of care may account, in part, for the differences in STEMI patients admitted during off-hours and regular hours. However, previously published data from 1999 to 2014 have shown conflicting results and demonstrated differences in reperfusion times among patients with STEMI based on the time of presentation, leading to outcome differences[2-14]. For example, previous studies showed that STEMI patients presenting during off-hours are less likely to achieve certain parameters of performance measures for STEMI care such as door-to-balloon time ≤90 minutes, door-to ECG time ≤10 minutes, and a smaller proportion of patients receiving aspirin within 24 hours than regular hours admission. Other concerns include the number and performance of physicians and hospital staff during off-hours which may differ from those encountered during regular office hours. Our study indicates that at an academic centre with an established programme for STEMI care these disparities do not exist.

There are several reasons which may explain the similar outcomes of STEMI patients admitted during off-hours and regular hours in this study. First, our hospital has similar performance for treating STEMI patients over time, as shown by the similar proportion of patients reaching a DTD time of ≤90 minutes and receiving aspirin within 24 hours between off-hours and regular hours admission. Second, the performance of the interventional cardiologist may also be similar due to the similar achievement of post-PPCI TIMI flow grade 3 of the culprit vessel in the two admission times. In addition, the higher number of thrombus aspiration procedures in the off-hours group than in the regular hours group may partly indicate that the performance of the treating interventional cardiologist in our hospital is not lacking during off-hours. Third, there are inherent structural and process characteristics of our hospital which may allow a similar quality of care during the day, at night and at weekends. For example, the catheterisation laboratory nurses on duty (two persons) stay in the hospital during the off-hours and are dedicated to support the 24 hr emergency services including PPCI. In addition, the medical residents and the cardiologist on duty also stay in the hospital during off-hours. This immediate availability of the catheterisation laboratory team is consistent with the findings from the GRACE registry that has shown higher primary PCI utilisation at academic centres[21]. The similar discharge treatment between the two groups may further explain the similar one-year mortality between the two groups. This is an important process-based performance measure and again supports the hypothesis that the system for STEMI set up at our hospital allows similar management of STEMI patients regardless of the time of day. Compared to our hospital, other hospitals in the region may have different healthcare resources and staffing patterns. Currently, only our hospital has a 24/7 service for primary PCI covered by the government healthcare insurance system and not all hospitals have an

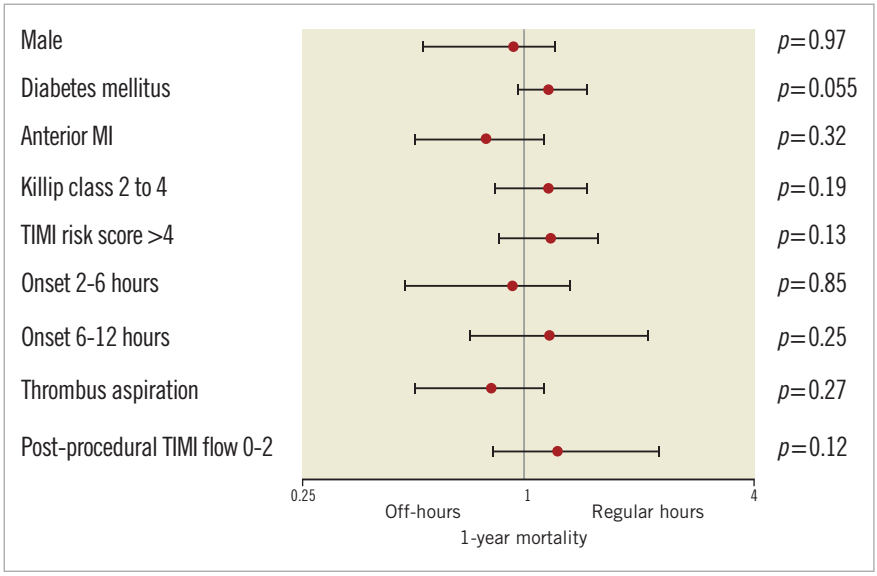


Figure 3. *Subgroup analysis of patients according to admission time and all-cause mortality at one year. Data are presented as hazard ratios and 95% confidence intervals. MI: myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction*

on-site cardiologist/interventional cardiologist or catheterisation laboratory nurses during off-hours. The mean number of board-certified cardiologists per million population in Jakarta is 18.9[17]. Our study suggests that increasing this number may optimise the care of STEMI patients in the region.

Quality improvement initiatives that focus on attainment of quality measures for STEMI care at all times of presentation include: 1) additional numbers of in-house catheterisation laboratory personnel (physician and nurses) at all PPCI centres; 2) implementation of a STEMI network in the community in order to increase the awareness of STEMI among the public and reduce the symptom onset-to-door time, thus reducing the proportion of non-reperfused STEMI patients.

Limitations

The reported results are based on a single-centre experience and should not be generalised to other hospitals in the region. Furthermore, several relevant variables have not been recorded in the database, and therefore cannot be evaluated, such as revascularisation history in multivessel disease patients and medication at one-year follow-up. However, the similar outcome at one-year follow-up in both off-hours and regular hours admission might somehow explain the good balance of the relevant variables in the two admission times. Finally, our study is observational and, like all observational studies, there may be unmeasured confounders that account for our findings.

Conclusion

STEMI patients who were admitted during off-hours to an academic hospital and treated with PPCI had similar survival at one year as compared to those with regular hours admission.

Impact on daily practice

This study described the methods to assess quality of care in patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention. The hospital performance should be similar for treating patients who are admitted during off-hours and regular hours. Thus, in daily practice, the results of this study will encourage the implementation of a regional STEMI network. When such a pathway works efficiently, reperfusion times are usually within the recommended guidelines, regardless of the admission times.

Acknowledgements

The authors thank all cardiologists who performed the PPCI procedures during the study period.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361:13-20.

2. Garot P, Juliard JM, Benamer H, Steg PG. Are the results of primary percutaneous transluminal coronary angioplasty for acute myocardial infarction different during the "off" hours? *Am J Cardiol.* 1997;79:1527-9.

3. Zahn R, Schiele R, Seidl K, Schuster S, Hauptmann KE, Voigtländer T, Gottwik M, Berg G, Kunz T, Glunz HG, Limbourg P, Senges J. Daytime and nighttime differences in patterns of performance of primary angioplasty in the treatment of patients with acute myocardial infarction. Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Study Group. *Am Heart J.* 1999;138:1111-7.

4. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N Engl J Med.* 2001;345:663-8.

5. Beohar N, Chandwaney R, Goodreau LM, Davidson CJ. In-hospital and long-term outcomes of patients with acute myocardial infarction undergoing direct angioplasty during regular and after hours. *J Invasive Cardiol.* 2001;13:669-72.

6. Henriques JP, Haasdijk AP, Zijlstra F; Zwolle Myocardial Infarction Study Group. Outcome of primary angioplasty for acute myocardial infarction during routine duty hours versus during off-hours. *J Am Coll Cardiol.* 2003;41:2138-42.

7. Sadeghi HM, Grines CL, Chandra HR, Mehran R, Fahy M, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Stuckey TD, Lansky AJ, O'Neill WW, Stone GW. Magnitude and impact of treatment delays on weeknights and weekends in patients undergoing primary angioplasty for acute myocardial infarction (the cadillac trial). *Am J Cardiol.* 2004;94:637-40.

8. Saleem MA, Kannam H, Aronow WS, Weiss MB, Kalapatapu K, Pucillo AL, Monsen CE. The effects of off-normal hours, age, and gender for coronary angioplasty on hospital mortality in patients undergoing coronary angioplasty for acute myocardial infarction. *Am J Cardiol.* 2004;93:763-4.

9. Magid DJ, Wang Y, Herrin J, McNamara RL, Bradley EH, Curtis JP, Pollack CV, French WJ, Blaney ME, Krumholz HM. Relationship between time of day, day of week, timeliness of reperfusion, and in-hospital mortality for patients with acute ST-segment elevation myocardial infarction. *JAMA.* 2005;294:803-12.

10. Kostis WJ, Demissie K, Marcella SW, Shao YH, Wilson AC, Moreyra AE; Myocardial Infarction Data Acquisition System (MIDAS 10) Study Group. Weekend versus weekday admission and mortality from myocardial infarction. *N Engl J Med.* 2007;356:1099-109.

11. Jneid H, Fonarow GC, Cannon CP, Palacios IF, Kilic T, Moukarbel GV, Maree AO, LaBresh KA, Liang L, Newby LK, Fletcher G, Wexler L, Peterson E; Get With the Guidelines Steering Committee and Investigators. Impact of time of presentation on the care and outcomes of acute myocardial infarction. *Circulation.* 2008;117:2502-9.

12. Glaser R, Naidu SS, Selzer F, Jacobs AK, Laskey WK, Srinivas VS, Slater JN, Wilensky RL. Factors associated with

poorer prognosis for patients undergoing primary percutaneous coronary intervention during off-hours: biology or systems failure? *JACC Cardiovasc Interv.* 2008;1:681-8.

13. Dasari TW, Roe MT, Chen AY, Peterson ED, Giugliano RP, Fonarow GC, Saucedo JF. Impact of time of presentation on process performance and outcomes in ST-segment-elevation myocardial infarction: a report from the American Heart Association: Mission Lifeline program. *Circ Cardiovasc Qual Outcomes.* 2014;7:656-63.

14. Sorita A, Lennon RJ, Haydour Q, Ahmed A, Bell MR, Rihal CS, Gersh BJ, Holmen JL, Shah ND, Murad MH, Ting HH. Off-hour admission and outcomes for patients with acute myocardial infarction undergoing percutaneous coronary interventions. *Am Heart J.* 2015;169:62-8.

15. Dharma S, Juzar DA, Firdaus I, Soerianata S, Wardeh AJ, Jukema JW. Acute myocardial infarction system of care in the third world. *Neth Heart J.* 2012;20:254-9.

16. Dharma S, Siswanto BB, Firdaus I, Dakota I, Andriantoro H, Wardeh AJ, van der Laarse A, Jukema JW. Temporal trends of system of care for STEMI: insights from the Jakarta Cardiovascular Care Unit Network System. *PLoS One.* 2014:9;e86665.

17. Dharma S, Andriantoro H, Dakota I, Purnawan I, Pratama V, Isnanijah H, Yamin M, Bagus T, Hartono B, Ratnaningsih E, Suling F, Basalamah MA. Organisation of reperfusion therapy for STEMI in a developing country. *Open Heart.* 2015;2:e000240.

18. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST segment elevation. *Eur Heart J.* 2012;33:2569-619.

19. Dharma S, Kedev S, Jukema JW. Thrombus management in the catheterisation laboratory in the setting of primary percutaneous coronary intervention: what is the current evidence? *Heart.* 2013;99:279-84.

20. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med.* 1985;312:932-6.

21. Fox KA, Goodman SG, Anderson JA Jr, Granger CB, Moscucci M, Flather MD, Spencer F, Budaj A, Dabbous OH, Gore JM; GRACE Investigators. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). *Eur Heart J.* 2003;24:1414-24.

AsiaIntervention 2015;1:116-123

Role of remote ischaemic preconditioning on myocardial injury in stable patients undergoing percutaneous coronary intervention: a randomised case-control study

Sudeep Kumar*, MD, DM, FACC, FSCAI, FESC, FAPSC, FCSI; Abhay Krishna, MD, DM; Aditya Kapoor, MD, DM, FACC, FAPSC; Satyendra Tewari, MD, DM, FACC, FSCAI, FAPSC; Naveen Garg, MD, DM, FACC, FSCAI; Pravin Kumar Goel, MD, DM, FACC, FSCAI

Department of Cardiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

KEYWORDS

- percutaneous coronary intervention
- periprocedural myocardial infarction
- remote ischaemic preconditioning
- troponin I

Abstract

Aims: Remote ischaemic preconditioning (RIPC) has been shown to reduce the incidence of myocardial injury in patients undergoing percutaneous coronary intervention (PCI) in preclinical and limited clinical trials. Our objective was to assess the applicability of RIPC before PCI in the effective reduction of myocardial injury among stable patients.

Methods and results: This was a single-centre, case-control, randomised study where 108 patients undergoing PCI were randomised to either RIPC or control group (n=54 each). Along with levels of troponin I and C-reactive protein (CRP), the incidence of PCI-related myocardial infarction (MI) was recorded at baseline, six, 12 and 24 hours after PCI. A significant reduction in troponin I release was seen in the RIPC group at both 12 (0.08±0.13 vs. 0.16±0.19 ng/ml, p=0.01) and 24 hours (0.06±0.04 vs. 0.22±0.3 ng/ml, p<0.01) post PCI as compared to that in the control group. RIPC was also found to be instrumental in reducing CRP levels in the RIPC group as compared to the control group at both 12 (p=0.04) and 24 hours (p=0.04) post PCI. A significant reduction in the incidence of PCI-related MI in the RIPC group was also noted when compared to the control group at 24 hours post PCI (14.8% vs. 38.9%, p<0.01), which however was found comparable at both six hours and 12 hours post PCI (p>0.05).

Conclusions: RIPC, administered by transient upper limb ischaemia, significantly reduces troponin I and CRP release at 12 and 24 hours post PCI, resulting in a significant reduction in the incidence of PCI-related MI at 24 hours post PCI.

**Corresponding author: Department of Cardiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, 226014, India. E-mail: sudeepkum@yahoo.com*

DOI: 10.4244/AsiaInterv_V1I2A22

Introduction

Troponin release is a sensitive and specific marker of myocyte necrosis and infarction resulting from a form of ischaemia/reperfusion injury, downstream embolisation of atheromatous material, and coronary side branch occlusion[1]. In addition to the strong diagnostic role of cardiac troponins, their prognostic value has become increasingly well established for patients presenting with acute coronary syndrome[2,3]. The inflammatory response and enzyme leakage during coronary angioplasty is increasingly becoming a recognised issue[4-6]. Elective percutaneous coronary intervention (PCI) is associated with troponin release in approximately one third of cases[7], and this troponin release is independently and significantly predictive of an increased risk of adverse events[8-11].

Transient sublethal episodes of ischaemia before a prolonged ischaemia/reperfusion injury, known as ischaemic preconditioning (IPC), have been shown to reduce the extent of myocardial injury[12]. Therefore, remote ischaemic preconditioning (RIPC) is a phenomenon in which brief episodes of ischaemia followed by reperfusion in one organ seem to provide systemic protection from prolonged ischaemia in the myocardial muscle and also to limit the myocardial infarction (MI) size[13]. This phenomenon has been observed in an animal model[13]. IPC has been used during cardiac surgery[14]. IPC has also been applied during angioplasty (regional vessel preconditioning) to reduce inflammation[15] and enzyme leakage[16,17]. A novel way to apply preconditioning via remote organ (e.g., limb) ischaemia reperfusion cycles has been described[18]. An added advantage is that the entire heart may thus be preconditioned, that is to say, globally, not regionally[19]. RIPC has been shown to protect against endothelial ischaemia/reperfusion injury[11] and the extent of MI after adult coronary bypass surgery[20,21], paediatric surgery[22], and non-cardiac surgery[23]. However, some studies failed to demonstrate a beneficial effect of RIPC during PCI[24].

Editorial, see page 96

The aim of our study was to determine whether RIPC before PCI reduces the cardiac enzyme release in stable patients (troponin I negative) with coronary artery disease.

Methods

STUDY POPULATION

This was a single-centre, prospective, randomised, case-control study. Patients (n=108) having stable angina (with negative troponin I) undergoing angioplasty were enrolled in the study during the period between March and December 2013. The present study was a one of a kind, a pilot project which attempted to explore the benefits of RIPC among subjects of Indian ethnicity. Thus, all qualifying patients were included for a flat 10-month recruitment period, and formal sample size calculation was reserved to the planned validation study with an increased follow-up duration (study still ongoing). After confirmation of their eligibility, all subjects duly consented and were then randomised to either RIPC or control group using sealed envelopes. Two clinicians from our author group, who were in charge of randomisation, prepared randomly generated treatment allocations within uniform sealed and opaque envelopes. Once the subject consented to the study, an envelope was opened and the patient was then placed in either the RIPC or the control group. These two clinicians were also responsible for administration of actual and mock preconditioning to the subjects. Other members of the study team were blinded to the procedures, including allotment of preconditioning/mock preconditioning and its administration to cases and controls. Patients with acute myocardial infarction, unstable angina, having elevated troponin I before PCI, additional cardiac disease, women of child-bearing age, nicorandil or glibenclamide use (preconditioning mimetic and preconditioning blocking medication, respectively), renal and hepatic insufficiency, malignancy, rheumatoid arthritis, active infection and severe comorbidity (estimated life expectancy <6 months) were excluded from this study.

PROCEDURAL INTERVENTIONS

During the time of admission, patients were instructed to avoid any strenuous activity which could provoke angina before their procedure. A baseline ECG was carried out in all patients. LV ejection fraction was calculated using Simpson's method of disc by echocardiography.

Patients randomised to RIPC had a blood pressure cuff placed around their non-dominant upper arm. The cuff was inflated to 200 mmHg pressures for five minutes followed by five minutes of deflation, to allow reperfusion. This was repeated for three cycles. Control patients had a similar cuff placed around the upper arm, but it was not inflated (mock preconditioning). These procedures were administered accordingly among the patient and control cohorts at 60-180 minutes prior to PCI with a mean duration of 95.15±27.36 minutes. Thereafter, all patients underwent PCI performed by an interventionist blinded to the study group allocation.

PCI was performed via the radial arterial approach using 6 Fr guiding catheters. All patients received 600 mg clopidogrel at least six hours before PCI. Patients were anticoagulated with a heparin bolus (70 to 100 U/kg) after arterial sheath insertion to achieve an activated clotting time >250 seconds. Glycoprotein IIb/IIIa antagonists were administered at the discretion of the primary operator. Stent inflation and balloon dilations were done in accordance with current clinical practice. For each patient, the number of vessels treated, number and type of stent, baseline and intraprocedural TIMI flow were noted. Aspirin and clopidogrel were advised to all patients after angioplasty as per standard practice. The severity of CAD was assessed by quantitative coronary angiography, and lesions were classified qualitatively according to the modified ACC/AHA classification[25] into type A, B and C. Chest pain severity during PCI was graded on a scale of zero for no pain to 10 for the most severe discomfort.

All patients were followed up after 30 days for any adverse event (death, reinfarction, stent thrombosis, recurrence of angina). Endpoint assessment was carried out by a team of two clinicians who were completely blinded to the whole randomisation process.

BIOCHEMISTRY

Venous blood samples were taken at the time of admission (baseline) and six, 12 and 24 hours after PCI for troponin I and C-reactive

protein (CRP). Serum creatinine samples at baseline and 24 hrs post PCI were also taken. Troponin I was analysed with an automated immunoassay (Triage® Cardiac panel; Biosite/Inverness Medical Innovations Inc., San Diego, CA, USA, now manufactured and distributed by Alere, Waltham, MA, USA). The 99th percentile of the troponin I level in a reference population (upper reference limit) of healthy volunteers was below the lower limit of detection of 0.04 ng/ml. The variation coefficient, a measure of precision within the analytical range was <10%, complying with the European Society of Cardiology/American College of Cardiology consensus requirements[25]. The analytical range was 0.05 to 30 ng/ml, with an assay sensitivity of 0.006 ng/ml. According to the joint task force of the European Society of Cardiology, American College of Cardiology Foundation, American Heart Association and World Heart Federation, a PCI-related MI (MI 4a) is defined as a rise in troponin >0.12 ng/ml (three times the upper reference limit)[26]. The World Health Organization definition for MI for this assay was ≥0.78 ng/ml. The lower limit for detection of CRP was 0.32 mg/dl.

STATISTICAL ANALYSIS

SPSS Version 16.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data entry and subsequent statistical analysis. Continuous data are represented as mean±standard deviation. Categorical data are represented as number (percentage). Difference of means between independent groups was analysed with the Student's t-test. Categorical variables were analysed with the chi-square test. Significance (two-tailed) was taken at a p-value of <0.05.

Table 1. Baseline demographic and clinical profile of patients.

Parameters	Whole cohort (n=108)	RIPC (n=54)	Control (n=54)	*p*-value*
Age, years (mean±SD)	57.67±8.82	57.19±7.31	58.15±10.16	0.57
BMI (kg/m^2)	24.14±3.12	24.04±3.04	24.23±3.22	0.76
Male, n (%)	92 (85.2)	50 (92.6)	42 (77.8)	0.06
Diabetes, n (%)	40 (37.0)	18 (33.8)	22 (40.7)	0.55
Smoker, n (%)	32 (29.6)	14 (25.9)	18 (33.3)	0.53
Hypertension, n (%)	68 (63.0)	30 (55.6)	38 (70.4)	0.16
Dyslipidaemia, n (%)	42 (38.9)	24 (44.4)	18 (33.3)	0.32
LVEF, % (mean±SD)	51.59±12.4	49.67±12.8	53.54±11.7	0.11
History of ACS/MI, n (%)	54 (50.0)	30 (55.6)	24 (44.4)	0.34
NYHA I/II, n (%)	86 (79.6)	42 (77.8)	44 (81.5)	0.81
NYHA III/IV, n (%)	22 (20.4)	12 (22.2)	10 (18.5)	0.81
Statins, n (%)	108 (100)	54 (100)	54 (100)	1.00
β-blockers, n (%)	106 (98.1)	54 (100)	52 (96.3)	0.50
ACE-I/ARB, n (%)	100 (92.6)	48 (88.9)	52 (96.3)	0.27
GP IIb/IIIa inhibitor use, n (%)	42 (38.9)	18 (33.3)	24 (44.4)	0.32
Prior PTCA, n (%)	8 (7.4)	2 (3.7)	6 (11.1)	0.27
Troponin I (ng/ml), (mean±SD)	0.051±0.002	0.050±0.002	0.051±0.003	0.41
CRP (mg/dl), (mean±SD)	0.43±0.27	0.46±0.24	0.39±0.29	0.22
Serum creatinine (mg/dl), (mean±SD)	1.10±0.40	1.12±0.53	1.08±0.20	0.64

*_p_-value shown is between RIPC group and control group; value of <0.05 considered as statistically significant. ACE-I: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; BMI: body mass index; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty

Results

One hundred and eight patients were randomised to RIPC and control arms (54 in each group). Normal distribution among the case and control groups was observed (p>0.05). RIPC was successfully administered to all 54 patients without any complication. The mean age of the study population was 57.67±8.82 years among which the majority were males (85.2%). Among conventional risk factors for CAD in our study cohort, around 37% of subjects had diabetes, 63% had hypertension, 29.6% had a history of smoking and 38.9% were dyslipidaemics. Both the study groups were comparable in terms of mean age, basal metabolic index (BMI) and gender distribution. The distribution of conventional risk factors for CAD was also found to be comparable among the two groups. The mean left ventricular ejection fraction (LVEF) of the whole cohort was 51.59±12.4%, which was also found to be comparable between the two groups **(Table 1)**.

Table 2 shows the angiographic parameters of the whole cohort and their distribution between both study groups. The left anterior descending (LAD) was found to be the most commonly treated artery (48.1%). A total of 25.9% of cases had double or triple-vessel percutaneous transluminal coronary angioplasty (PTCA), the distribution of which between RIPC and control groups was comparable. A total of 140 lesions were treated (68 in the RIPC group and 72 in the control group). Most of the treated lesions were type B1/B2 or type C (51.9% and 5.6%, respectively). The mean stent diameter and length used in the whole cohort was 3.07±0.33 mm and 20.55±6.36 mm, respectively. The mean lengths and diameters of the stents used were comparable between the two study groups. The subjects in the whole cohort were treated by a mean number of 1.54±0.84 stents/patient. Most (96.29%) of the subjects in the whole cohort were treated with at least one drug-eluting stent, the distribution of which was comparable between the two study groups (p>0.05) **(Table 2)**.

Table 3 shows the clinical and angiographic parameters during PCI of the total study population and both groups. Blood pressure and heart rate during PCI were comparable between both groups. A total of 15 (13.9%) patients had chest pain during PCI. Significantly more patients, i.e., 12 (22.2%), in the control group had a chest pain score >1 as compared to three (5.5%) patients in the RIPC group (p=0.02). Only seven (6.5%) patients had TIMI flow <3 during the procedure. However, the distribution of this was not significantly different between both groups, but it suggested a trend towards a lower incidence of cases with TIMI flow <3 during the procedure in the RIPC group (one [1.8%] vs. six [11.1%], p=0.12, in the RIPC and control group, respectively) **(Table 3)**.

Table 4 shows the troponin I, CRP levels and the incidence of PCI-related MI at six, 12 and 24 hours after PCI. Mean troponin I

Table 2. Angiography and angioplasty-related parameters.

Variable		Whole cohort (n=108)	RIPC (n=54)	Control (n=54)	*p*-value*
Target vessel	Left main only, n (%)	2 (1.8)	0 (0)	2 (3.7)	0.48
	LAD/ramus only, n (%)	52 (48.1)	28 (51.9)	24 (44.4)	0.56
	LCX only, n (%)	12 (11.1)	8 (14.8)	4 (7.4)	0.36
	RCA only, n (%)	14 (12.9)	4 (7.4)	10 (18.5)	0.15
	Double/triple-vessel PTCA, n (%)	28 (25.9)	14 (25.9)	14 (25.9)	1.00
Lesion classification (according to AHA/ACC)	Type A, n (%)	46 (32.8)	22 (32.3)	24 (33.3)	0.90
	Type B1/B2, n (%)	80 (57.1)	41 (60.3)	39 (54.2)	0.57
	Type C, n (%)	14 (10.0)	5 (7.3)	9 (12.5)	0.46
Stent diameter, mm (mean±SD)		3.07±0.33	3.07±0.32	3.07±0.33	0.97
Stent length, mm (mean±SD)		20.55±6.36	21.11±6.30	19.99±6.43	0.37
No. of stents (mean±SD)		1.54±0.84	1.44±0.74	1.63±0.92	0.25
DES, n (%)		104 (96.29)	50 (92.59)	54 (100)	0.13

**p*-value shown is between RIPC group and control group; value of <0.05 considered as statistically significant. AHA: American Heart Association; ACC: American College of Cardiology; DES: drug-eluting stent; LAD: left anterior descending artery; LCX: left circumflex artery; PTCA: percutaneous transluminal coronary angioplasty; RCA: right coronary artery

level was comparable between the two groups at six hours post PCI (p=0.14), but significantly lower in the RIPC group as compared to the control group at 12 and 24 hours post PCI (0.08±0.13 vs. 0.16±0.19 ng/ml, p=0.01, and 0.06±0.04 vs. 0.22±0.31 ng/ml, p<0.01, respectively). The CRP levels were also found to be comparable between the two groups at six hours post PCI (p=0.09) but significantly lower in the RIPC group as compared to the control group at 12 and 24 hours after PCI (0.46±0.35 vs. 0.71±0.78 mg/dl, p=0.04, and 0.53±0.48 vs. 1.16±2.26 mg/dl, p=0.04, respectively).

The incidence of PCI-related MI (MI 4a) was found to be comparable in the RIPC group at six hours (two [3.7%] vs. four [7.4%], p=0.68) and 12 hours (six [11.1%] vs. four [7.4%], p=0.74). However, RIPC seemed to have reduced the incidence of PCI-related MI (MI 4a) as compared to the control group at 24 hrs post PCI (eight [14.82%] vs. 21 [38.89], p<0.01) **(Table 4)**.

The distribution of subjects with undetectable troponin I was comparable between the RIPC group and the control group both at six hours (46 [85.2%] vs. 41 [75.9%], p=0.33) and 12 hours (45 [83.3%] vs. 36 [66.7%], p=0.08) post PCI, respectively, but was found to be significantly higher at 24 hours post PCI in the RIPC group as compared to the control group (42 [77.7%] vs. 28 [51.9%], p<0.01, respectively) **(Figure 1)** .

At 30-day follow-up, no patient in either group had any adverse cardiac event (death, reinfarction, stent thrombosis, recurrence of angina).

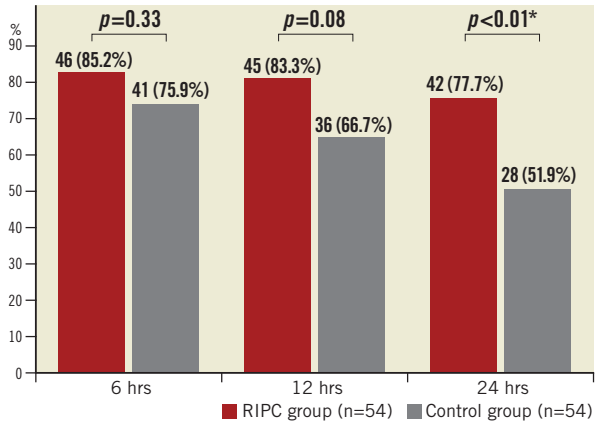


Figure 1. *Frequency of subjects with undetectable troponin I (<0.05 ng/ml) among RIPC group and controls.*

Table 3. Periprocedural clinical and angiographic parameters.

Variable		Whole cohort (n=108)	RIPC (n=54)	Control (n=54)	*p*-value*
SBP, mmHg (mean±SD)		124.9±11.40	124.3±11.84	125.6±11.01	0.57
DBP, mmHg (mean±SD)		82.2±6.33	81.3±5.87	83.2±6.67	0.11
Heart rate, bpm (mean±SD)		73.8±8.01	74.1±8.12	73.6±7.9	0.78
Chest pain score >1, n (%)		15 (13.9)	3 (5.5)	12 (22.2)	0.02*
ECG ST deviation >1 mm, n (%)		10 (9.3)	2 (3.7)	8 (14.8)	0.09
TIMI flow grade	0-2, n (%)	7 (6.5)	1 (1.8)	6 (11.1)	0.12
	3, n (%)	101 (93.5)	53 (98.1)	48 (88.9)	

**p*-value shown is between RIPC group and control group; value of <0.05 considered as statistically significant. DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure; TIMI: Thrombolysis In Myocardial Infarction

Table 4. Post-procedure troponin I and CRP values (at 6, 12 and 24 hours) and the incidence of MI.

Variable	6 hours			12 hours			24 hours		
	RIPC (n=54)	Control (n=54)	*p*-value	RIPC (n=54)	Control (n=54)	*p*-value	RIPC (n=54)	Control (n=54)	*p*-value
Troponin I, ng/ml (mean±SD)	0.06±0.03	0.07±0.04	0.14	0.08±0.13	0.16±0.19	0.01*	0.06±0.04	0.22±0.31	<0.01*
CRP, mg/dl (mean±SD)	0.37±0.09	0.46±0.38	0.09	0.46±0.35	0.71±0.78	0.04*	0.53±0.48	1.16±2.26	0.04*
MI 4a, n (%) ¶	2 (3.7)	4 (7.4)	0.68	6 (11.1)	4 (7.4)	0.74	8 (14.82)	21 (38.89)	<0.01*

**p*-value of <0.05 was considered as statistically significant. ¶ The joint task force of the European Society of Cardiology, American College of Cardiology Foundation, American Heart Association and World Heart Federation, defined PCI-related MI (MI 4a) as a rise in troponin >0.12 ng/ml (three times the upper reference limit)

Discussion

Our study showed that remote IPC, administered by transient upper limb ischaemia, significantly reduces all signs of post-procedural myocardial injury, including PCI-related troponin I (p<0.01), CRP (p=0.04) release and the incidence of PCI-related MI (p<0.01) at 24 hrs after PCI.

Several studies have shown that PCI-related troponin I release is associated with a worse prognosis, especially in those patients with the most marked elevation in troponin I concentration[8,10-12]. A post-procedure increase in troponin concentration of fivefold baseline levels is an independent predictor of a composite of death, MI, and revascularisation at one year (hazard ratio=2.39; 95% CI: 1.09-5.26)[11]. As discussed earlier, a PCI-related MI (MI 4a) is defined as >0.12 ng/ml (3 times the upper reference limit)[26]. Gadolinium late enhancement with cardiac magnetic resonance has demonstrated that procedural troponin I release is due to MI both downstream of the stented lesion and adjacent to the implanted stent[1,27].

Przyklenk et al[13] demonstrated that brief episodes of ischaemia in one vascular bed (circumflex branch occlusion) protected remote virgin myocardium from subsequent sustained left anterior descending coronary artery occlusion in a canine model. Birnbaum et al[23] demonstrated that a brief remote ischaemia of a skeletal muscle induced by muscle stimulation combined with a reduction of femoral arterial blood flow reduced myocardial infarct size considerably in rabbits. A less invasive method of inducing hind limb ischaemia as an RIPC stimulus was introduced by Oxman et al who demonstrated that applying a tourniquet to the hind limb to induce 10 min of limb ischaemia had the ability to reduce reperfusion arrhythmias in a rat heart following a sustained ischaemic insult[28].

Cheung et al[22] first successfully applied RIPC in the clinical setting and reported that a standard RIPC stimulus using four five-minute cycles of lower limb ischaemia was able to reduce myocardial injury, improve airway resistance and decrease inotrope score in 17 children undergoing corrective cardiac surgery for congenital heart disease. Ali et al[21] demonstrated in abdominal aortic aneurysm repair that there was no difference in mortality between the two groups either in hospital or at discharge, but RIPC reduced the incidence of myocardial infarction and renal impairment. Kharbanda et al[29] demonstrated that transient upper limb ischaemia, induced by a blood pressure cuff inflated around the upper arm for three five-minute cycles, with intervening periods of reperfusion, ameliorated contralateral forearm ischaemia/reperfusion endothelial dysfunction in human volunteers. A pooled analysis of the four trials related to cardiovascular surgery demonstrated a statistically significant reduction in biomarkers of myocardial injury with RIPC relative to control (standardised mean difference -0.81, 95% CI: 1.29-0.33, p=0.001)[30].

During coronary angioplasty, mechanical disruption of a stable atherosclerotic plaque and possible microemboli induced by the balloon may cause a systemic inflammatory response, as reflected by a rise in CRP levels. In our study there was no significant increase in CRP level at six hours, but a significant increase was recorded at 12 and 24 hours after PCI.

The actual mechanism through which an episode of brief ischaemia and reperfusion in an organ or tissue exerts protection against a subsequent sustained insult of ischaemia-reperfusion injury in a remote organ or tissue is currently unclear. Humoral and neural hypotheses are suggested to explain RIPC. The finding that a period of reperfusion of the remote preconditioning organ was required in addition to the brief ischaemia suggested that the reperfusion period may be needed to "wash out" a substance or humoral factor generated by the preconditioning ischaemia, which was then transported to the heart[28-31]. RIPC has a biphasic pattern of myocardial protection. An early classic phase is believed to act within a few minutes to two hours after the preconditioning stimulus and is mediated through opening of mitochondrial ATP-sensitive potassium channels[32,33]. A delayed second window of protection occurs at 24 to 72 hours and is probably the result of modified gene expression that suppresses the proinflammatory response to the ischaemia/reperfusion injury. Activation of the mitogen-activated protein kinases (MAPKs) p38, Erk1/2 and JNK within the remote organ may also contribute to RIPC-induced cardioprotection. Konstantinov et al[34] noted a reduction in the extent of MI after RIPC in a porcine transplanted heart, in agreement with the original work on IPC that argued for a circulating humoral mediator.

RIPC to protect the heart from ischaemia as a therapeutic modality, particularly for elective intervention, is an attractive option. There are limited numbers of studies exploring the effect of RIPC on myocardial injury during elective PCI which are mostly small with limited data and outcomes.

Iliodromitis et al[24] reported that no myocardial protection was conferred by remote IPC induced by three five-minute cycles of bilateral upper limb ischaemia in the catheterisation laboratory immediately before PCI. In contrast, they observed that remote IPC exacerbated

troponin I release after PCI and enhanced the inflammatory response in the absence of statin therapy in low-risk patients undergoing single-vessel elective PCI. In our study, almost all patients in both groups were taking statins that nullify the beneficial effect of statin, affecting the result. The rationale for performing RIPC within one hour of PCI came from the CRISP STENT study that had shown protection is time-dependent and that the greatest benefit occurred with shorter cuff to balloon time. The CRISP STENT study[35], a prospective randomised controlled study of 202 patients, concluded that remote IPC reduces ischaemic chest discomfort during PCI, attenuates procedure-related troponin I release, and appears to reduce subsequent cardiovascular events. Also noteworthy is the study by Bøtker et al[36], who demonstrated the potential for pre-hospital use of RIPC in the setting of 333 patients of AMI (four cycles of five-minute forearm cuff inflation and deflation, delivered in the ambulance). They demonstrated an improvement in myocardial salvage index (%) at 20 days after primary PCI in the group which received preconditioning[36]. In a substudy of the same patients, RIPC delivered before hospital resulted in modest improvement in LV function among high-risk patients prone to developing large myocardial infarcts[37].

In a meta-analysis of 17 clinical trials, Alreja et al reported an association of RIPC with a favourable effect on serological markers of myocardial or renal injury (troponin T or I and CK-MB) during cardiovascular interventions[38]. Similarly, in our study, PCI-related MI and troponin release were significantly reduced in the RIPC group at 24 hours after PCI. The CRP level was not significantly different between the RIPC and the control group six hours after PCI. Chest discomfort and ECG ST-segment deviation during PCI were not significantly improved after RIPC.

Another meta-analysis of five randomised clinical trials indicated that RIPC reduces the risk of periprocedural MI amongst subjects with multivessel disease[39]. Pei et al in their meta-analysis also found RIPC to be protective against post-procedural events amongst stable CAD patients, which probably validates the results of the present study[40].

The definition of post-PCI MI is, however, debatable, but elevations of cardiac biomarkers from normal (before PCI) to above five times the 99th percentile URL (after PCI) are currently considered to be indicative of a post-procedural MI[41]. This criterion has been upgraded from a >3 times increase in cardiac biomarkers[26]. Since there is no valid scientific basis for defining a biomarker threshold for such a condition and this recent increase to >5 times has been done by arbitrary convention, we decided to use the guidelines published in 2007 for this study[26]. Another reason why the criterion of >3 times the biomarkers was used in the present study is because it has been used in almost all studies published so far investigating this subject; using a different criterion would have made the present study incomparable with other similar randomised studies and their meta-analyses. Importantly, reclassification from one definition to another has not been shown to improve accuracy in the diagnosis of periprocedural MI[42].

Presently, none of the available therapeutic interventions holds sufficient promise to act against the detrimental effects of ischaemia-reperfusion injury to the myocardium (at least in ACS). The main reason for the same is that studies examining the role of RIPC in preventing ischaemia-reperfusion injury cannot possibly be designed to adjust for several known confounding factors[43]. Relevant confounding factors have been amply described in a recently published review on this subject[44]. However, most of these confounding factors do not act against the effectiveness of RIPC in stable CAD subjects, which probably explains the positive effects of the aforementioned intervention deduced in our subject cohort.

Limitations

There were some study limitations. Firstly, the study population was small. Although PCI-related MI and undetectable troponin I (at six and 12 hours) in the RIPC and in the control group were less in absolute numbers, this difference was found to be statistically insignificant. Even then, a clear trend was seen as the RIPC group had a lesser incidence of PCI-related MI with a higher frequency of subjects having undetectable troponin values at these time intervals. If the study population had been larger, even this difference could also have been statistically significant. Secondly, the pre and post balloon dilatation duration during PCI was not recorded in this study and we feel that it may have been a key factor influencing the outcome. Thirdly, long-term clinical follow-up is needed to see clinical transformation of biochemical outcome. Our study only explored PCI-related troponin release and, since symptoms were not recorded, it does not necessarily translate into PCI-related MI. This also constitutes a major limitation of our study.

Conclusions

The present study concludes that administration of remote ischaemic preconditioning prior to PCI significantly reduces troponin I and CRP release at both 12 and 24 hours post PCI. The incidence of PCI-related MI was also found to be significantly lower in the RIPC group at 24 hours after PCI. However, studies with a larger number of patients and longer clinical follow-up are warranted to establish the beneficial effect of RIPC, which could possibly help in reducing the incidence of myocardial injury during PCI.

Impact on daily practice

In the light of the presented results, we recommend the use of RIPC as an adjunctive strategy for reducing post-PCI myocardial ischaemia-reperfusion injury. Clinical applicability of RIPC becomes all the more recommendable, as none of the other examined adjunctive cardioprotective strategies (pharmacological or mechanical) has so far been able to demonstrate convincing clinical benefit.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Selvanayagam JB, Porto I, Channon K, Petersen SE, Francis JM, Neubauer S, Banning AP. Troponin elevation after

percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: insights from cardiovascular magnetic resonance imaging. *Circulation.* 2005;111:1027-32.

2. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med.* 1996;335:1342-9.

3. Ohman EM, Armstrong PW, Christenson RH, Granger CB, Katus HA, Hamm CW, O'Hanesian MA, Wagner GS, Kleiman NS, Harrell FE Jr, Califf RM, Topol EJ. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med.* 1996;335:1333-41.

4. Moliterno DJ, Penn MS. Angioplasty, inflammation, and antiplatelet agents. *Am Heart J.* 2003;145:563-6.

5. Gomes WJ, Giannotti-Filho O, Paez RP, Hossne NA Jr, Catani R, Buffolo E. Coronary artery and myocardial inflammatory reaction induced by intracoronary stent. *Ann Thorac Surg.* 2003;76:1528-32.

6. Kini AS, Lee P, Marmur JD, Agarwal A, Duffy ME, Kim MC, Sharma SK. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. *Am J Cardiol.* 2004;93:18-23.

7. Porto I, Blackman DJ, Nicolson D, Niccoli G, Kahn FZ, Ormerod O, Forfar C, Channon K, Banning AP. What is the incidence of myocardial necrosis in elective patients discharged on the same day following percutaneous coronary intervention? *Heart.* 2004;90:1489-90.

8. Nageh T, Sherwood RA, Harris BM, Thomas MR. Prognostic role of cardiac troponin I after percutaneous coronary intervention in stable coronary disease. *Heart.* 2005;91:1181-5.

9. Ramirez-Moreno A, Cardenal R, Pera C, Pagola C, Guzman M, Vazquez E, Fajardo A, Lozano C, Solís J, Gassó M. Predictors and prognostic value of myocardial injury following stent implantation. *Int J Cardiol.* 2004;97:193-8.

10. Kizer JR, Muttrej MR, Matthai WH, McConnell J, Nardone H, Sonel AF, Keane MG, Wilensky RL. Role of cardiac troponin T in the long-term risk stratification of patients undergoing percutaneous coronary intervention. *Eur Heart J.* 2003;24:1314-22.

11. Cantor WJ, Newby LK, Christenson RH, Tuttle RH, Hasselblad V, Armstrong PW, Moliterno DJ, Califf RM, Topol EJ, Ohman EM; SYMPHONY and 2nd SYMPHONY Cardiac Markers Substudy Investigators. Prognostic significance of elevated troponin I after percutaneous coronary intervention. *J Am Coll Cardiol.* 2002;39:1738-44.

12. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation.* 1986;74:1124-36.

13. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation.* 1993;87:893-9.

14. Pasupathy S, Homer-Vanniasinkam S. Surgical implications of ischemic preconditioning. *Arch Surg.* 2005;140:405-9.

15. Lee TM, Lin MS, Tsai CH, Chang NC. Effect of ischaemic preconditioning on regional release of inflammatory markers. *Clin Sci (Lond).* 2005;109:267-76.

16. Laskey WK. Beneficial impact of preconditioning during PTCA on creatine kinase release. *Circulation.* 1999;99:2085-9.

17. Laskey WK, Beach D. Frequency and clinical significance of ischemic preconditioning during percutaneous coronary intervention. *J Am Coll Cardiol.* 2003;42:998-1003.

18. Heusch G, Schulz R. Remote preconditioning. *J Mol Cell Cardiol.* 2002;34:1279-81.

19. Przyklenk K, Darling CE, Dickson EW, Whittaker P. Cardioprotection 'outside the box'--the evolving paradigm of remote preconditioning. *Basic Res Cardiol.* 2003;98:149-57.

20. Hausenloy DJ, Mwamure PK, Venugopal V, Harris J, Barnard M, Grundy E, Ashley E, Vichare S, Di Salvo C, Kolvekar S, Hayward M, Keogh B, MacAllister RJ, Yellon DM. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet.* 2007;370:575-9.

21. Ali ZA, Callaghan CJ, Lim E, Ali AA, Nouraei SA, Akthar AM, Boyle JR, Varty K, Kharbanda RK, Dutka DP, Gaunt ME. Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. *Circulation.* 2007;116:I98-105.

22. Cheung MM, Kharbanda RK, Konstantinov IE, Shimizu M, Frndova H, Li J, Holtby HM, Cox PN, Smallhorn JF, Van Arsdell GS, Redington AN. Randomized controlled trial of the effects of remote ischemic preconditioning on children undergoing cardiac surgery: first clinical application in humans. *J Am Coll Cardiol.* 2006;47:2277-82.

23. Birnbaum Y, Hale SL, Kloner RA. Ischemic preconditioning at a distance: reduction of myocardial infarct size by partial reduction of blood supply combined with rapid stimulation of the gastrocnemius muscle in the rabbit. *Circulation.* 1997;96:1641-6.

24. Iliodromitis EK, Kyrzopoulos S, Paraskevaidis IA, Kolocassides KG, Adamopoulos S, Karavolias G, Kremastinos DT. Increased C reactive protein and cardiac enzyme levels after coronary stent implantation. Is there protection by remote ischaemic preconditioning? *Heart.* 2006;92:1821-6.

25. [No authors listed]. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *J Am Coll Cardiol.* 1988;12:529-45.

26. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP,

Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernández-Avilés F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N. Universal definition of myocardial infarction. *Circulation.* 2007;116:2634-53.

27. Porto I, Selvanayagam JB, Van Gaal WJ, Prati F, Cheng A, Channon K, Neubauer S, Banning AP. Plaque volume and occurrence and location of periprocedural myocardial necrosis after percutaneous coronary intervention: insights from delayed-enhancement magnetic resonance imaging, thrombolysis in myocardial infarction myocardial perfusion grade analysis, and intravascular ultrasound. *Circulation.* 2006;114:662-9.

28. Oxman T, Arad M, Klein R, Avazov N, Rabinowitz B. Limb ischemia preconditions the heart against reperfusion tachyarrhythmia. *Am J Physiol.* 1997;273:H1707-12.

29. Kharbanda RK, Li J, Konstantinov IE, Cheung MM, White PA, Frndova H, Stokoe J, Cox P, Vogel M, Van Arsdell G, MacAllister R, Redington AN. Remote ischaemic preconditioning protects against cardiopulmonary bypass-induced tissue injury: a preclinical study. *Heart.* 2006;92:1506-11.

30. Takagi H, Manabe H, Kawai N, Goto SN, Umemoto T. Review and meta-analysis of randomized controlled clinical trials of remote ischemic preconditioning in cardiovascular surgery. *Am J Cardiol.* 2008;102:1487-8.

31. Gho BC, Schoemaker RG, van den Doel MA, Duncker DJ, Verdouw PD. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation.* 1996;94:2193-200.

32. Loukogeorgakis SP, Williams R, Panagiotidou AT, Kolvekar SK, Donald A, Cole TJ, Yellon DM, Deanfield JE, MacAllister RJ. Transient limb ischemia induces remote preconditioning and remote postconditioning in humans by a K(ATP)-channel dependent mechanism. *Circulation.* 2007;116:1386-95.

33. Broadhead MW, Kharbanda RK, Peters MJ, MacAllister RJ. KATP channel activation induces ischemic preconditioning of the endothelium in humans in vivo. *Circulation.* 2004;110:2077-82.

34. Konstantinov IE, Li J, Cheung MM, Shimizu M, Stokoe J, Kharbanda RK, Redington AN. Remote ischemic preconditioning of the recipient reduces myocardial ischemia-reperfusion injury of the denervated donor heart via a Katp channel-dependent mechanism. *Transplantation.* 2005;79:1691-5.

35. Hoole SP, Heck PM, Sharples L, Khan SN, Duehmke R, Densem CG, Clarke SC, Shapiro LM, Schofield PM, O'Sullivan M, Dutka DP. Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial. *Circulation.* 2009;119:820-7.

36. Botker HE, Kharbanda R, Schmidt MR, Bottcher M, Kaltoft AK, Terkelsen CJ, Munk K, Andersen NH, Hansen TM, Trautner S, Lassen JF, Christiansen EH, Krusell LR, Kristensen SD, Thuesen L, Nielsen SS, Rehling M, Sørensen HT, Redington AN, Nielsen TT. Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. *Lancet.* 2010;375:727-34.

37. Munk K, Andersen NH, Schmidt MR, Nielsen SS, Terkelsen CJ, Sloth E, Bøtker HE, Nielsen TT, Poulsen SH. Remote Ischemic Conditioning in Patients With Myocardial Infarction Treated With Primary Angioplasty: Impact on Left Ventricular Function Assessed by Comprehensive Echocardiography and Gated Single-Photon Emission CT. *Circ Cardiovasc Imaging.* 2010;3:656-62.

38. Alreja G, Bugano D, Lotfi A. Effect of remote ischemic preconditioning on myocardial and renal injury: meta-analysis of randomized controlled trials. *J Invasive Cardiol.* 2012;24:42-8.

39. D'Ascenzo F, Moretti C, Omede P, Cerrato E, Cavallero E, Er F, Presutti DG, Colombo F, Crimi G, Conrotto F, Dinicolantonio JJ, Chen S, Prasad A, Biondi Zoccai G, Gaita F. Cardiac remote ischaemic preconditioning reduces periprocedural myocardial infarction for patients undergoing percutaneous coronary interventions: a meta-analysis of randomised clinical trials. *EuroIntervention.* 2014;9:1463-71.

40. Pei H, Wu Y, Wei Y, Yang Y, Teng S, Zhang H. Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: a meta-analysis of 11 randomized trials. *PLoS One.* 2014;9:e115500.

41. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation.* 2012;126:2020-35.

42. Gili S, D'Ascenzo F, Moretti C, Omede P, Vilardi I, Bertaina M, Biondi Zoccai G, Sheiban I, Stone GW, Gaita F. Impact on prognosis of periprocedural myocardial infarction after percutaneous coronary intervention. *J Interv Cardiol.* 2014;27:482-90.

43. Ferdinandy P, Hausenloy DJ, Heusch G, Baxter GF, Schulz R. Interaction of risk factors, comorbidities, and comedications with ischemia/reperfusion injury and cardioprotection by preconditioning, postconditioning, and remote conditioning. *Pharmacol Rev.* 2014;66:1142-74.

44. Heusch G, Botker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. *J Am Coll Cardiol.* 2015;65:177-95.

AsiaIntervention 2015;1:124

Multimodality imaging in the evaluation of recurrent very late stent thrombosis

G. Sengottuvelu*, MD, DM, FSCAI, FRCP; Rajendran Ravindran, MD

Department of Cardiology, Apollo Hospital, Chennai, India

Both authors contributed equally to this manuscript.

A 48-year-old diabetic lady with prior percutaneous coronary intervention (PCI) to the left circumflex artery (LCX) in 2008 with a first-generation sirolimus-eluting stent had an episode of definite very late stent thrombosis (VLST) in 2012. PCI was carried out with a balloon angioplasty (BA) and she was maintained on prasugrel and aspirin. Within weeks after changing prasugrel to clopidogrel after 18 months of BA, she again presented with VLST in 2014. A coronary angiogram showed occlusion of the LCX stent **(Figure 1A)**. After thrombus aspiration, optical coherence tomography (OCT) imaging **(Figure 1B-Figure 1F)** showed thrombus within the stent (no uncovered struts) and areas of high attenuation within the neointima, suggesting neoatherosclerosis **(Figure 1C, #)**. Intravascular ultrasound (IVUS) imaging **(Figure 1G-Figure 1K)** showed areas of positive remodelling of the vessel wall outside the stent with aneurysmal dilatation causing late acquired stent malapposition which was the obvious cause for recurrent VLST. Neoatheroma seen by OCT is possibly an innocent bystander as shown by thick intima with superimposed thrombus. High-pressure non-compliant balloon post-dilation followed by re-stenting with a bare metal stent was carried out and she was continued on aspirin and prasugrel **(Figure 1L)**.

Late acquired malapposition seen by IVUS is the cause of VLST, and neoatherosclerosis seen on OCT is possibly an innocent bystander. OCT with high resolution is excellent for intraluminal evaluation, such as for uncovered struts and neoatherosclerosis, whereas IVUS with good penetration is better for imaging beyond the stent and vessel wall such as in the case of positive remodelling. Thrombus obscures optimal OCT imaging, whereas IVUS is poor for assessment of strut coverage or neoatherosclerosis. The use of a single imaging modality would have missed the diagnosis in this case where multimodality imaging was crucial to get a complete diagnosis.

Conflict of interest statement

The authors have no conflicts of interest to declare.

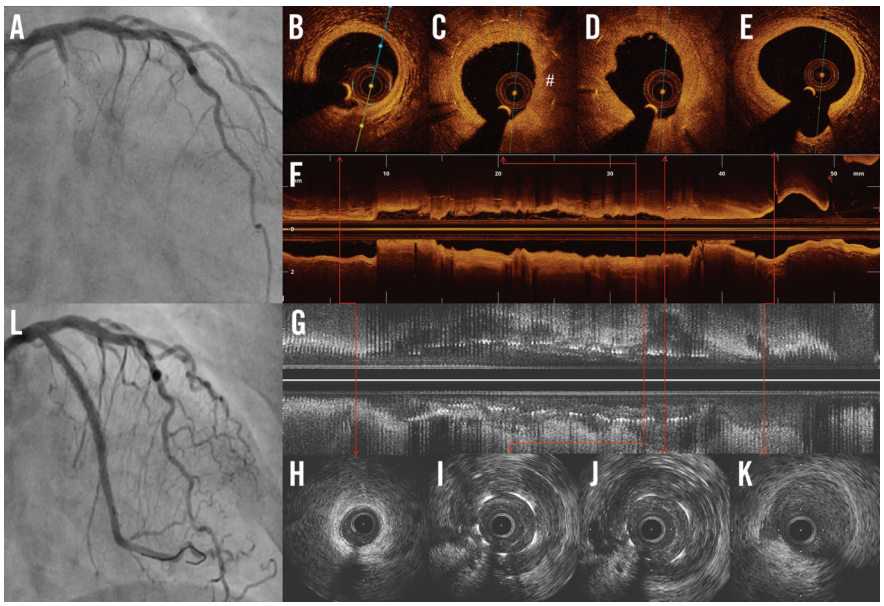


Figure 1. *Multimodality imaging of recurrent VLST. Angiogram with longitudinal and axial images of IVUS and OCT. A) Initial angiogram showing total occlusion of the stent in proximal LCX. B) OCT image distal to stent. C) & D) OCT images across a stented segment corresponding to areas of positive remodelling on IVUS showing thrombus and neoatherosclerosis (#). E) Vessel proximal to stent. F) Longitudinal OCT reconstruction of the stented segment. G) Longitudinal IVUS image showing areas of acquired late malapposition. H) - K) IVUS sections corresponding to B to E showing covered struts and positive remodelling of the vessel. L) Final result after PCI.*

*Corresponding author: Cardiology Department, Apollo Hospital, 21 Greams Lane, off Greams Road, Chennai - 600006, India. E-mail: drgseng@gmail.com

DOI: 10.4244/AsiaInterv_V1I2A23

AsiaIntervention 2015;1:125

Side branch restenosis treated with reverse minimum overlapping culotte stenting: confirmation by instant stent-accentuated three-dimensional optical coherence tomography

Fumiaki Nakao*, MD, PhD

Department of Cardiology, Yamaguchi Grand Medical Center, Hofu, Japan

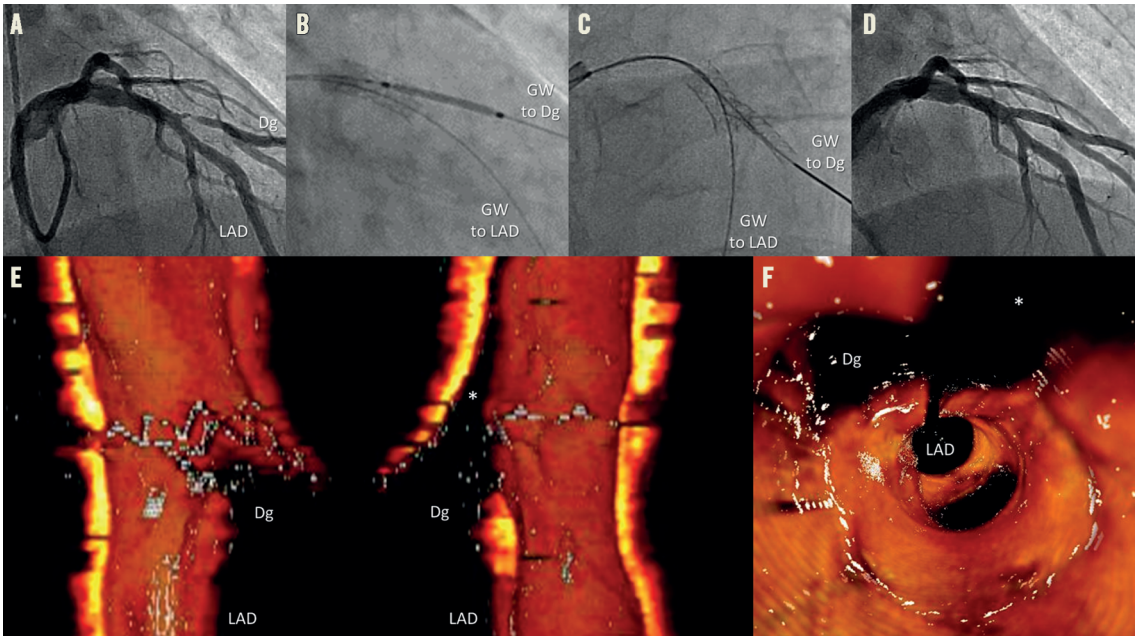


Figure 1. *Reverse minimum overlapping culotte stenting (R-MOCS) for side branch restenosis. A) Baseline coronary angiography showing restenosis of the diagonal branch (Dg). B) A platinum-chromium everolimus-eluting stent was deployed from the left anterior descending artery (LAD) to the Dg. C) Guidewire (GW) recrossed to the distal LAD. D) Final angiographic result. Longitudinal cut-away view (E), and fly-through view (F), of final iSA3D-OCT showing R-MOCS. Asterisks indicate GW shadow artefacts.*

A 77-year-old woman, who had previously had single crossover stenting and kissing balloon dilation (KBD) for a bifurcation lesion of the left anterior descending artery (LAD) and the diagonal branch (Dg), had percutaneous coronary intervention performed for restenosis of the Dg with angina **(Figure 1A)**. Guidewires were inserted to the Dg and the LAD. After the Dg was predilated, a platinum-chromium everolimus-eluting stent (PROMUS Element™ 2.5×16 mm; Boston Scientific Co, Marlborough, MA, USA) was deployed from the LAD to the Dg **(Figure 1B)** with only one strut overlapping as confirmed by intravascular ultrasonography (IVUS). The guidewire was recrossed to the distal LAD through the stent cell with x-ray fluorographic guidance **(Figure 1C)**, confirmed by IVUS. After KBD was performed, final coronary angiography showed a good result **(Figure 1D)**. Final instant stent-accentuated three-dimensional optical coherence tomography (iSA3D-OCT) reconstructed using an off-line workstation showed that the reverse minimum overlapping culotte stenting (R-MOCS) had been achieved **(Figure 1E, Figure 1F)**.

Side branch (SB) restenosis is one of the issues with a single-stent strategy for a bifurcation lesion. Culotte stenting or T-stenting and small protrusion (TAP) technique has been performed for an SB restenosis if additional stenting was needed. R-MOCS may be an effective strategy for a restenosis of a gently angled SB at points of lesser influence to the main vessel than culotte stenting, and lesser metallic carina than the TAP technique.

Conflict of interest statement

The author has no conflicts of interest to declare.

**Corresponding author: Department of Cardiology, Yamaguchi Grand Medical Center, 77 Ohsaki, Hofu, Yamaguchi, 747-8511, Japan. E-mail: nakao-ymghp@umin.ac.jp*

DOI: 10.4244/AsiaInterv_V1I2A24

AsiaIntervention 2015;1:126-128

Minimally invasive coronary angioscopy: observation using a new non-occlusive fibrescope through a 4 Fr guiding catheter

Masamichi Takano[1,2]*, MD; Takahiro Imaizumi[2], MD; Akihiro Tabata[2], MD; Noritake Hata[1], MD; Yoshihiko Seino[1], MD; Wataru Shimizu[3], MD; Kyoichi Mizuno[4], MD

1. Cardiovascular Center, Nippon Medical School, Chiba Hokusoh Hospital, Chiba, Japan; 2. Division of Cardiology, Kobayashi Hospital, Hokkaido, Japan; 3. Department of Cardiovascular Medicine, Nippon Medical School, Tokyo, Japan; 4. Mitsukoshi Health and Welfare Foundation, Tokyo, Japan

KEYWORDS

- imaging
- plaque
- stent
- thrombus

Abstract

Aims: Coronary angioscopy (CAS) is a robust tool for the qualitative evaluation of atherosclerotic plaque, thrombus, and vascular healing after stent implantation. However, adequate visualisation by CAS requires balloon occlusion and a larger than 6 Fr compatible guiding catheter for complete replacement of coronary blood with transparent fluid. The invasive and complex procedures limit the wide utilisation of this imaging device. We attempted less invasive observation by CAS with a slender fibrescope catheter.

Methods and results: The culprit lesion in a patient with stable angina pectoris in the proximal right coronary artery was observed using a non-occlusive fibrescope through a 4 Fr guiding catheter. The coronary lumen was adequately observed before and after stent implantation.

Conclusions: Angioscopic observation through a 4 Fr guiding catheter was possible without deterioration of image quality. Minimally invasive procedures of CAS may be practical for patient care.

Corresponding author: Cardiovascular Center, Nippon Medical School, Chiba Hokusoh Hospital, 1715 Kamakari, Inzai, Chiba, 270-1694, Japan. E-mail: takanom@nms.ac.jp

DOI: 10.4244/AsiaInterv_V1I2A25

Introduction

Coronary angioscopy (CAS) provides morphological information on atherosclerotic plaque, thrombus, and vascular healing after stent implantation[1-3]. However, adequate observation by CAS requires balloon occlusion and a larger than 6 Fr compatible guiding catheter for complete replacement of coronary blood with transparent fluid. The invasive nature and complexity of the procedures limit the wide utilisation of this imaging device. Herein, we present a novel method of CAS using a slender fibrescope catheter.

Case description

A 78-year-old female with stable angina pectoris received coronary angiography (CAG) via the right radial artery. Focal stenosis was found in the proximal right coronary artery, and catheter intervention was performed using a 4 Fr Judkins Right guiding catheter (Kiwami™; Terumo Corp., Tokyo, Japan). We attempted to observe the target lesion using a new type of slender fibrescope (Smart-i™ type S11; iHeart Medical Co., Ltd, Tokyo, Japan). The tip of the catheter traversed the lesion along a 0.014 inch guidewire, and a manual pullback image of CAS was recorded during continuous infusion of contrast media by autoinjector (4 mL/sec, total 12 mL) **(Figure 1)**. After implantation of a drug-eluting stent (Resolute Integrity™ 2.75/12 mm; Medtronic, Minneapolis, MN, USA), the lumen was visualised using the same method **(Figure 2)**. This non-occlusion catheter consists of a radiopaque metal tip and a flexible shaft including optical fibres. Only the tip has a guidewire lumen and the length of the monorail port is 2.5 mm. The diameters of the tip and shaft are 0.8/1.2 mm and 0.6 mm, respectively **(Figure 3)**. The slender fibrescope provides high crossability and a large flush lumen from the guiding catheter. Although the use of a larger size of guiding catheter would permit better images than the current method, the less invasive nature of the procedure would be lost.

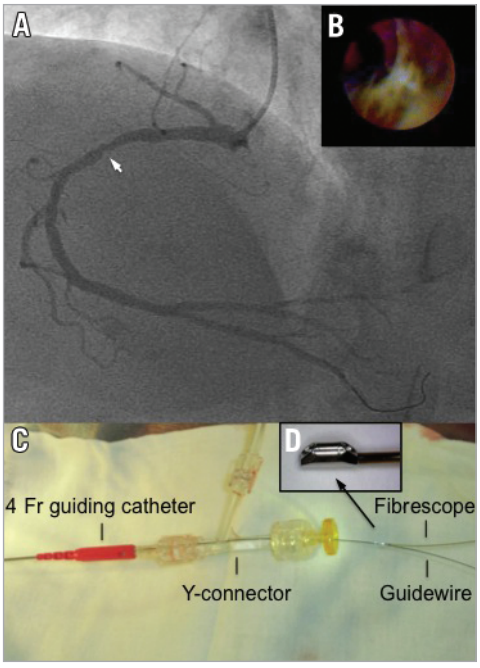


Figure 1. *Angiographic and angioscopic findings at baseline and image of the catheter system. A) Coronary angiography showed the culprit lesion in a case of angina pectoris (arrow) in the proximal right coronary artery (RCA). B) Yellow plaque and mural red thrombi were recognised by coronary angioscopy (CAS). C & D) A short monorail type of fibrescope was advanced along a 0.014 inch guidewire through a 4 Fr guiding catheter.*

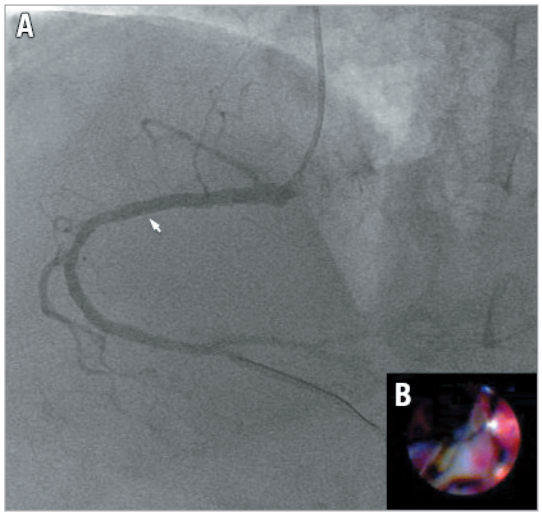


Figure 2. *Angiographic and angioscopic findings after coronary intervention. A) Stenosis of the RCA completely disappeared after stent implantation (arrow). B) CAS showed the attachment of the implanted stent to the vessel wall.*

Conclusion

For the first time, this case has shown the possibility of angioscopic observation through a 4 Fr guiding catheter without deterioration of image quality. Direct visualisation of the plaque surface by CAS can identify vulnerable plaque, including thin-cap fibroatheroma, as intense yellow plaque[4], something which is helpful to pinpoint a vulnerable patient. Both plaque characteristics and also healing response after stenting are validated by angioscopic observation.

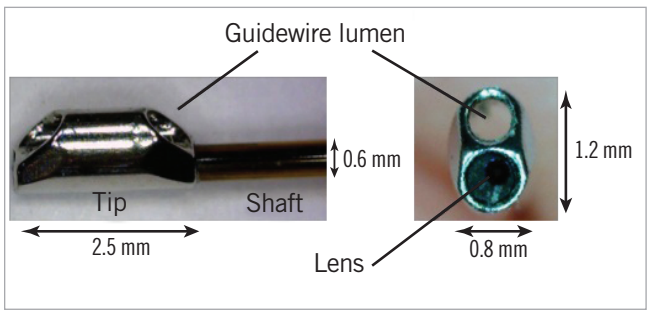


Figure 3. *The tip of the angioscopic catheter. The rigid tip (0.8/1.2 mm in diameter) has an object lens and guidewire lumen, and the flexible shaft (0.6 mm in diameter) contains 3,000 pixels of optical fibres. The length of the tip is 2.5 mm, and this portion serves as a radiopaque marker and monorail port.*

Diagnostic or stent follow-up CAG using a 4 Fr transradial approach is now prevalent. Therefore, minimally invasive and simple procedures of CAS are practical, and the findings may contribute to the improvement of patient care.

Impact on daily practice

This novel angioscopic method through a 4 Fr guiding catheter is less invasive and is simple, and may be beneficial for patient care.

Conflict of interest statement

M. Takano has received a consultancy fee from iHeart Medical. The other authors have no conflicts of interest to declare.

References

1. Takano M, Mizuno K, Yokoyama S, Seimiya K, Ishibashi F, Okamatsu K, Uemura R. Changes in coronary plaque color and morphology by lipid-lowering therapy with atorvastatin: serial evaluation by coronary angioscopy. *J Am Coll Cardiol.* 2003;42:680-6.

2. Takano M, Ohba T, Inami S, Seimiya K, Sakai S, Mizuno K. Angioscopic differences in neointimal coverage and in persistence of thrombus between sirolimus-eluting stents and bare metal stents after a 6-month implantation. *Eur Heart J.* 2006;27:2189-95.

3. Yokoyama S, Takano M, Yamamoto M, Inami S, Sakai S, Okamatsu K, Okuni S, Seimiya K, Murakami D, Ohba T, Uemura R, Seino Y, Mizuno K. Extended follow-up by serial angioscopic observation for bare-metal stents in native coronary arteries: from healing response to atherosclerotic transformation of neointima. *Circ Cardiovasc Interv.* 2009;2:205-12.

4. Takano M, Jang IK, Inami S, Yamamoto M, Murakami D, Okamatsu K, Seimiya K, Ohba T, Mizuno K. In-vivo comparison of optical coherence tomography and angioscopy for the evaluation of coronary plaque characteristics. *Am J Cardiol.* 2008;101:471-6.

AsiaIntervention 2015;1:129-134

How should I treat a common femoral arterial haemorrhage and deep vein thrombosis post percutaneous coronary intervention for non-ST-elevation myocardial infarction?

Chor W.P. Daniel[1], MBBS, MCEM; Edgar L.W. Tay[2]*, MBBS, MRCP

1. Department of Emergency Medicine, National University Health System, Singapore; 2. National University Heart Centre, National University Health System, Singapore

Invited Experts: Cheol Whan Lee[1], MD; Hirooki Higami[2], MD; Toshikazu Jinnai[2], MD, PhD; Takeshi Kimura[3]*, MD, PhD*

1. Division of Cardiology, Heart Institute, Asan Medical Center, University of Ulsan, Seoul, South Korea; 2. Department of Cardiovascular Medicine, Otsu Red Cross Hospital, Japan; 3. Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Japan

CASE SUMMARY

BACKGROUND: A 71-year-old Chinese male presented with a non-ST-elevation myocardial infarction and was started on dual antiplatelet therapy. A percutaneous coronary intervention (PCI) via the right femoral artery was complicated by a deep vein thrombosis (DVT) post removal of the access sheath, probably related to prolonged compression and immobility. Subcutaneous enoxaparin was started for the DVT.

INVESTIGATION: A computed tomography angiogram (CT-A) of the right lower limb was carried out as there was worsening swelling and bruising over the right groin after starting subcutaneous enoxaparin and bridging warfarin. The CT-A showed a focal arterial blush adjacent to the right common femoral artery.

DIAGNOSIS: Common femoral arterial haemorrhage complicating enoxaparin use for the treatment of DVT post PCI.

MANAGEMENT: Anticoagulation was stopped but dual antiplatelet therapy was continued. C-clamp compression of the puncture site was performed overnight. A repeat CT-A the next day showed resolution of bleeding with a stable haematoma. Intravenous heparin was subsequently started for the DVT and bridged to subcutaneous enoxaparin and warfarin.

KEYWORDS: deep vein thrombosis, femoral arterial haemorrhage, post percutaneous coronary intervention

PRESENTATION OF THE CASE

A 71-year-old male was admitted for an acute coronary syndrome. The electrocardiogram showed T inversions in V3 and V4 which were associated with a significant rise in cardiac enzymes. He was loaded with aspirin 300 mg and ticagrelor 180 mg and continued on aspirin 100 mg daily, ticagrelor 90 mg twice a day and subcutaneous enoxaparin 60 mg twice a day.

The patient underwent a coronary angiogram via the transradial approach on day four which showed 50% occlusion of the distal left main (LM) coronary artery, 90% occlusion of the mid left anterior descending (LAD) artery and 50% occlusion of the ostial left circumflex artery. The patient refused a coronary artery bypass and thus a percutaneous coronary intervention (PCI) was performed. A transfemoral PCI was performed with drug-eluting stents placed in the mid LAD and distal LM/proximal LAD. The right groin vascular access site was subsequently closed with a collagen plug vascular closure device (Angio-Seal™; St. Jude Medical, St. Paul, MN, USA) and the patient was continued on aspirin and ticagrelor thereafter. Subcutaneous enoxaparin was stopped after PCI.

Extensive bruising and a large haematoma were noted post PCI. Manual haemostasis was initially achieved and a compression bandage was applied. Unfortunately, a right lower limb duplex scan three days after the PCI showed a deep vein thrombosis (DVT) of the distal external iliac and common femoral vein **(Figure 1)**. In view of the DVT, the patient was again started on subcutaneous enoxaparin 50 mg twice a day, and ticagrelor was changed to clopidogrel. Bridging warfarin was started two days after enoxaparin. However, the right groin haematoma expanded. A computed tomography (CT) angiogram of the right lower limb

Corresponding author: National University Heart Centre, National University Health System, 1E Kent Ridge Road, NUHS Tower Block Level 9, Singapore 119228, Singapore. E-mail: edgar_tay@nuhs.edu.sg

DOI: 10.4244/AsiaInterv_V1I2A26

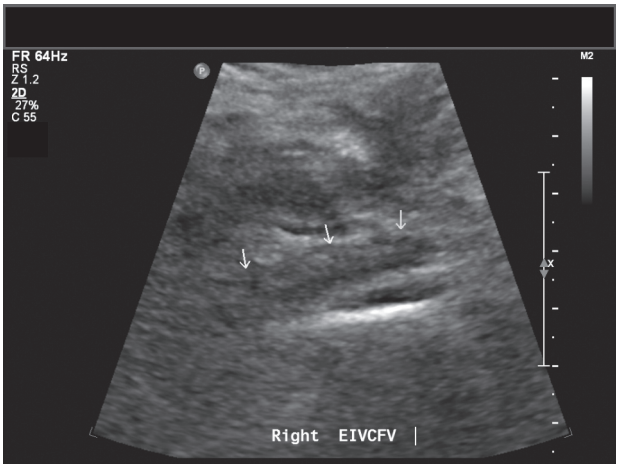


Figure 1. *Right lower limb duplex scan. Arrows: right external iliac vein and common femoral vein deep vein thrombosis.*

was carried out three days after starting enoxaparin. This showed a focal arterial blush adjacent to the right common femoral artery which was consistent with an active haemorrhage **(Figure 2, Figure 3)**.

How should this acute haemorrhage be managed, given that the patient has a provoked DVT with a recent PCI (for which the patient is also on dual antiplatelet therapy)?

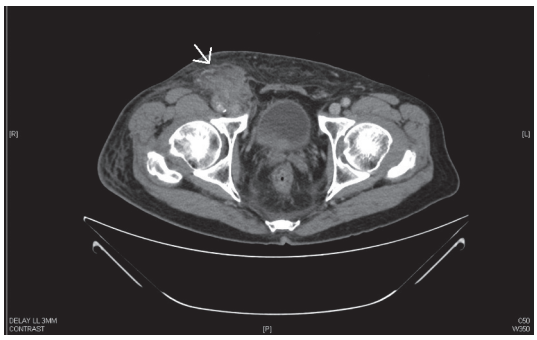


Figure 2. *Computed tomography (CT) angiogram of the right lower limb. Arrow: right groin haematoma.*

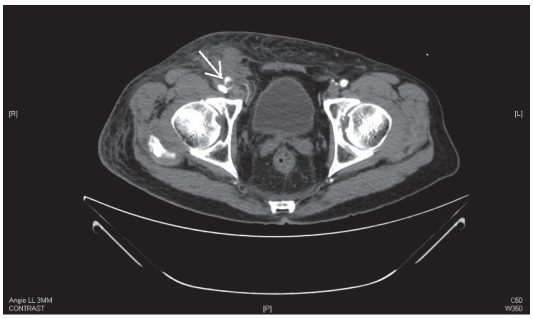


Figure 3. *Computed tomography (CT) angiogram of the right lower limb. Arrow: right groin focal arterial blush adjacent to the common femoral artery.*

AsiaIntervention 2015;1:129-134

How would I treat?

THE INVITED EXPERT'S OPINION

Cheol Whan Lee*, MD

Division of Cardiology, Heart Institute, Asan Medical Center, University of Ulsan, Seoul, South Korea

A collagen plug-based vascular closure device (VCD) is commonly used to achieve haemostasis after percutaneous coronary intervention with femoral artery access. Compared with mechanical compression of the femoral artery access site, it has been shown to reduce time to haemostasis, and to allow early ambulation with improved patient satisfaction. However, VCD failure is not rare (~3%), and is associated with significantly higher vascular complications as compared to VCD success[1]. Vascular complications may include thigh haematoma, retroperitoneal haematoma, pseudoaneurysm, arteriovenous fistula, and arterial occlusion, increasing morbidity, mortality, and medical costs. In the present case, a femoral artery pseudoaneurysm seemed to arise due to incomplete haemostasis of an arterial puncture site by VCD, leading to arterial blood oozing into the surrounding tissues and forming a pulsating encapsulated haematoma. Computed tomography angiography of the lower extremities revealed arterial blood flow into the pseudoaneurysm. Duplex ultrasound scanning can definitely confirm the pseudoaneurysm sac with a swirling colour flow and the neck of the pseudoaneurysm with a "to and fro" flow pattern.

A number of therapeutic modalities have been developed to treat femoral artery pseudoaneurysms. Although open surgical repair is still considered the gold standard, less invasive treatment strategies, including ultrasound-guided probe compression, ultrasound-guided thrombin injection, and insertion of covered stents, are available[2]. However, each modality has its own advantages and disadvantages.

My approach is to destroy the neck of the pseudoaneurysm using a guidewire, and then briefly compress the arterial access site. The neck of the pseudoaneurysm is the narrow track of blood flow between the femoral artery and the pseudoaneurysm sac. Once the fistula track is mature, it is hard to close the track by mechanical compression only. I propose the following treatment. The pseudoaneurysm sac should be punctured before the next enoxaparin dose, and a 5 Fr femoral sheath should be inserted into the pseudoaneurysm sac. An angiogram via a femoral sheath should be obtained to visualise the femoral artery, neck, and pseudoaneurysm. Under fluoroscopic guidance, the pseudoaneurysm neck should be mechanically destroyed and disconnected from the feeding femoral artery using the guidewire via the femoral sheath. Once the pseudoaneurysm neck is destroyed, the bleeding usually stops immediately with clotting of blood within the pseudoaneurysm sac. Brief manual compression of the puncture site is often needed to complete haemostasis. The remaining haematoma will be absorbed over several weeks. Before this procedure, I usually wait five to seven days for maturation of the pseudoaneurysm sac. If the procedure is performed too early, it is technically difficult to puncture into a poorly encapsulated pseudoaneurysm. In addition, considering the high risk of bleeding complications, clopidogrel plus warfarin will be used until deep vein thrombosis resolves.

In summary, a femoral artery pseudoaneurysm is not a rare complication after VCD failure. Mechanical destruction of the pseudoaneurysm neck, followed by brief compression of the arterial access site, is a simple and effective method to treat this troublesome complication.

Conflict of interest statement

The author has no conflicts of interest to declare.

**Corresponding author: Division of Cardiology, Heart Institute, Asan Medical Center, University of Ulsan, 88, Olympic-ro 43-gil, Songpa-gu, Seoul, 138-736, South Korea. E-mail: cheolwlee@amc.seoul.kr*

How would I treat?

THE INVITED EXPERTS' OPINION

Hirooki Higami[1], MD; Toshikazu Jinnai[1], MD, PhD; Takeshi Kimura[2]*, MD, PhD

1. Cardiovascular Division, Otsu Red Cross Hospital, Japan; 2. Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Japan

This is a troublesome case that requires treatment for both thrombosis and active bleeding. The main discussion points in treating this troublesome case consist of the following three issues: a) medication therapy, the necessity of dual antiplatelet therapy (DAPT) post implantation of a drug-eluting stent (DES) and anticoagulant therapy for deep vein thrombosis (DVT); b) how to repair an expanding right groin haematoma; and c) the pros and cons of invasive intervention for DVT.

In general, DAPT should be continued for at least 12 months after PCI to prevent stent thrombosis (ST)[3]. However, the effect of discontinuing DAPT within one month after DES implantation for acute coronary syndrome is unknown. In this particular case, although right groin haematoma with active arterial bleeding has expanded, the most critical issue should be to avoid ST, and treatment for the pseudoaneurysm should be considered subsequently. DVT would be less important for this patient as long as severe pulmonary embolism has not occurred.

We would therefore continue DAPT and stop anticoagulant therapy immediately after inferior vena cava (IVC) filter implantation to prevent pulmonary embolism in the first instance.

The next step would be to consider how to repair the right groin haematoma. The puncture hole of the right common femoral artery (CFA) must have caused the haematoma. Therefore, to occlude the bleeding point will lead to recovery of the pseudoaneurysm.

Since manual haemostasis and a compression band were not successful, but rather caused the DVT, additional, invasive treatment for the pseudoaneurysm should be conducted. We would try ultrasound-guided thrombin injection into the pseudoaneurysm first. This therapy has been developed as a less invasive and highly successful treatment for a femoral pseudoaneurysm and was originally reported by Liau in 1997[4]; however, this therapy has the risk of thrombin contamination to the artery[5]. Therefore, we would perform thrombin injection with balloon occlusion for the right CFA (which was approached by the contralateral CFA) to prevent thrombin contamination to the right CFA. If complete occlusion with thrombi of the pseudoaneurysm is not achieved, surgical repair would be required. Even if surgical treatment were to be performed, we do not recommend stopping antiplatelet therapy during the perioperative period.

After repair of the pseudoaneurysm, we would start anticoagulation therapy for DVT and implant an IVC filter. We would stop aspirin (that is, single antiplatelet therapy with clopidogrel alone), based on the results of the WOEST trial which showed increasing bleeding events in DAPT and anticoagulant therapy compared to single antiplatelet therapy (clopidgrel) with an anticoagulant[6]. A month later, if contrast computed tomography shows complete disappearance of the DVT, we would actively retrieve the IVC filter and change anticoagulant therapy to DAPT.

Conflict of interest statement

The authors have no conflicts of interest to declare.

**Corresponding author: Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin Kawaharacho Sakyo-ku, Kyoto, 606-8507, Japan. E-mail: taketaka@kuhp.kyoto-u.ac.jp*

How did I treat?

ACTUAL TREATMENT AND MANAGEMENT OF THE CASE

As the haemorrhage site was deemed compressible, the patient had manual compression with a C-clamp and haemostasis was achieved. Enoxaparin and warfarin were stopped but dual antiplatelet therapy was continued. A repeat CT angiogram the next day showed resolution of bleeding with a stable haematoma. A vascular surgeon was consulted and the patient was started on intravenous heparin for the DVT. This was subsequently bridged to subcutaneous enoxaparin with re-initiation of warfarin one day later. The patient was subsequently discharged well 18 days after admission with plans for dual antiplatelet therapy for one year with concomitant warfarin for three months.

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the therapy recommended by both the American Heart Association and the European Society of Cardiology to reduce stent thrombosis post PCI. Premature discontinuation of therapy has been associated with an increased risk of stent thrombosis[7]. However, this is not adequate for the treatment of venous thromboembolism. Oral anticoagulation therapy with a Vitamin K antagonist, such as warfarin, is indicated for the treatment of venous thromboembolism[8]. It is believed that the different mechanisms behind the thrombosis process necessitate treatment via different inhibitory pathways to achieve the desired antithrombotic effect.

In recent years, triple antithrombotic therapy (TAT) with both DAPT and an oral anticoagulant has been used increasingly for patients with atrial fibrillation (AF)/venous thromboembolism post PCI. However, a meta-analysis by Andrade et al[9] evaluating the risk of bleeding while on triple antithrombotic therapy post PCI showed that triple antithrombotic therapy (which was commonly indicated for AF and prosthetic heart valves) is associated with a significant risk of major bleeding events with an odds ratio of more than two at both 30 days and six months post PCI compared to DAPT alone. Some guidance was provided by the European Society of Cardiology in 2010[10] and the American College of Chest Physicians in 2012[8] for patients with atrial fibrillation who require triple therapy. Both recommend triple antithrombotic therapy post PCI for AF depending on the stent placed – one month for a bare metal stent, and three to six months for a drug-eluting stent. This is followed by a single antiplatelet agent with warfarin up to one year, with lifelong warfarin thereafter. Unfortunately, these guidelines were largely based on limited evidence from small, single-centre and retrospectively analysed cohorts, with most of the data available being for triple antithrombotic therapy post PCI in patients with concurrent AF.

More recent studies may shed new light on possible therapies. In an open-label, randomised controlled trial by the WOEST study group[6] in 2013 of patients on oral anticoagulant therapy, the use of clopidogrel with oral anticoagulant therapy (dual therapy) was compared with TAT in patients undergoing PCI. The use of dual therapy was associated with a significant reduction in bleeding complications (hazard ratio [HR] 0.36, 95% confidence interval [CI] 0.26 to 0.5) as compared with TAT. Further analysis of the severity of the bleeding episodes (using surrogates of number of bleeding events, need for transfusions and bleeding classifications) also suggested that those in the dual therapy group had less severe episodes compared to those in the TAT group. The use of dual therapy was not associated with an increased incidence of secondary endpoint markers that included death, myocardial infarction and stent thrombosis (although the study was not powered to detect the differences in occurrences). Barring the limitations of the study, the data would suggest that the use of clopidogrel with an oral anticoagulant alone would be a safe option for patients who require an oral anticoagulant and who have undergone PCI. The latest findings of the ISAR-TRIPLE trial, which was recently presented at the Transcatheter Cardiovascular Therapeutics scientific symposium 2014 (TCT 2014) in September 2014, also suggest that prolonged TAT may not be as necessary as was previously thought. In the open-label, randomised controlled trial, patients who had drug-eluting stents implanted were randomised into two groups, with one group started on six weeks of clopidogrel, and the other group six months of clopidogrel together with aspirin and an oral anticoagulant. A variety of primary endpoints (including death, stent thrombosis and TIMI major bleeding) and secondary endpoints (including the composite ischaemic endpoint and bleeding complications) was assessed. The group on the shortened duration of TAT did not demonstrate a significant difference in the primary or secondary endpoints compared to the group on the longer duration of TAT. The findings would suggest that physicians need to consider carefully the ischaemic and bleeding risks when choosing a longer or shorter duration of TAT.

Moreover, there is limited knowledge with regard to the use of newer $P2Y_{12}$ inhibitors, such as prasugrel or ticagrelor, as a component of triple antithrombotic therapy, although a recently published observational study by Sarafoff et al[11] seems to suggest a higher incidence of TIMI bleeding incidents when prasugrel is used instead of clopidogrel as part of triple antithrombotic therapy.

Bleeding is a common non-cardiac complication post PCI. Risk factors for bleeding include increased age, female gender and renal impairment[7,12]. Various scores[12] have been proposed for predicting bleeding post PCI but none has been prospectively validated as yet. When bleeding occurs post PCI, it is often difficult to manage because such patients are often on dual antiplatelet agents after stent placement. Interestingly, data extrapolated from the GRACE registry suggest that patients who had major bleeding episodes (defined as life-threatening bleeding requiring ≥2 U of packed red blood cells, resulting in a decrease in haematocrit of ≥10%, occurring intracerebrally, or resulting in stroke or death) had higher mortality rates if aspirin or $P2Y_{12}$ inhibitors were stopped compared to those whose DAPT was continued[13]. This suggests that one should persist with DAPT while managing bleeding complications to avoid preventable mortality.

It is unfortunate that our patient developed both a DVT and an arterial bleeding event after PCI. When treating both events concurrently, it is important to consider the severity of the bleeding, the extent of the venous thromboembolism and the nature of the PCI performed. These factors will help guide the therapy choices, which include local haemostatic control, the subsequent use of suitable antiplatelet and antithrombotic therapy, as well as the duration of therapy.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Bangalore S, Arora N, Resnic FS. Vascular closure device failure: frequency and implications: a propensity-matched analysis. *Circ Cardiovasc Interv.* 2009;2:549-56.

2. Tisi PV, Callam MJ. Treatment for femoral pseudoaneurysms. *Cochrane Database Syst Rev.* 2013;11:CD004981.

3. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2014;35:2541-619.

4. Liau CS, Ho FM, Chen MF, Lee YT. Treatment of iatrogenic femoral artery pseudoaneurysm with percutaneous thrombin injection. *J Vasc Surg.* 1997;26:18-23.

5. Khoury M, Rebecca A, Greene K, Rama K, Colaiuta E, Flynn L, Berg R. Duplex scanning-guided thrombin injection for the treatment of iatrogenic pseudoaneurysms. *J Vasc Surg.* 2002;35:517-21.

6. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van 't Hof AW, ten Berg JM; WOEST study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet.* 2013;381:1107-15.

7. van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, Koolen JJ, Brueren BR, Dambrink JH, Hautvast RW, Verheugt FW, ten Berg JM. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. *J Am Coll Cardiol.* 2009;53:1399-409.

8. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ. Antithrombotic Therapy and Prevention of Thrombosis, 9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141: 7S-47S.

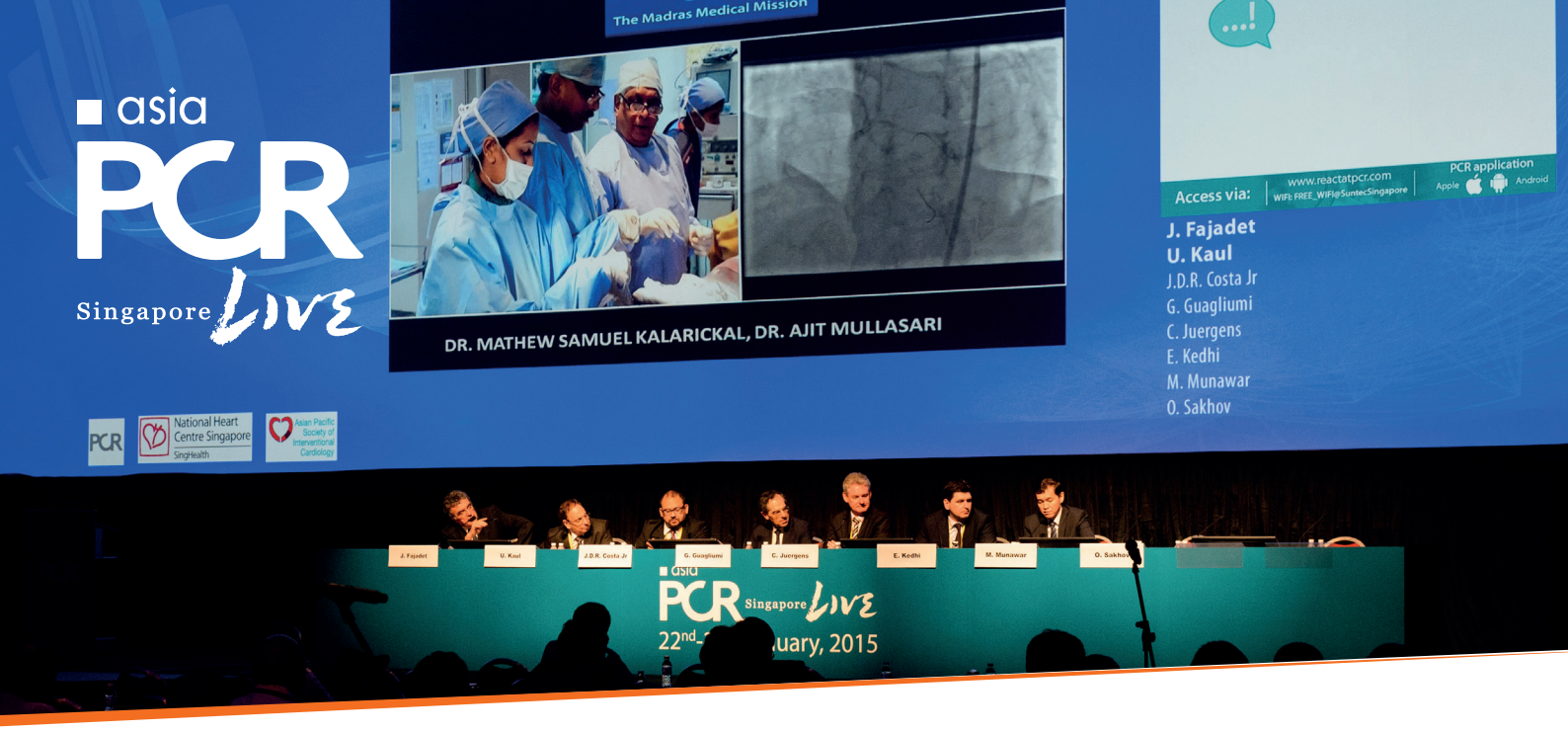
9. Andrade JG, Deyell MW, Khoo C, Lee M, Humphries K, Cairns JA. Risk of bleeding on triple antithrombotic therapy after percutaneous coronary intervention/stenting: a systematic review and meta-analysis. *Can J Cardiol.* 2013:29:204-12.

10. Lip GY, Huber K, Andreotti F, Arnesen H, Airaksinen JK, Cuisset T, Kirchhof P, Marin F; Consensus Document of European Society of Cardiology Working Group on Thrombosis. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting: executive summary – a Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J.* 2010:31:1311-8.

11. Sarafoff N, Martischnig A, Wealer J, Mayer K, Mehilli J, Sibbing D, Kastrati A. Triple therapy with aspirin, prasugrel and vitamin K antagonists in patients with drug eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol.* 2013;61:2060-6.

12. Mehta SK, Frutkin AD, Lindsey JB, House JA, Spertus JA, Rao SV, Ou FS, Roe MT, Peterson ED, Marso SP; National Cardiovascular Data Registry. Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the National Cardiovascular Data Registry. *Circ Cardiovasc Interv.* 2009;2:222-9.

13. Spencer FA, Moscucci M, Granger CB, Gore JM, Goldberg RJ, Steg PG, Goodman SG, Budaj A, FitzGerald G, Fox KA; GRACE Investigators. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? *Circulation.* 2007;116:2793-801.



The premier Cardiovascular Course in Asia

JOIN US!

21-23 January 2016

Suntec Singapore Convention & Exhibition Centre

Course Directors: KOH Tian-Hai, Eric EECKHOUT, Christoph NABER, Upendra KAUL