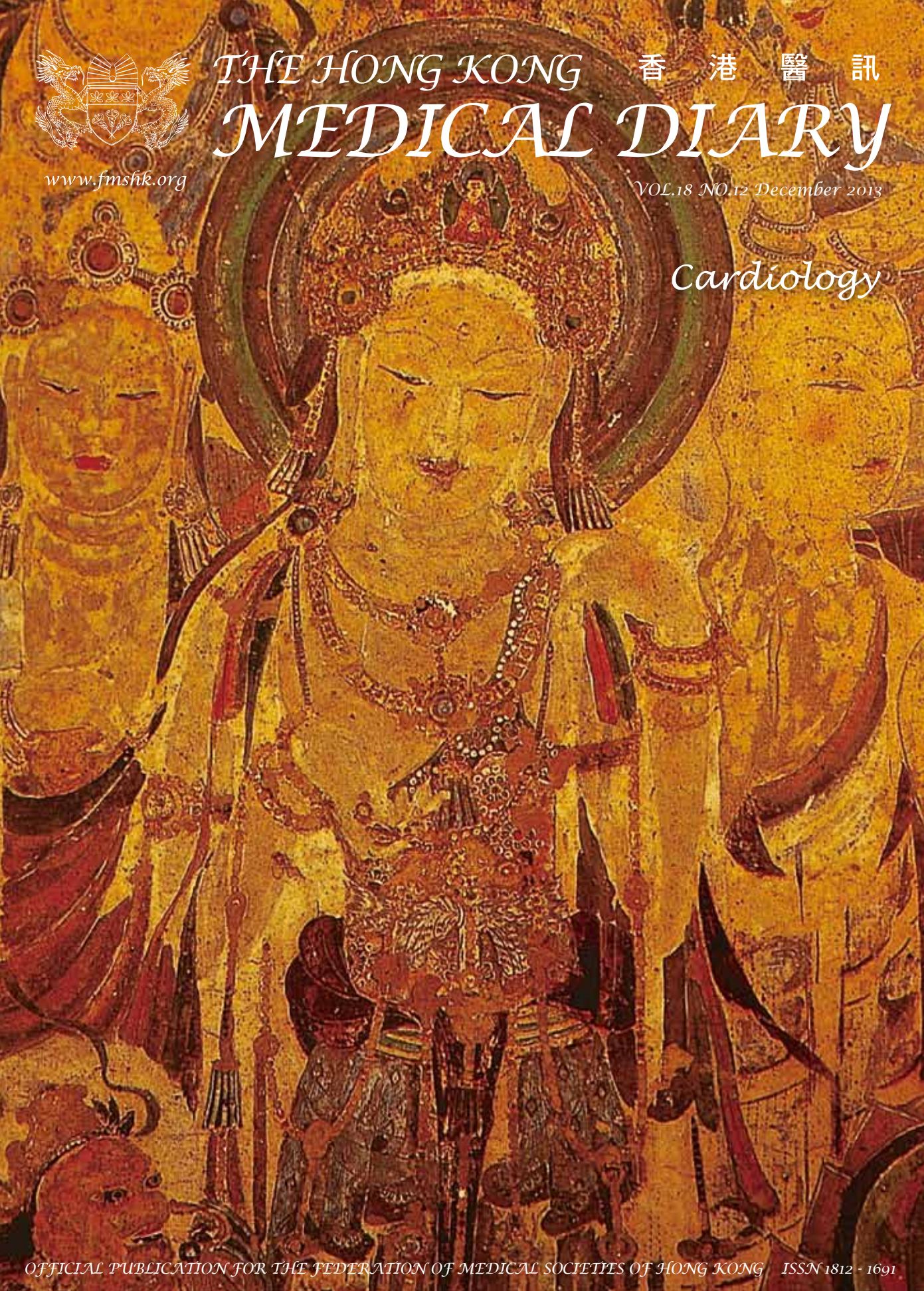
www.fmshk.org

THE HONG KONG MEDICAL DIARY

香 港 醫 訊

VOL.18 NO.12 December 2013

Cardiology



OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

20th Norvasc Anniversary

Norvasc™
amlodipine besylate

Proven Evidence in BP Reduction and Stroke Prevention[1]

Reference 1. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendrofluazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. Lancet. 2005;366:895-906.

NORVASC® ABBREVIATED PACKAGE INSERT
TRADE NAME: Norvasc™ **PRESENTATION:** 5mg tablet x 30's and 10mg tablet x 30's **INDICATIONS:** First line treatment of hypertension and first line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. **DOSAGE: Adults:** Initially 5mg once daily. Max: 10mg. Children (6-17 years): 2.5mg to 5mg once daily. **CONTRAINDICATIONS:** Known sensitivity to dihydropyridines, amlodipine, or any of the inert ingredients. **WARNINGS & PRECAUTIONS:** Patients with heart failure or impaired hepatic function. **INTERACTIONS:** None known. **PREGNANCY AND LACTATION:** Pregnancy Category C. Safety of amlodipine in lactation has not been established. **COMMON SIDE EFFECTS:** Flushing, fatigue, edema, dizziness, headache, abdominal pain, nausea, palpitations, somnolence. Children (6-17 years): headache, asthenia, dizziness, abdominal pain, vasodilatation and epistaxis.
Reference: HK PI (version date: Jan2008) Date of preparation: MAR2011 Identifier number: NORV0311
FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

Pfizer 輝瑞 Address: 16/F, Stanhope House, 738 King's Road, North Point, Hong Kong
Tel: (852) 2811 9711 Fax: (852) 2579 0599 Website(HK): http://www.pfizer.com.hk

NOR1311 #FJUL

Contents

Scan the QR-code

To read more about The Federation of Medical Societies of Hong Kong

New Edition of Medical and Dental Directory
Submit your data NOW!
http://www.fmshk.org/directory2012.php

Disclaimer

The Cover Shot

This is one of the most famous grottoes, and is known as the grotto with the "most famous Avalokitesvara or bodhisattva, constructed during mid-Tang AD 618-704. The Avalokitesvara wears a tiara, necklace with pendants and bangles gilted and decorated with layered ceramics. The painting is skilfully done, expressing the feminine beauty of Avalokitesvara to the fullest. Zhang Da Qian 張大千, the famous painter, who learnt and copied paintings in Mogao Caves from 1938-41, exalted "so beautiful they make my heart pump"!

I took this photo with my camera Nikon D3X 70-200 F 4, from an album, and the reference has been quoted in Page 37.

Dr. Patrick TH KO
MD(Alberta), FRCPC, FHKCP, FHKAM(Med), FACC
Specialist in Cardiology

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Editorial

Dr. Chung-seung CHIANG

MBBS (HK), MRCP(UK) , FHKCP, FHKAM (Medicine), FRCP (Edin), FRCP (Glasg), FRCP(Lond)
Head and Consultant, Division of Cardiology, Department of Medicine, Queen Elizabeth Hospital
Editor

Dr. Chung-seung CHIANG

Medical innovation has no boundaries. Therapeutic options that one can only dream of in the past can become the standard of care at present. This is particularly true for Cardiology. Since the introduction of percutaneous transluminal coronary angioplasty by Dr. Andreas Gruentzig in 1997, we are now seeing the fourth revolution in percutaneous coronary intervention, the invention of the bioresorbable vascular scaffold (BVS). Dr. KT Chan will give us a detailed review of the current evidence for BVS. Similarly, the concept of surgical treatment of hypertension which dated back to the 1930s by surgical sympathectomy has now been revived in a new form. Dr. Steven Li will give us a full description on renal denervation therapy for treatment of resistant hypertension.

Equally exciting advancements have been made in the field of transcatheter structural heart disease intervention. Since the introduction of transcatheter aortic valve implantation (TAVI) in Hong Kong in December 2010, we have gained more experience in this technology. Dr. Michael Lee will give us a review on TAVI. Dr. Jason Chan will write an article on left atrial appendage occlusion in the management of atrial fibrillation which is the commonest form of cardiac arrhythmia found in adults. In addition to LAA occluder, there are now available novel oral anticoagulants for stroke prevent in patients with atrial fibrillation. These new agents have additional benefits in comparison with warfarin, the traditional treatment. Dr. CP Lau will give us an update on this.

These new technologies are undoubtedly fascinating. However, when we go back to the fundamentals of good health, nothing is more basic than the food we eat. Ms. Ingrid Yung and Ms. Alice Chen will enlighten us on dietary approach to stop hypertension and using plant sterols to lower cholesterol.

In this issue of the Medical Diary, I have asked Dr. Patrick Ko to write an article on Dunhuang Grotto Art. I hope our readers will have a deeper understanding of this invaluable treasure of our country through Dr. Ko's vivid and interesting descriptions.

Lastly I would like to wish you all merry Christmas and a prosperous and happy new year.

Nebivolol is different from other antihypertensives because it combines highly selective ß-blockade with nitric oxide-mediated vasodilation.[1] In fact, the European Society of Hypertension states that Nebivolol appears to have positive differences from non-vasodilating ß-blockers.[2] Nebivolol can significantly reduce mortality and is well tolerated.[3] Nebivolol isn't just different, it helps protect lives.[2]

Nebilet®
nebivolol hydrochloride
One treatment, Dual action

References: 1. Ignarro LJ. Different pharmacological properties of two enantiomers in a unique ß-blocker, nebivolol. *Cardiovascular Ther* 2008;26:115-134. **2.** Mancia G, Laurent S, Rosei EA *et al.* Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertension* 2009;27:2121-2158. **3.** Moen MD, Wagstaff AJ. Nebivolol: a review of its use in the management of hypertension and chronic heart failure. *Drugs* 2006;66(10):1389-1409.

MENARINI

A. Menarini Hong Kong Ltd.
Unit 2107-11, 21/F.,
C-Bons International Center,
108 Wai Yip Street, Kwun Tong,
Hong Kong
Tel: +852 3605 5888
Fax: +852 2597 5251
www.menarinipac.com

1. TRADENAME OF THE MEDICINAL PRODUCT. [illegible] **2. QUALITATIVE AND QUANTITATIVE COMPOSITION.** [illegible] **3. THERAPEUTIC INDICATIONS.** [illegible] **4. DOSAGE. Hypertension:** [illegible] **Chronic heart failure.** [illegible] **5. CONTRAINDICATIONS.** [illegible] **6. WARNING AND PRECAUTIONS.** [illegible] **7. UNDESIRABLE EFFECTS.** [illegible] **8. LIST OF EXCIPIENTS.** [illegible]

Renal Denervation in the Management of Resistant Hypertension

Dr. Steven SL LI

MBBS(HK), MRCP(UK), FHKCP, FHKAM (Med), FRCP (Glasg), FRCP(Edin), FRCP(Lond), FACC

Specialist in Cardiology
Director of Heart Centre, Head of Department of Medicine, Union Hospital

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 December 2013.

Introduction

Hypertension is a major public health burden with an astonishing prevalence of 1 in 3 adults. It is the single largest contributor to death and it dramatically increases the risk of heart attack, stroke, heart failure, renal failure and insulin resistance.

Resistant hypertension is defined as the failure to achieve a target blood pressure (commonly a systolic blood pressure of 140mmHg and 130mmHg in diabetic patients), despite compliance to maximally tolerated doses of three or more anti-hypertensive agents, preferably including a diuretic. The true prevalence of resistant hypertension is largely unknown and it varied in different series. Some observational studies suggested a prevalence of 10-20%. A survey of the Kaiser Permanente Colorado and Northern California healthcare systems found the incidence and prevalence of resistant hypertension to be 1.9% and 16.2% respectively. Patients with resistant hypertension were about 50% more likely to experience an adverse cardiovascular event when compared with those controlled with less than three medications.

Renal sympathetic nervous system

It has been known that renal sympathetic nervous system plays an important role in the development and progression of hypertension. Chronic augmentation of the sympathetic signals leads to an increase in renin secretion, which in turn activates the renin-angiotensin-aldosterone system. Denervation of the renal sympathetic system to treat hypertension therefore becomes a very attractive concept. The observation from kidney transplantation that transplanted kidneys, which have been denervated, can still effectively maintain fluid and electrolyte balance has relieved some of the concerns of the procedure.

As early as in the 1930s, there had been attempts to treat malignant hypertension by surgical sympathectomy, which indeed was highly effective, despite the high operative mortality and morbidity. With the advances of transcatheter techniques in recent decades, a minimally invasive approach for sympathectomy became a possibility.

The renal sympathetic nervous system comprises a dense network of postganglionic efferent fibres that run from the hypothalamus to the kidney via pre- and paravertebral sympathetic ganglia. Both the efferent and afferent fibres follow the course of the renal artery to each kidney and lie primarily within the adventitia, the only location where these nerves travel together in the body. Such a strategic occurrence gives rise to a unique target for transcatheter intervention.

The transcatheter renal denervation procedure

The current understanding and experience of the technique of transcatheter denervation comes from the Symplicity Renal Denervation system (Medtronic Inc, Minneapolis, MN), which is currently a 6F catheter system introduced via the femoral artery (Figure 1). Extensive animal research in >300 wine revealed significant reduction in renal tissue norepinephrine, with no stenosis or luminal reduction in treated arteries as evidenced by serial follow up angiography and pathology up to 180 days post-operation.

Figure 1. Symplicity renal denervation system – catheter and radiofrequency energy generator

The procedure with the Symplicity Catheter system and generator, the first commercially available and approved system, is typically done with a 6F catheter system via the femoral artery under local anaesthesia and intravenous sedation. The patient is pre-treated with aspirin. After engagement of a guiding catheter to the renal artery, the Symplicity ablation catheter is introduced into the renal artery, where 4-6 ablations, each lasting 2 min, from distal to proximal sites are done (Figure 2). The procedure will then be repeated at the opposite renal artery. The procedure may induce pain and discomfort, which make intra-operative sedation and pain management essential. The whole procedure with the first generation single electrode catheter takes about 45 minutes. After haemostasis is achieved, the patient will usually stay overnight for observation and then discharged the following day. While there is no a

universally accepted protocol, patients will generally receive 2-4 weeks of aspirin after the procedure in most centres.

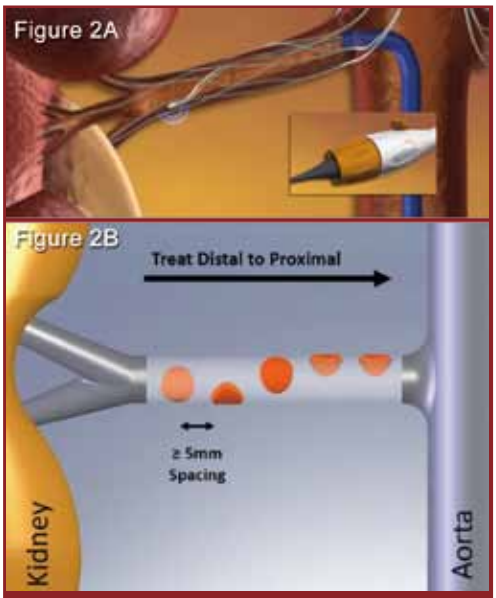


Figure. 2A and 2B. Schematic diagrams of the renal denervation procedure. (Medtronic, Minneapolis, MN).

Clinical data

The first clinical study on renal denervation was published in the Lancet in 2009. In this study, Symplicity HTN-1, more than 150 patients with resistant hypertension (SBP >160mmHg on >3 anti-Hypertensive drugs, or >150mmHg in type 2 diabetes) were recruited. It was found that at 6 months, 84% of the denervated patients had >10mmHg reduction in SBP with a mean reduction of SBP of about 32mmHg. The subsequent Symplicity HTN-2 study further consolidated the procedure feasibility by producing similar results. In particular, the effect of reduction of the blood pressure was sustained up to three years (Figure 3).

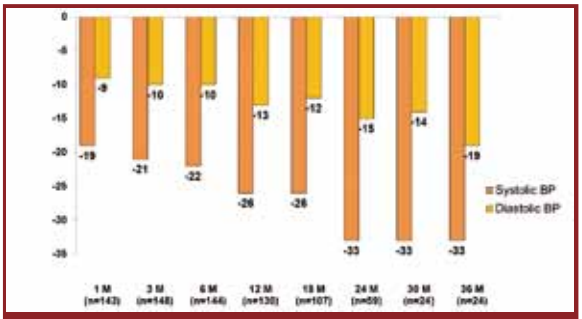


Figure 3. Three years post renal deneravtion trial result in the HTN-1 trial.

Response towards the therapy is usually not obvious until after a few weeks with more apparent improvement in 3 to 6 months. In general about 85% of patients having received renal denervation will have significant response, which is defined as > 10mmHg reduction in SBP. In the HTN2 trial, there was a -32/-12mmHg reduction in office blood pressure. It was also shown that even first month non-responders, if they were followed up closely, would show gradual response with time in the majority in three years. In about 20% of patients, the number of anti-hypertensive medicines may be reducedIn these studies, apart from the exclusion of cases with secondary hypertension and pseudo-hypertension, the following were also excluded from the trials:

1. Main renal arteries <4mm in diameter and <20mm in length before any major branch bifurcation.
2. Dual or multiple renal arterial anatomy.
3. Significant ostial or body renal arterial atheroma/ calcification (stenosis >50%)
4. Fibromuscular dysplasia.
5. Significant renal impairment (eGFR<45mL/min per 1.73m2)
6. Those with previous renal artery interventions such as stenting

Safety and complications of renal denervation procedure

The renal denervation procedure appears to be a safe procedure with no major complications reported. There had been a few cases of catheter related injuries to the renal artery and groin wound vascular complications, which were all treated without further sequelae. Vascular stenosis was rarely reported and renal function showed no deterioration after the procedure. There was no significant changes in renal function in either treatment arm up to one year.

Current development

Up till now, more than 8,000 cases have been performed globally. In Hong Kong, since its introduction two years ago, more than 50 cases have been performed with similar results as in international trials. The second generation catheters (Figure 4) with multi-electrode design will soon be available. They allow four electrodes to ablate simultaneously in a shorter period of time (30 to 60 seconds) with a lower energy. This will significantly reduce the procedure time and the pain induced during the procedure.

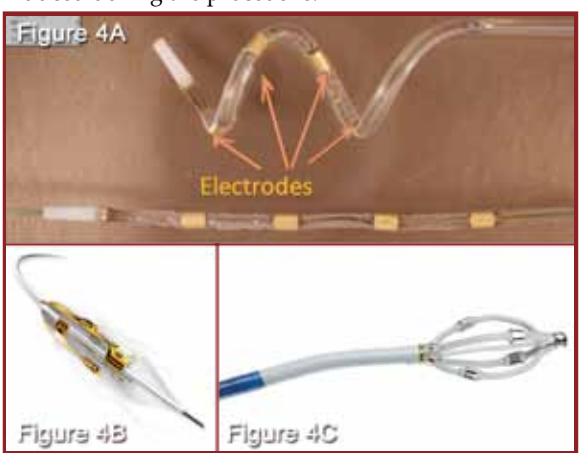


Figure 4. New second generation catheters. A. Medtronic Symplicity Spyral?Spiral Catheter. B. Boston Scientific Vessix Renal Denervation System. C. St Jude Medical EnligHTN catheter.

Conclusions

Despite the advances of modern anti-hypertensives, many patients still fail to achieve a target blood pressure despite good drug compliance and life style modification. A novel treatment strategy is eagerly awaited to fill this clinical gap.

Renal denervation has been shown to be a safe and effective procedure with sustained efficacy up to three years. Currently the data base is still not large, more studies and a longer follow up period are needed to assess this innovative procedure. At present, the procedure is restricted to those resistant hypertension patients. With more data, it is hope that the therapy may be extended to other indications and those with milder degree of hypertension. Until then, this minimally invasive therapy has to be used in a meticulous and evidence-based manner.

References

1. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet. 2009;373:1275–1281.
2. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. N Engl J Med. 2009;361:932–934.
3. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, B.hm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010;376:1903–1909.
4. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension. 2011; 57:911–917. 5. Esler MD, Krum H, Schlaich M, Schmieder RE, B.hm M, Sobotka PA; Symplicity HTN-2 Investigators. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. Circulation. 2012;126:2976–2982.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Renal Denervation in the Management of Resistant Hypertension" by Dr. Steven SL LI and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 December 2013. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **Resistant hypertension is defined as the failure to achieve a target blood pressure (commonly a systolic blood pressure of 140mmHg and 130mmHg in diabetic patients), despite compliance to maximally tolerated doses of two or more anti-hypertensive agents.**
2. **Patients with resistant hypertension are more likely to experience an adverse cardiovascular event when compared with those controlled with less than three medications.**
3. **Chronic augmentation of the sympathetic signals leads to a decrease in renin secretion, which in turn activates the renin-angiotensin-aldosterone system, thereby causing a higher blood pressure.**
4. **Transplanted kidneys, which have been denervated, can still effectively maintain fluid and electrolyte balance.**
5. **Transcatheter renal denervation is done under general anaesthesia.**
6. **Transcatheter renal denervation is done using radiofrequency ablation inside both renal arteries via a femoral artery approach.**
7. **It was found that in HTN-1 trial at 6 months, 84% of the denervated patients had >10mmHg reduction in SBP with a mean reduction of SBP of about 32mmHg.**
8. **Response towards the therapy is usually obvious in about one week after the procedure.**
9. **At three years after renal denervation, results and effects of improved blood pressure control were seen to be sustained.**
10. **Significant renal impairment (eGFR<45mL/min per 1.73m2) is not a contraindication for renal denervation.**

ANSWER SHEET FOR DECEMBER 2013

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2013 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Renal Denervation in the Management of Resistant Hypertension

Dr. Steven SL LI

MBBS(HK), MRCP(UK), FHKCP, FHKAM (Med), FRCP (Glasg), FRCP(Edin), FRCP(Lond), FACC

Specialist in Cardiology

Director of Heart Centre, Head of Department of Medicine, Union Hospital

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No.: _____ (for reference only)

Answers to November 2013 Issue

Mandibular Condylar Fracture – A Review of Management and Case Reports

1. T 2. F 3. T 4. F 5. T 6. T 7. F 8. T 9. T 10. F

PRACTICE MANAGEMENT FOR PRIVATE MEDICAL PRACTICES

February 10 to April 14, 2014 (3-month short course)

SCHOOL OF PUBLIC HEALTH
THE UNIVERSITY OF HONG KONG
香 港 大 學 公 共 衞 生 學 院

About the Course

This is an applied course where students will work in small groups to:

1. Perform **critical analysis** and **develop in-depth understanding** of healthcare management problems;
2. **Develop ideas and proposals** about how these might be resolved;
3. Determine the **intended and unintended consequences** of actions taken by the management team; and
4. Provide participants with **essential knowledge and skills** required to manage private healthcare services.

Course Objectives

On completing this course, participants will be able to:

1. Acquire general and practical management skills for managing private healthcare services;
2. Apply the acquired management skills in resolving the practical problems of managing private healthcare services;
3. Adopt best practices of management skills in strategic planning and operating private healthcare services.

Who should join?

The course is suitable for all **health professionals** from the private sector and those who are involved in managing healthcare services.

Details

Date: Feb 10th to April 14, 2014 (Every Monday)
Time: 6:30 - 8:30 pm
Venue: Seminar Room 4, G/F, Laboratory Block, LKS Faculty of Medicine Building, 21 Sassoon Road, HK. (T.B.C.)
Course Fee: HK$7,500
CME points: Pending for approval

Date	Lecture Topic	Guest Experts
10 Feb 2014	1. Overview of the private sector - Hong Kong's and Southeast Asia perspectives	Dr. Nelson Wong
17 Feb 2014	2. Laws, regulations and policies	
24 Feb 2014	3. Business continuity, operations plan and Workflow	
03 Mar 2014	4. Communication	Mr. Tony Tan
10 Mar 2014	5. Business development	
17 Mar 2014	6. Finance	Dr. Ronnie Hui
24 Mar 2014	7. Manpower planning, professional development and training	Dr. Brian Chan
31 Mar 2014	8. Supply chain and resources management	Dr. Bennet Fung
07 Apr 2014	9. Clinical governance	Dr. Ares Leung
14 Apr 2014	10. Quality control and patient safety	

Early birds (application before January 10, 2014) — **50% off**

HKU Staff & Students — **50% off**

Research Postgraduates with a Hong Kong tertiary institution — **$200**

Special Offer

The application will be processed on a first-come-first served basis.
Places for research postgraduates are limited. Notification will be sent to successful applicants.

About the Tutor

Mr. Peng KONG is currently a healthcare management specialist at School of Public Health of the University of Hong Kong. Peng has obtained **MPH**, **MHSM** and **MBA** through local and oversea university. Peng has professional experience with particular insights and know-how on operations management, strategic planning and business development for private healthcare industry in Hong Kong.

Guest experts

Dr. Brian CHAN
MBBS (HK), DCH (RCP & SI), DPD (Cardiff)

Dr. Bennet FUNG
MBBS (HK), DCH (London), DFM (CUHK), MRCGP (UK), Dip Med (CUHK)

Dr. Ronnie HUI, J.P.
MBBS (HK), FHKAM (Paediatrics), FHKC Paediatrics, CFA, MBA

Dr. Ares LEUNG
MBBS (HK), FRCOG, FHKCOG, FHKAM (O & G)

Mr. Tony TAN
BSc (Management), BSc (Chemistry), MBA

Dr. Nelson WONG
LRCP (London), MRCS (England), MBBS (London), MRCP (UK), FLMI (with Distinction)

Apply Now

Application Form

http://mph.sph.hku.hk/en/prospective_students/form/MPH_Form_(Occasional)_2013.pdf

Please keep check of our website for the latest information:
http://mph.sph.hku.hk/

Enquiry : Tel: 2819 9140 | Fax: 2855 9528 | Email: mphsph@hku.hk | Website: http://mph.sph.hku.hk/

Update on Bioresorbable Vascular Scaffolds

Dr. Kam-tim CHAN

MBBS, MRCP, FRCP (Lond, Glas, Edin), FHKCP, FHKAM, FACC

Consultant Cardiologist
Department of Medicine, Queen Elizabeth Hospital

Dr. Kam-tim CHAN

Introduction

After Dr. Andreas Gruentzig performed the first Percutaneous Coronary Intervention (PCI) with a balloon catheter in 1977,[1] there have been significant revolutionary changes in the field of coronary interventions. The widespread application of coronary stents, initially bare metal stents and later drug eluted stents (DES), has markedly improved the efficacy and safely of PCI. However, the inherent limitations and potential complications of permanent coronary stenting still pose an important challenge for cardiologists.[2-8] This has led to the continuous development of new stent designs and platforms, with aims to overcome these limitations and further enhance the management of coronary artery diseases.

Inherent limitations of Metallic Coronary Stents

There are currently many long term limitations inherent in the technology of metallic stents (Table 1). The persistence of the metallic material or the non-absorbable polymer may induce a chronic inflammatory response and contribute to the occurrence of late or very-late stent thrombosis. Patients will be required to take dual antiplatelet therapy (DATP) for a prolonged period of time and hence carry the risks of bleeding complications. Late fractures of the stent struts have been reported to be the cause of in-stent restenosis and late stent thrombosis. These stented vessels also exhibit impaired endothelial vasomotor function and render the patients unsuitable for subsequent arterial bypass grafting or re-interventions. Other imaging modality like the computerised tomography angiography (CTA) or Magnetic Resonance Imaging (MRI) might be difficult to be applied to these stented segments owing to the imaging artifacts.[2-8] In order to overcome these problems, a temporary scaffold that can be entirely resorbed by the body after completing its defined role is a very attractive innovation.

Table 1: Current limitations of permanent metallic stents

chronic inflammatory response
stent thrombosis
prolonged dual antiplatelets
Re-intervention or CABG difficult
Limit imaging modalities

Differences between the Scaffolds and Stents

As different from a coronary stent which constitutes a permanent implant, a scaffold is a temporary backbone placed inside the vessel. After it fulfils its transient role in supporting the vessel and elutes a drug to inhibit neointimal hyperplasia, the scaffold can be completely resorbed by the body and hence permanent metallic caging of the artery is avoided. Many of the inherent limitations of metallic stents can be prevented and the artery can then have the potential to restore its native vasomotor function.

Key Features of an Ideal Bioresorbable Scaffold

The ideal bioresorbable vascular scaffold should possess three cardinal features for it to be effective and safe. It should have adequate initial and subsequent radial as well as longitudinal strength to prevent the recoil of the vasculature. The bioresorbable material should also have an optimal degradation profile and timing so that there would not be problems of particulate material embolisation to the distal vascular tree. Lastly, the complete biocompatibility of these bioresorbable materials and the inability to elicit any inflammatory response are also important factors.

The ABSORB Bioresorbable Scaffold (BVS)

Actually, the concept of having a bioresorbable scaffold was not new to interventional cardiologists. Tamai et al had published the data on the first-in-man bioabsorbable Igaki-Tamai stents (Igaki- Medical Ltd.), which was a bare metal stent, in the Journal of Circulation in 2000. Owing to the relatively disappointing results, no further large scaled clinical trials had been performed.[9]

It is only until Abbott Vascular (Santa Clara, CA, USA) first produced the fully Bioresorbable Vascular Scaffold (BVS), which has been demonstrated to have a very satisfactory safety profile and clinical outcomes in clinical trials, that this new technology is then regarded as an important step forward in the field of PCI. The Absorb BVS is comprised of a poly L-lactide (PLLA) backbone, a proven biocompatible material commonly used in medical implants like resorbable sutures. The anti-proliferative drug used is Everolimus (Novartis Pharmac.), and is effective in inhibiting the neointimal hyperplasia and smooth muscle cell proliferation. The PLLA backbone is coated with a matrix composed of Everolimus and polymer Poly-DL-Lactic acid (PDLLA) in a 1:1 ratio to form an amorphous drug eluting coating containing 100u Everolimus/cm^2. Both PDLLA and PLLA can be completely metabolised and resorbed by the body and leave no material inside the artery after 2 to 3 years, apart from the two tiny markers. The ultimate degradation product of both PDLLA and PLLA is lactic acid, which is metabolised via the Krebs cycle into CO_2 and H20. The blood vessels can then resume the normal ability to flex, contract and pulsate with response to

various stimuli, similar to an untreated native vessel (The concept of Vascular Restoration Therapy).[10-20]

The diagram of the ABSORB BVS

The ABSORB Clinical Trials

In order to prove its clinical efficacy and safety, the ABSORB trial (a prospective, non-randomised, open label, two phase study) had enrolled 131 patients from New Zealand, Australia and Europe. The first stage was started in March 2006 (30 patients were in the Cohort A – the first-in-man study; single de-novo lesion); the second phase in March 2009 (the next 101 patients in Cohort B with an improved scaffold design). The endpoints were the acute results of the BVS, Major Adverse Cardiac Events (MACE) rate and stent thrombosis (ST) rate at 30 days, 6, 9, 12 and 24 months. The patients would be followed up clinically up to five years. Various imaging studies by angiography, Intravascular Ultrasound (IVUS) and Optical Coherence Tomography (OCT) would be performed at 6, 12, 18, 24 and 36 months. For the Cohort A subgroup, five year clinical follow up data were available in 29 patients. The hierarchical Ischaemic-driven MACE rate was 3.4% and there was no late thrombosis reported.[21] The three year data of the 101 patients of the ABSORB Cohort B trial were recently presented in the 2013 American College of Cardiology meeting. The rate of major adverse cardiac events (MACE) was 10% at 3 years, which was similar to a comparative set of data with a best-in-class drug eluting stent (Xience-V; Abott Vascular) in the same follow up period. Moreover, in a subset of 45 patients, state-of-the-art imaging techniques revealed improvement in vasomotion. The treated segment was able to react to changes in blood flow and physiological stimuli like exercises or certain drugs (acetylcholine-vasodilatation; methergine-vasoconstriction). There was a 7.2% increase in late lumen gain from measurements taken at baseline and a reduction in the total plaque area inside the vessels between one and three years. These findings were unique to the BVS and were not typically observed in the other metallic drug eluted stent platforms. OCT studies also confirmed the scaffold being resorbed by 3 years. [10-20, 22]

The ABSORB EXTEND trial is a single arm study that enrolls patients at up to 100 centres in Europe, Latin America, Canada and Asia Pacific regions. It aims to recruit approximately 800 patients, including patients with more complex coronary artery anatomies. Key endpoints of the study include MACE and scaffold thrombosis rates at 30 days, 6, 12, 24 and 36 months, as well as an assessment of the acute performance of the bioresorbable vascular scaffold, including successful deployment of the system. The 6 and 12 months clinical outcomes of the initial 512 patients have been presented in the 2013 European Society of Cardiology meeting held in Amsterdam. At 12 month follow up, the cardiac death rate, hierarchical MACE rate and the scaffold thrombosis rate of the BVS group were 0.4%, 4.3%, 0.8% respectively.(Table 2) The full results of the ABSORB EXTEND study will provide more data on the efficacy and safety of the BVS in a more real-life patient population and better define the potential role of this innovative technology.[23]

ABSORB EXTEND : Clinical Outcomes at 6 and 12 Months

	6 months (N= 512)	12 months (N = 512)
Cardiac Death %	0.2	0.4
Myocardial Infarction %	2.7	2.9
Ischaemia driven TLR %	0.6	1.8
Hierarchical MACE %	2.9	4.3
Hierarchical TVF %	3.3	4.9
Scaffold thrombosis % ARC (def/prob)	0.6	0.8

Chevalier et al. An Interim 12-month Clinical Outcomes of ABSORB EXTEND patients. 9-2013, ESC Amsterdam

Other ABSORB Clinical Trials

ABSORB II is a prospective, randomised (2:1) active control, single blinded, parallel two-arms, multi-centre trial, comparing the ABSORB BVS with the Xience Everolimus Eluting Coronary Stent System. The study was started in November 2011, and the estimated primary completion date will be 2015.[24] This will provide a direct head to head comparison of the ABSORB BVS with the current second generation DES in use and its results will provide important information on the definite efficacy of this new scaffold system.

ABSORB III is another randomised controlled trial conducted in the United States with the aim to enroll around 2250 patients. The aim is to compare the performance of the Abbott's drug eluting Absorb Bioresorbable Vascular Scaffold (BVS) to the Xience stent.[25] Other clinical trials are also being conducted in Japan and China, and the results of these trials may lead to the approval of this device in the relevant areas and its more widespread penetration into their markets.

Other Bioresorbable Vascular Scaffolds

After the initial satisfactory results of the ABSORB BVS system, most people believe that the bioresorbable scaffold will be the revolutionary change in the management of coronary artery diseases. Many companies have shown their interest and invested a lot of resources in the research and development of other types of bioresorbable vascular scaffold. It is beyond the scope of this article to discuss on all of them and I just briefly describe a few devices that have got some preliminary data.

The Magnesium Bioresorbable Scaffold

Magnesium is an essential element of the human body and it is an ideal bioresorbable material to make a vascular scaffold. Initially, the magnesium based bioresorbable bare metal stents had very disappointing short term results. In the first-in-man study, the magnesium scaffold was associated with a binary restenosis rate of 50% and a 23.8% ischaemic driven target vessel revascularisation rate at 4 months.[26]

The second generation magnesium scaffold, DREAMS (Drug Eluting Absorbable Metal Scaffold, Biotronik Ltd) is based on a proprietary magnesium alloy technology, and uses a degradable polymer and paclitaxel elution to inhibit the neointimal hyperplasia.

BIOSOLVE-I trial is a prospective, multi-centre, first-in-man trial of the DREAMS in 46 patients (47 de-novo lesions) in five European centres. Patients were assigned to angiographic and intravascular ultrasonographic follow ups at 6 months and 12 months and they were clinically followed up to 36 months. OCT was also done in some subgroups. The overall procedural and device success was 100%. At 1 year follow up, the target lesion failure rate was 7% and there was no cardiac deaths and scaffold thrombosis. The events included 2 target lesion revascularisations at 6 month and 1 peri-procedural Myocardial Infraction during angiography at 12 month. The mean in-scaffold late loss was 0.52mm+/- 0.39mm, which was somewhat higher when compared with the ABSORB BVS.[27]

BIOSOLVE II trial will evaluate the newer generation DREAM II scaffold that uses the magnesium alloy with PLLA polymer coating and sirolimus as the anti-proliferative drug. There will be changes in the architecture, composition and strut thickness of the scaffold. The one year safety and efficacy data will be available by early 2005.

The ReZolve Scaffold

The RESTORE trial was designed to study the performance and safety of the first generation ReZolve sirolimus-eluting bioresorbable coronary scaffold (REVA Medical. Inc) in 26 patients at multiple centres in Brazil and Europe. In the Transcatheter Cardiovascular Therapeutics (TCT) meeting 2013 held in San Francisco, Dr. Ricardo Costa from the Institute Dante Pazzanese of Cardiology, presented the 12 month data of patients who were enrolled in the RESTORE pilot clinical trial between December 2011 and July 2012. At twelve-month angiographic follow-up on the patients who remained event free after treatment, imaging results demonstrated a mean in-stent late loss of 0.29 mm, which was well within the safety range and performance of currently used drug-eluting metal stents and bioresorbable scaffolds. For patients who had undergone retreatment for focal in-stent restenosis, the mean in-stent late loss was 0.69 mm.[28]

The ReZolve2 vascular scaffold utilises a proprietary desaminotyrosine polycarbonate polymer, which is developed specifically for bioresorbable scaffold performance and provides adequate radial strength both initially and over time. A unique feature of the polymer is its visibility under x-ray, allowing the scaffold to be visualised during the implantation and subsequent follow ups. The scaffold is coated with the anti-proliferative agent sirolimus on the abluminal surface using a polymer solution. The polymer used for the coating is the same polymer used in the scaffold structure. There is a controlled release of the drug over 30 days, with the majority released within 90 days. This early and slow release characteristic may help with the initial healing process.

The RESTORE II Clinical trial uses the next generation ReZolve2 bioresorbable scaffold (REVA Medical. Inc), which has a lower profile and an approximate 30% increase in radial strength when compared to the first degeneration ReZolve device. It aims to recruit 125 patients from Australia, Brazil, Europe and New Zealand and the data will be available at the end 2014.

DESolve Novolimus Eluting Bioresorbable Coronary Scaffold System

DESolve is another PLLA-based ultrathin polymeric scaffold (Elixir Medical Corporation) and the drug novolimus is used to inhibit neointimal hyperplasia. DESolve is degraded in about 1 year's time, leaving behind a thin neointimal lining and a well-maintained lumen, similar to a de novo vessel.

The DESolve First-In-Man Trial recruited 15 patients in Europe and New Zealand. At 12 month follow up, there was no scaffold thrombosis and no MACE directly attributable to the scaffold. At 6 month, the in-scaffold late lumen loss was 0.19+/-0.19 mm by angiography. Intravascular ultrasound showed a relatively low neointimal volume of 7.19+/-3.56 %, with no evidence of scaffold recoil or malapposition. These were confirmed with OCT which revealed a uniform and thin neointimal coverage (0.12+/-0.04mm) of the scaffold.[29]

DESolve Nx Trial is a multi-centre, prospective study enrolling 120 patients at up to 15 centres in Belgium, Poland, Brazil and New Zealand designed to evaluate the safety and efficacy of the DESolve bioresorbable system.

CONCLUSION

Despite all the enthusiasm in this new technology, long term data are only available for the relatively simple lesions. All these novel scaffolds have not yet been fully tested in those more complex lesions, bifurcations, left main diseases, heavily calcified lesions, total occlusions and very tortuous vessels. At the present moment, caution should be exercised when applying the new scaffolds to these lesion subsets. Nevertheless, with better devices and more solid evidences accumulating, we may definitely have more bioresorbable scaffolds that can improve the outcome of coronary artery disease patients.

References

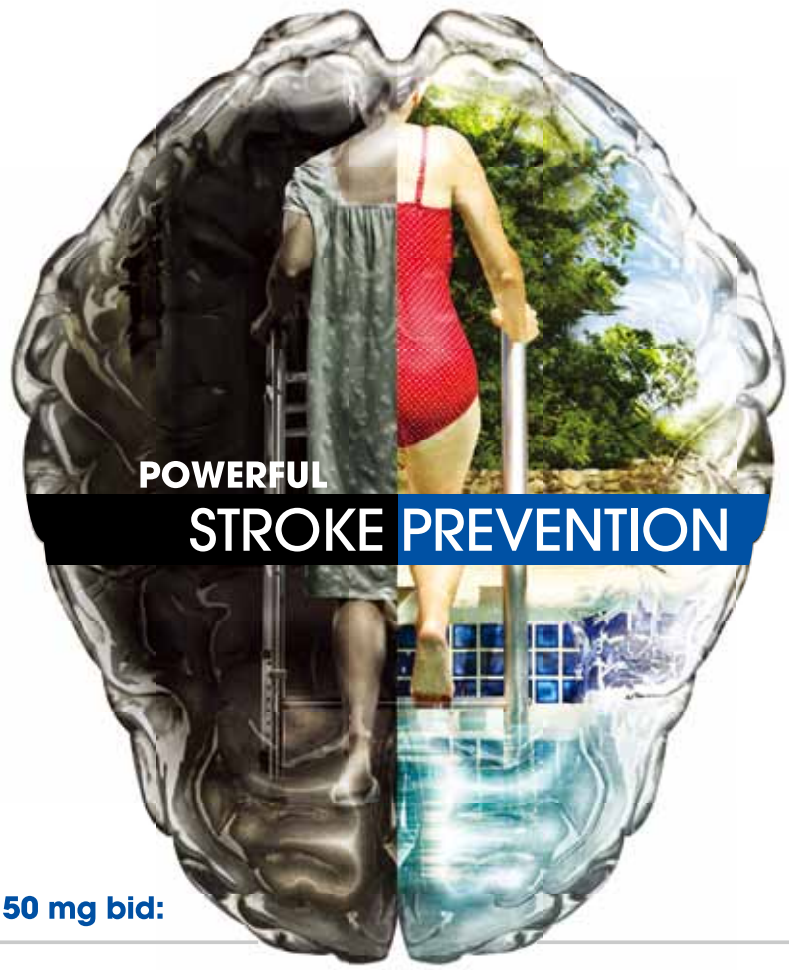
1. Gruentzig AR. Transluminal dilatation of coronary artery stenosis. Lancet 1978; 1: 263.
2. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005; 293: 2126-2130.
3. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. for the BASKETLATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006; 48: 2584-2591.
4. Stone GW, Ellis SG, Colombo A, et al. Offsetting impact of thrombosis and restenosis on the occurrence of death and myocardial infarction after paclitaxel-eluting and bare metal stent implantation. Circulation 2007; 115: 2842-2847.
5. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network metaanalysis. Lancet 2007; 370: 937-948.
6. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet.2007; 369: 667-678.
7. Camensind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first- generation drug eluted stents: a cause for concern. Circulation 2007; 115: 1440-55.
8. Garg G, Serruys PW. Benefits of and safety concerns associated with drug eluting coronary stents. Expert Rev Cardiovasc Ther 2010; 8: 449-70.
9. Tamai H. et al. Initial and 6 month results of biodegradable poly-l-lactic acid coronary stents in human Circulation 2000.102:399-404

10. Tanimoto S, Serruys PW, Thuesen L, et al. Comparison of in vivo acute stent recoil between the bioabsorbable everolimus-eluting coronary stent and the everolimus-eluting cobalt chromium coronary stent: insights from the ABSORB and SPIRIT trials. Catheter Cardiovasc Interv. 2007 Oct 1; 70(4): 515-23.
11. Ormiston JA, Webster MW, Armstrong G. First-in-human implantation of a fully bioabsorbable drug-eluting stent: the BVS poly-L-lactic acid everolimus-eluting coronary stent. Catheter Cardiovasc Interv. 2007 Jan; 69(1): 128-31.
12. Ormiston JA, Serruys PW, Regar E, et al. A bioabsorbable everolimus eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet. 2008; 371(9616): 899-907.
12. Bruining N, Tanimoto S, Otsuka M, et al. Quantitative multi-modality imaging analysis of a bioabsorbable poly-L-lactic acid stent design in the acute phase: a comparison between 2- and 3D-QCA, QCU and QMSCT-CA. EuroIntervention 2008 (2): 285-91.
14. Tanimoto S, Bruining N, van Domburg RT, et al. Late stent recoil of the bioabsorbable everolimus-eluting coronary stent and its relationship with plaque morphology. J Am Coll Cardiol. 2008; 11; 52(20): 1616-20.
15. Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods, Lancet 2009 Mar; 373 (9667): 897-910.
16. García HM, Gonzalo N, Pawar R, et al. Assessment of the absorption process following bioabsorbable everolimus-eluting stent implantation: temporal changes in strain values and tissue composition using intravascular ultrasound radiofrequency data analysis. A substudy of the ABSORB clinical trial. EuroIntervention 2009 4(4): 443-8.
17. Ormiston,John A. and Patrick W.S. Serruys. Bioabsorbable Coronary Stents. Circ Cardiovasc Intervent 2009; 2: 255-260.
18. Oberhauser, James, et.al. Design Principles and Performance of Bioresorbable Polymeric Vascular Scaffolds. EuroIntervention 2009; 5: F15-F22.
19. Yoshinobu O; Serruys PW, The ABSORB Investigators. ABSORB Trial: Three Year Clinical Results of the Evaluation of the Bioabsorbable Everolimus-Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions. Circulation 2009; 120: S951.
20. Yoshinobu O, Serruys PW, Ormiston JA; et al. Three year results of clinical follow up after a bioresorbable everolimus- eluting scaffold in patients with de novo coronary artery diseases: the ABSORB trial.Eurointervention.org 10; 2010 online publish.
21. Dudek D et al. Four year clinical follow up of the ABSORB Trial Evaluating the Absorb Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Patients with de novo Native Coronary Artery Lesions. EuroIntervention 2012 Jan,9:1060-1
22. Chevalier et al. First Report of the Four Year Clinical Results of the ABSORB Trial Evaluating the Absorb Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Patients with de- novo Native Coronary Artery Lesions. JACC 2013.62, (18_S1) B11-B11
23. Chevalier et al. An Interim 12-month Propensity Adjusted Comparison of Clinical Outcomes of ABSORB patients to Xience V patients. 9-2013, ESC Amsterdam.
24. Diletti R et al. ABSORB II randomized controlled trial : a clinical evaluation to compare the safety, efficacy and performance of the Absorb everolimus eluting bioresorbable vascular scaffold system against the XIENCE everolimus eluting coronary stent system in the treatment of subjects with ischemic heart disease caused by de novo native coronary artery lesions; rationale and study design. AHJ 2012 Nov 164(5):654-63.
25. Clinicaltrials.gov/show/NCT01751906
26. Erbel R et al. Temporary scaffolding of the coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomized, multicenter trial. Lancet 2007; 369: 1869-75.
27. Haude M et al. Safety and performance of the DREAMS (Drug Eluting Absorbable Metal Scaffold) In patients with de-novo coronary lesions: 12 month results of the prospective, multicenter, first-in-man BIOSOLVE-I trial. Lancet 2013 Mar 9,381(9869):836-44
28. Ricardo Costa et al. 12 clinical outcomes of the RESTORE I trial. TCT San Francisco 10-13
29. Verheye S. et al. A Next generation Bioresorbable Coronary Scaffold System- from Bench to First Clinical Evaluation: Six and 12- Month Clinical and Multimodality Imaging Results. JACC Cardiovasc Interv 2013 Oct 10. Pii:S 1936-8798.

PRADAXA®
THE ONLY ANTICOAGULANT

NO INR monitoring[1]

SHOWN TO BE SUPERIOR FOR BOTH ISCHEMIC AND HEMORRHAGIC STROKE RISK REDUCTION VS WELL-CONTROLLED WARFARIN IN NON-VALVULAR AF PATIENTS[1-3]



PRADAXA 150 mg bid:

-25%
SUPERIOR REDUCTION in ISCHEMIC STROKE
vs warfarin[1-3]
p = 0.03

-74%
SUPERIOR REDUCTION in HEMORRHAGIC STROKE
vs warfarin[1-3]
p < 0.001

-59%
SIGNIFICANTLY LOWER RATE of INTRACRANIAL BLEEDING
vs warfarin[1-3]
p < 0.001

PRADAXA® (dabigatran etexilate) is indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors†.

† Risk factors: previous stroke, transient ischemic attack, or systemic embolism (SEE); left ventricular ejection fraction < 40 %; symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2; age ≥ 75 years; age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension.[1]

Pradaxa® (dabigatran etexilate) is a prescription medicine. For complete information, please refer to the full prescribing information.

Reference: 1. Pradaxa® Prescribing information, HK. 2. Connolly SJ et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med.* 2009;1139-1151. 3. Connolly SJ et al. Newly Identified Events in the RE-LY Trial. *N Engl J Med.* 2010;363:1875-1876.

Pradaxa® dabigatran etexilate 百達生®

Simply superior stroke prevention

Boehringer Ingelheim

Boehringer Ingelheim (H.K.) Ltd.
Suites 1504-9, Great Eagle Center, 23 Harbour Road, Wanchai
Tel: 2596 0033 Fax: 2827 0162 www.boehringer-ingelheim.com

www.pradaxa.com

PRA-04-2013-53

Update on Transcatheter Aortic Valve Implantation (TAVI)

Dr. Alan KC CHAN
MBBS(HK), MRCP(UK), FHKCP, FHKAM(Medicine)
Specialist in Cardiology
Resident Specialist, Division of Cardiology, Department of Medicine, Queen Elizabeth Hospital

Dr. Michael KY LEE
MBBS(HK), MRCP(UK), FRCP(Glasg), FACC, FHKCP, FHKAM(Medicine)
Specialist in Cardiology
Consultant Cardiologist, Division of Cardiology, Department of Medicine, Queen Elizabeth Hospital


Dr. Alan KC CHAN Dr. Michael KY LEE

Introduction

The treatment of symptomatic aortic stenosis was traditionally by surgical aortic valve replacement (SAVR) until the introduction of transcatheter aortic valve implantation (TAVI) just over a decade ago. Following the first case in 2002 by Cribier and colleagues[1], this new percutaneous technique was rapidly utilised and, to date, more than 90,000 TAVI and 45,000 CoreValve procedures have been performed worldwide. Recently, TAVI became the only intervention for aortic stenosis shown to prolong life in a randomised trial as compared with medical treatment[2]; TAVI is now the standard of care for extremely high-risk or "inoperable" patients and is an alternative to surgery for high risk but "operable" patients.[2,3] Since the first review of the topic by our group in this Diary[4], there have been many advances with abundant latest clinical data available. We will briefly review the technology and highlight the latest advances, clinical data and future development.

Transcatheter valves

Two types of transcatheter aortic valves are widely used in the clinical setting, the balloon expandable Edwards SAPEIN valve (Edwards Lifesciences Corporation, Irvine, CA, USA) and the self-expandable CoreValve (Medtronic, Minneapolis MN). Both devices received CE Mark approval for European commercial sale in 2007 and the Edwards SAPIEN valve received FDA approval in the USA in November 2011.

Balloon expandable Edwards valve

The first two generations of the Edwards valve (Cribier-Edwards and Edwards SAPIEN) comprised three leaflets of bovine pericardium mounted in a stainless steel frame. 23 and 26mm valves are available and they are implanted using 22 and 24 French delivery catheters respectively. The Edwards SAPIEN XT is the third generation of this technology which consists of a trileaflet pericardial bovine valve mounted in a cobalt chromium frame. Four sizes are available (20, 23, 26 and 29mm).The improved design of the Edwards SAPIEN XT enables implantation of the valve by using an 18 French delivery catheter. Smaller 16 French expandable sheaths (eSHEATH, Edwards Lifesciences Corporation) are also available for clinical use in various parts of the world.

Self expandable CoreValve

The CoreValve ReValving system utilises a self-expanding nitinol frame. The leaflets and annular seal area are constructed of porcine pericardium. The supra-annular design of the CoreValve maximises blood flow and allows allows more optimal leaflet coaptation and haemodynamic performance even in non-circular annuli. The device is compressed in an Accutrak delivery catheter (Medtronic) and introduced through an 18 French sheath into the common femoral or subclavian artery. Currently 4 sizes are available (23, 26, 29 and 31mm).

Patient evaluation

One of the critical aspects for a successful TAVI programme is the patient selection process. Whether TAVI is advisable depends not only on various technical considerations but also on the likelihood of functional and survival benefits. Traditionally, the recruitment of patients into clinical trials depends on clinical risk scoring systems derived from cardiac surgeries. The STS (Society of Thoracic Surgeons) score and logistic EuroSCORE are the 2 most widely used risk scoring systems[2,3,5]. However, these scores share important limitations in high-risk patient subsets, most notably a limited predictive capacity and an inability to capture significant comorbid conditions in what is a heterogeneous patient group. The logistic EuroSCORE, for example, has a low discriminatory power in TAVI patients (C statistics 0.61 to 0.64)[6]. As such, the applicability of these scores in patient selection for TAVI has been questioned[7-9]. Despite these limitations, patient enrolment in TAVI trials has been determined by an EuroSCORE >15% or an STS score >10%[2,10]. Increasingly, evaluation is directed on identifying patients in whom a significant improvement in quality and duration of life is likely and avoiding unnecessary intervention in patients whose benefit is minimal due to advanced age and comorbidities. The term "Cohort C" describes this subset of inoperable patients who have poor survival and quality of life (QoL) despite TAVI (Figure. 1). Cohort C patients may be able to be identified by the concept of frailty. Frailty is increasingly recognised as a major determinant of clinical outcome after TAVI. It is considered to be a distinct clinical syndrome characterised by decreasing muscle mass, energy expenditure, and malnutrition,

and imparts extreme vulnerability to adverse events[11]. Recently, a modified Fried frailty index composed of 4 criteria had been developed at the Columbia University (21). It consisted of (1) activity of daily living (ADL) impairment, (2) serum albumin <3.5 g/dL, (3) grip strength <30 kg for males and <18 kg for females, and (4) 15-feet walk test ≥7 seconds. The study showed that a frailty score >5 had a >3-fold increase in 1-year mortality after TAVI. In another study by Stortecky et al[22], the use of multidimensional geriatric assessment was found helpful in predicting the 30-day and 1-year mortality and major adverse cardiac and cerebrovascular events, In brief, it is important to identify patients who are too ill or in their advanced stage of the disease that further intervention will not alter their clinical outcome.

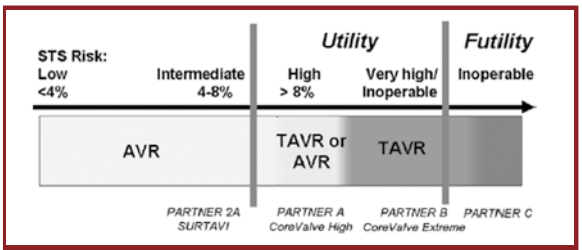


Figure 1. Spectrum of risk profiles in patients with severe aortic stenosis

For patients who are clinically indicated for further aortic valvular intervention, a comprehensive anatomical screening is necessary. It includes aortic root anatomy for detailed sizing and peripheral vascular anatomy for possible vascular access.

Accurate measurement of the annulus is essential in guiding the right choice of valve size to avoid aortic rupture and paravalvular leak. It is traditionally done by trans-thoracic and trans-oesophageal echocardiography. However, they are known to underestimate the true annular size because of the oval shape of the anatomy. Currently, CT angiography is more commonly used as it can clearly show this complex anatomy of the annulus and give the best accurate measurement[12].

After determining the aortic valvular anatomy for TAVI, the choice of vascular access would be the next step of evaluation. Traditionally, transfemoral and transapical were commonly used. The femoral artery is considered to be the default vascular access site for TAVI. When more experience is gained for this technology, other possible routes have been explored. It included the subclavian access[13], transaortic[14] (by means of mini-thoracotomy and direct aortic puncture) and iliofemoral vascular conduit. CT can help to delineate the detailed anatomy and suitability of these vascular accesses. The diameter, tortuosity and degree of calcification of iliofemoral arteries are mandatory to determine the suitability of the most commonly used transfemoral approach.

A final aspect of patient evaluation is the "Heart" Team approach. It is commonly agreed that TAVI is not done by a single specialty but instead a multidisciplinary team. The team should include the interventional cardiologist with expertise in structural heart disease, cardiac surgeon, cardiac anaesthesiologist, cardiac imaging specialist, vascular surgeon and specialised nurses. This cooperative noncompetitive approach is most desirable to deal with this complex procedure.

Latest Clinical data

Large registry series document procedural success (defined as implantation of a functional valve with the patient surviving the procedure) in over 95% and 30-day survival of over 90% of high risk patients[15-17]. More rigorous clinical results are now available from the landmark randomised PARTNER trials.

The Edwards SAPEIN valve was studied in the PARTNER trial with 2 parallel arms. The PARTNER 1B trial randomised 358 inoperable patients to either transfemoral TAVI or best medical management[2]. It documented a dramatic 20% absolute reduction in mortality at 1 year with transfemoral TAVI. At 2 years the survival curves continued to diverge with an additional 16.9% difference in mortality accruing between 1 and 2 years[18]. TAVI patients had a sustained lower 3-year mortality rate than those treated with medical therapy alone (54.1% vs. 80.9%, $P < 0.001$), with numbers needed to treat of 3.7 patients to save 1 life[19]. However, those with STS scores ≥15 had no benefit with TAVI over medical therapy. The PARTNER 1A trial randomised 699 high risk patients to either TAVI (transfemoral or transapical) or SAVR[3]. TAVI was shown to be non-inferior to SAVR in terms of mortality at 1 year (24.2% vs. 26.8% p=0.44), at 2 years (33.9% vs. 35.0%, $P = 0.31$) and at 3 years (44.2% vs. 44.8% p=0.483)[20]. In summary, the PARTNER trial demonstrates that TAVI maintains a sustained superiority over medical treatment in inoperable patients with symptomatic severe aortic stenosis, and equivalent outcomes between TAVI and SAVR in high-risk patients.

The US Medtronic CoreValve Pivotal trial has completed enrollment in both the "high risk" and "extreme risk" groups. Because of the publication of the PARTNER 1B results while the "extreme risk" arm was under enrollment, it was no longer deemed ethical to randomise patients between CoreValve and medical therapy. Instead, that cohort was divided into patients with iliofemoral access to receive the CoreValve using the TF approach or an observational group of 200 patients via alternate accesses. The "high risk" group, defined by an operative mortality of ≥15%, was randomised to SAVR or CoreValve TAVI, with up to 30% of patients having no iliofemoral access. Preliminary clinical data on 487 patients at extreme surgical risk – defined as 50% or greater 30-day risk of operative mortality were recently presented and confirmed that TAVI improved clinical outcome in inoperable patients[43]. At 12 months, the primary endpoint of all-cause mortality or major stroke was 25.5%. The result is highly significant as it was lower than was expected with standard therapy (a pre-specified performance goal of 43.0%). Major stroke occurred at a rate of 2.4% at 30 days and 4.1% at 12 months. Overall haemodynamic performance was good with a mean gradient of 8.5 mmHg at one month and 8.8 mmHg at one year, similar to the gold standard surgical valves. Paravalvular leak rates were low and improved over time with only 11.5% of patients having more than mild PVL at one month, which improved to only 4.1% at one year. Major vascular complication rates were 8.3% at one month and

8.5% at one year. Permanent pacemaker rate was 22.2% at one month and, importantly, pacemaker implants were not associated with mortality.

Several multicentre national registries have been tracking TAVI patients consisting of the SAPEIN valve, CoreValve, or both devices. Overall, outcomes such as 30-day, longer term mortalities and stroke rates were similar across different registries. No significant differences between the SAPIEN valve and CoreValve were observed, except the CoreValve was associated with a higher incidence of heart block and the need for a pacemaker.

Specific risk of TAVI

The risks and complications of TAVI had been described in detail in the previous review by our group[4]. We will highlight some updated knowledge from the latest literature.

Stroke

There had been concerns of increased stroke risk in the early post-operative phase of TAVI in the PARTNER 1A trial. (30 days stroke risk of 4.6% vs. 2.4% for TAVI and SAVR respectively)[3]. However, long-term follow ups showed catch up of stroke risk in SAVR and so there were no differences up to 2 years. Miller et al.[23] identified 2 hazard phases for neurological events in the PARTNER trial, with early neurological complications occurring more frequently in TAVI than SAVR and late events influenced more by patient and disease-related factors. Multiple steps may cause stroke/TIA during TAVI which include wiring manipulation across the aortic arch, balloon valvoplasty, valve deployment, post-dilatation to correct paravalvular leakage and post-procedure atrial fibrillation. However, there are no major differences of stroke risk between the transfemoral and transapical routes suggesting that the traditional belief of embolisation of aortic arch atheroma during device manipulation may be less of a concern. Various embolic protection devices are under development and evaluation to capture those embolic substances. Hopefully, better understanding of the pathophysiology of TAVI-related strokes can help to develop a strategy to reduce this complication.

Paravalvular leak

It is very uncommon to have significant aortic regurgitation (both transvalvular and paravalvular leak) after SAVR and they will be corrected during the operation. The 2-year PARTNER data showed that TAVI has significantly more paravalvular leakage (PVL) and total aortic regurgitation than SAVR, with >50% of TAVI patients having mild or greater PVL and aortic regurgitation (AR) after the procedure with follow ups to 2 years[24]. It was shown that even mild PVL and AR after TAVR were associated with 10–15% higher mortality at 2 years than patients with none or trace PVL but this has not been confirmed by the recent US CoreValve Pivotal Trial.[43] There are several mechanisms for PVL. Suboptimal position (both too high and too low) of the transcatheter heart valve in relation to the annulus, inadequate expansion of the metal frame because of underlying calcified valve and also undersizing of the heart valve. Treatments of PVL depends on the possible aetiology and include post-dilation, put in another transcatheter heart valve (so called Valve in Valve), snaring to a higher position if the CoreValvehas been deployed too low (not for Edwards valve) and rarely converted to open heart surgery if haemodynamic significant leakage remains. Future developments of the next generation of heart valves will be necessary to address this common problem.

Heart block

The incidence of heart block requiring permanent pacemaker was 3-6% for the Edwards Sapien valve in the PARTNER trial and ranged from 5 to 18% among institutions. In a large systemic review on this phenomenon with more than 5,000 TAVI patients[25], the incidence was 6.5% and 25.8% for Edwards and CoreValve respectively. It was also found that new onset LBBB increased significantly after TAVI[25]. The conduction system and in particular the left bundle is located near the LV outflow tract (LVOT). The mechanism of post-procedure heart block/LBBB included injury of the conduction system during balloon aortic valvoplasty and stent deployment. The CoreValve had a higher incidence because of its continuous radial force and depth of device implant in the LVOT. It is also easy to understand that patients with pre-existing RBBB had a higher chance of developing heart block. The implantation of the CoreValve at a less deep position in LVOT and choosing a "not-so-oversize" device may potentially reduce this complication.

Vascular Complications

Vascular complications were the most common complication of TAVI. It was shown that for those patients who underwent transfemoral TAVI, 15% of them will have a major vascular complication within 30 days with associated higher 30-day and 1-year mortalities.[26] The rate of this complication ranged from 2% to 13% and decreased with increasing procedural experience[27]. Vascular complications ranged from groin haematoma, vascular dissection, vascular occlusion with lower limb ischaemia, retroperitoneal bleeding to life-threatening vascular perforation. Treatment options depended on the extent of vascular injury and may include supportive transfusion, percutaneous balloon angioplasty, vascular stenting and rarely open surgical repair. Percutaneous puncture technique and subsequently vascular closure by various devices was the mainstream technique of the transfemoral approach. Two Proglides are used more widely nowadays than one Prostar to close the groin wound. The contralateral balloon occlusion technique was shown in one study to reduce the rate of this complication[28]. It involved sheath removal and percutaneous arterial closure in a "bloodless" field while a balloon from the contralateral femoral access was used to occlude the antegrade blood flow to the main access site.

Long term durability of transcatheter heart valves

Unlike its surgical counterpart, long term data on structural integrity and durability of transcatheter heart valve were limited. Limited data from the PARTNER trial showed that the valvular function, in terms of mean gradient and area, can be maintained up to 3 years of clinical follow up. Willson et al[29] evaluated the structural integrity of 50 stents from the Edwards family at an average of 2.5 years after implantation and showed

that all valves could maintain circularity with minimal eccentricity. The haemodynamics of those that were found under-expanded and noncircular remained stable on annual echocardiographic follow ups. One pathology study of 20 explanted transcatheter heart valves at up to 30 months of implantation showed that there were only fibrous tissue ingrowths but no structural degeneration [30].

Future direction

Intermediate risk group patients

There are currently limited clinical data on the outcomes of patients with intermediate risk who have been subjected to TAVI treatment. The PARTNER 2 clinical trial is currently underway to evaluate patients with intermediate risk to TAVI using the Edwards Sapien XT valve or SAVR (STS mortality risk score of 4% to 10%). A Cohort of patients will also be evaluated for the performance of this new Sapien XT valve with the original Edwards Sapien valve used in the PARTNER 1 trial. Similarly, the SURTAVI (The multicentre SUrgical Replacement and Transcatheter Aortic Valve Implantation) trial, a multicentre randomised noninferiority study will evaluate the CoreValve with SAVR in patients with intermediate surgical risk (STS mortality risk score of 4-10%). Before further results are available, it is currently not recommended to treat patients without high surgical risks. However, we believe that this might be the group of patients who will benefit from the technology in the future.

Bicuspid aortic valve

The bicuspid aortic valve was traditionally excluded from randomised controlled trials and various reasons precluded the widespread use of TAVI in this patient group. Severe aortic stenosis secondary to the bicuspid anatomy was unusual in the elderly population and most patients were treated at an earlier age with SAVR. The bicuspid aortic valve has commonly asymmetric distribution of calcium and may preclude complete apposition of the transcatheter heart valve against the annulus and hence may increase the risk of PVL. Furthermore, the annular shape of the bicuspid valve tends to be elliptical and hence circular expansion of the heart valve may be difficult. Bicuspid valves have large annular diameters and they may not be fitted by currently available heart valves. Despite the above limitations, there were limited reports on the success of TAVI in treating this group of patients[31-35]. The CoreValve might be more suitable for the bicuspid valves because of its self-expanding nature and supra-valvular position of the 3 leaflets. Given the anatomical challenges and lack of long-term clinical data, TAVI in bicuspid valve patients should be assessed on a case-by-case basis.

Pure aortic regurgitation

Previously, there has been almost no attempts in using TAVI to treat patients with pure aortic regurgitation (AR) despite the success of treatment to aortic stenosis. Unlike aortic stenosis, there were many more aetiologies for AR and degenerative calcific cause contributed a less significant portion of the affected patients. There were very limited case studies by using TAVI in treating very high surgical risk patients with predominantly AR[36,37] but evidence is accumulating and there are several on-going registries to assess its efficacy and safety. Special techniques have to be used to treat patients with pure AR. Similar to patients with bicuspid valves, TAVI to treat this group of patients should be assessed only on a case –by- case basis.

Treating bioprosthetic valve dysfunction

Because of the success of TAVI in treating high surgical risk patients, this technology was then used to treat patients with dysfunctional bioprosthetic valves who cannot undergo or redo surgery. It had been described in the literature of using the Edwards valve in treating bioprosthetic aortic and mitral valve dysfunction while the CoreValve had been described in treating bioprosthetic aortic valves.[38-40] Treatment of mitral bioprosthetic dysfunction by the Edwards valve can be done via various approaches including the transapical, transeptal and rarely left atrial via a right mini-thoracotomy. A whole spectrum of valvular dysfunctions had been attempted to be treated by TAVI which included stenosis, regurgitation and combined problems. Overall the transvalvular gradient remained significantly higher across a transcatheter heart valve within a stenotic bioprosthesis. In the largest Global valve-in-valve Registry[41], procedural success was high with the CoreValve and Edwards Valve and achieved 96.8% and 87.2% respectively. 30-days mortality was reported to be 7.8%. In considering the feasibility of using TAVI to treat this group of patients, it is very important to fully understand the type, size and the design of the original surgical prosthesis before planning on a TAVI procedure.

Future Valve development

Future transcatheter heart valves will try to overcome the limitations of the current generation. The improved profile and design of the device will avoid the use of large delivery catheters. The CoreValve has been downsized from 18 French to 14 French. The improved ease of positioning will avoid suboptimal deployment while complete sealing of the annulus will be able to eliminate PVL. Full repositioning and retrievability of the device is desirable. This advancement in technology may reduce the associated complications and improve procedural success. The Portico 23mm valve (St. Jude Medical Inc.) was CE Marked in November 2012. It allows complete re-sheathing of the partially deployed valve at the implant site. The Direct Flow valve (Direct Flow Medical Inc.) received CE Mark in January 2013 and is currently available commercially in Europe. Rather than a metal stent, the Direct Flow valve incorporates a polymer frame, which is initially expanded using pressurised saline and contrast for placement, assessment and repositioning. The saline/contrast solution is easily exchanged for a quick-curing polymer that solidifies and secures the valve in place once optimal positioning is reached. The unique double-ring design of the valve creates a tight seal around the annulus. The system is fully repositionable and retrievable until polymer exchange. The Lotus valve (Boston Scientific Inc.) recently received CE mark in Oct 2013. The design of the system enables repositioning and it is fully retrievable until the very last step. The Lotus valve System also incorporates a unique Adaptive Seal™ technology designed to minimise aortic regurgitation. Preliminary clinical data confirmed the safety and efficacy of the device with marked reduction of any degree of PVL.

Conclusions

The rapid development of the technology will continue to improve the outcome of this high risk group of patients. Many more intermediate-risk patients will be candidates for TAVI when further encouraging clinical data become available. With the refinement of the devices and accumulating knowledge on how to reduce complications, the use of percutaneous techniques to treat significant valvular heart disease opens a new era of structural heart intervention. This offers new hope for the previously high-risk patients when open surgery is not an ideal option. Similar to the advancement of coronary intervention in the last decades, percutaneous valvular intervention may become the predominant mode of treatment for patients with valvular heart disease in the very near future.

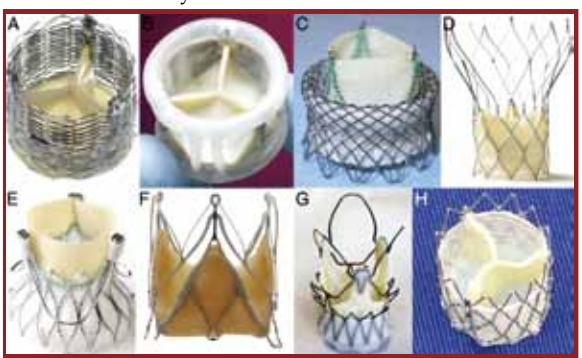


Figure 2 (A) Lotus (Boston Scientific Inc., Natick, Massachusetts), (B) Direct Flow (Direct Flow Medical Inc., Santa Rosa, California), (C) HLT (Bracco Inc., Princeton, New Jersey), (D) Portico (St. Jude Medical Inc., St. Paul, Minnesota), (E) Engager (Medtronic Inc., Minneapolis Minnesota), (F) JenaClip (JenaValve Inc., Munich, Germany), (G) ?Accurate valve (Symetis Inc., Ecublens, Switzerland), and (H) Inovare (Braile Biomedica Inc., São José do Rio Preto, Brazil) valves (Adapted from Webb and Wood)

References

1. Cribier, A. et al. Percutaneous transcatheter implantation of aortic valve prosthesis for calcific aortic stenosis. First human case description. Circulation 106, 3006-3008 (2002).
2. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010; 363: 1597-607.
3. Smith CR, Leon MB, Mack M, et al. Transcatheter versus surgical aortic-valve implantation in high-risk patients. N Engl J Med 2011; 364: 2187-98.
4. KY LEE. Transcatheter Aortic Valve Implantation (TAVI) - The time has come. The Hong Kong Medical Diary. Vol 16 No 1. January 2011
5. Conradi L, Seiffert M, Treede H, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement: a propensity score analysis in patients at high surgical risk. J Thorac Cardiovasc Surg 2012; 143:64-71
6. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010; 122:62-9.
7. Thomas M, Schymik G, Walther T, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: A European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010; 122:62-9.
8. Dewey TM, Brown D, Ryan WH, et al. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 2008; 135:180-7.
9. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2--isolated valve surgery. Ann Thorac Surg 2009; 88:S23-42.
10. Buellesfeld L, Gerckens U, Schuler G, et al. 2-year followup of patients undergoing transcatheter aortic valve implantation using a self-expanding valve prosthesis. J Am Coll Cardiol 2011; 57:1650-7.
11. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56:M146-56
12. Suhultz, C.J et al. Three dimensional evaluation of the aortic annulus using multislice computer tomography: are manufacturer's guidelines for sizing for percutaneous aortic valve replacement helpful? Eur. Heart J. 31, 849-856 (2010)
13. Petronio AS, De Carlo M, Bedogni F, et al. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. Circ Cardiovasc Interv 2010; 3:359-66.
14. Latsios G, Gerckens U, Grube E. Transaortic transcatheter aortic valve implantation: a novel approach for the truly "no-access option" patients. Catheter Cardiovasc Interv 2010; 75:1129-36
15. Moat NE, Ludman P et al. Long term outcomes after transcatheter aortic valve implantation in high risk patients with severe aortic stenosis: The U.K TAVI registry. J Am Coll Cardiol 2011; 58:2130-8
16. Thomas M, Schymik G, et al. One- year outcomes of cohort 1 in the Edwards SAPEIN aortic bioprothesis European Outcome (SOURCE) registry: The European registry of transcatheter aortic valve implantation using the Edwards SAPEIN valve. Circulation 2011; 124:425-33
17. Thomas M, The global experience with percutaneous aortic valve replacement. J Am Coll Cardiol Intv. 2010: 3; 1103-9
18. Makkar RR, Fontana GP. et al. Transcatheter aortic valve replacement for inoperable severe aortic stenosis. N Eng J Med 2012; 366: 1696-704
19. Kapadia SK. Three-year outcomes of transcatheter aortic valve replacement (TAVR) in "inoperable" patients with severe aortic stenosis: the PARTNER Trial. Transcatheter Cardiovascular Therapeutics (TCT) symposium. Miami, FL; 2012.
20. Thourani VH. Three-year outcomes after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis. Presented at: American College of Cardiology Scientific Session/i2 Summit; March 11, 2013; San Francisco, CA
21. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovasc Interv.2012;5:974–981
22. Stortecky S, Schoenenberger AW, Moser A, et al. Evaluation of multidimensional geriatric assessment as a predictor of mortality and cardiovascular events after transcatheter aortic valve implantation. JACC Cardiovasc Interv. 2012;5:489–496.
23. Miller DC, Blackstone EH, Mack MJ, et al.; PARTNER Trial Investigators and Patients; PARTNER Stroke Substudy Writing Group and Executive Committee.Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. J Thorac Cardiovasc Surg. 2012;143:832–843
24. Kodali SK, Williams MR, Smith CR, et al.; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. NEngl J Med. 2012;366:1686–1695.
25. Erkapic D, De Rosa S, Kelava A, et al. Risk for permanent pacemaker after transcatheter aortic valve implantation: a comprehensive analysis of the literature. J Cardiovasc Electrophysiol. 2012;23:391–397.
26. Genereux P, Webb JG, Svensson LG, et al.; PARTNER Trial Investigators. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. J Am Coll Cardiol. 2012;60:1043–1052.
27. Gurvitch R, Tay EL, Wijesinghe N, et al. Transcatheter aortic valve implantation:lessons from the learning curve of the first 270 high-risk patients.Catheter Cardiovasc Interv. 2011;78:977–984.
28. Genereux P, Kodali S, Leon MB, et al. Clinical outcomes using a new crossover balloon occlusion technique for percutaneous closure after transfemoral aortic valve implantation. JACC Cardiovasc Interv. 2011;4:861–867.
29. Willson AB, Webb JG, Gurvitch R, et al. Structural integrity of balloon expandable stents after transcatheter aortic valve replacement: assessment by multidetector computed tomography. JACC Cardiovasc Interv.2012;5:525–532
30. Nietlispach F, Webb JG, Ye J, et al. Pathology of transcatheter valve therapy. JACC Cardiovasc Interv. 2012;5:582–590.
31. Chiam PT, Chao VT, Tan SY, et al. Percutaneous transcatheter heart valve implantation in a bicuspid aortic valve. JACC Cardiovasc Interv.2010;3:559–561.
32. Ferrari E, Locca D, Sulzer C, et al. Successful transapical aortic valve implantation in a congenital bicuspid aortic valve. Ann Thorac Surg.2010;90:630–632.
33. Kochman J, Huczek Z, Koltowski Ł, et al. Transcatheter implantation of an aortic valve prosthesis in a female patient with severe bicuspid aortic stenosis. Eur Heart J. 2012;33:112.
34. Wijesinghe N, Ye J, Rodes-Cabau J, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. JACC Cardiovasc Interv.2010;3:1122–1125.
35. Himbert D, Pontnau F, Messika-Zeitoun D, et al. Feasibility and outcomes of transcatheter aortic valve implantation in high-risk patients with stenotic bicuspid aortic valves. Am J Cardiol. 2012;110:877–883.
36. Chandola R, Cusimano R, Osten M, et al. Postcardiac transplant transcatheter core valve implantation for aortic insufficiency secondary to Impella device placement. Ann Thorac Surg. 2012;93:e155–e157.
37. Dumonteil N, Marcheix B, Lairez O, et al. TAVI for severe, non-calcified aortic regurgitation and narrow aortic root: Description from a case report of a new approach to potentially avoid coronary artery obstruction. Catheter Cardiovasc Interv. 2012 Jun 28
38. Webb JG, Wood DA, Ye J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. Circulation. 2010;121:1848–1857.
39. Gurvitch R, Cheung A, Ye J, et al. Transcatheter valve-in-valve implantation for failed surgical bioprosthetic valves. J Am Coll Cardiol. 2011;58:2196–2209.
40. Toggweiler S, Wood DA, Rodes-Cabau J, et al. Transcatheter valve-in-valve implantation for failed balloon-expandable transcatheter aortic valves. JACC Cardiovasc Interv. 2012;5:571–577
41. Dvir D, Webb J, Brecker S, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-invalve registry. Circulation. 2012;126:2335–2344.
42. Webb JG, Wood DA. Current status of transcatheter aortic valve replacement. J Am Coll Cardiol. 2012;60:483–492.
43. Jeffrey Popma et al , CoreValve US Pivotal Trial Extreme risk ilieofemoral Study results . TCT 2013

Left Atrial Appendage Occlusion (LAAO) In Atrial Fibrillation

Dr. Jason LK CHAN

MBBS (HK), MRCP (UK), PDipPH (HK), FHKCP, FHKAM (Medicine)

Division of Cardiology, Department of Medicine, Queen Elizabeth Hospital, Hong Kong

Structural heart interventions have become more common and important nowadays. With all the recent innovations in interventional cardiology, researches and improvement in technology, several interventions have become routine procedures such as Transcatheter aortic valve implantation (TAVI), mitral clip and left atrial appendage occlusion (LAAO). In this article, we would try to review the basic principle of left atrial appendage closure, the most important clinical evidence and the recent clinical data.

Atrial fibrillation (AF) is very common and the prevalence increases with age. The lifetime risk of developing AF is approximately 1 in 4[1]. The true prevalence may be underestimated, as it can be difficult to detect paroxysmal AF. No matter of paroxysmal AF or chronic AF, the main concern is the increased risk of stroke associated with AF. AF is one of the main causes of stroke (accounts for ~15-20% of ischaemic stroke)[2] and disabilities from AF-related strokes are especially severe.

The oral anticoagulant, warfarin has been used for a long time in the prevention of stroke in AF patients. The effectiveness of warfarin has been proven by many historical studies[3]. However, the prevalence of use of warfarin has been limited by its narrow therapeutic window, risk of bleeding, diet restriction and regular blood monitoring. Only around 54% of the patients with AF-related high risk of thromboembolic events actually receive warfarin[4]. In a study of 41,900 patients with chronic AF, only 70% of patients treated with warfarin remained on the therapy at 1 year[5].

Novel anticoagulants, such as dabigatran, rivaroxaban, apixaban have gained interest in the treatment of AF in recent years. Studies showed similar efficacy in terms of prevention of stroke but with a lower risk of bleeding when comparing the novel drugs with warfarin[6,7,8]. No strict diet restriction is required when using novel anticoagulants. Despite the advancement of these drugs, the risk of bleeding is still a problem associated with these novel agents. The dilemmas in the treatment of AF patients who are at high risk of stroke but have a history of bleeding still exist.

Among patients with non-valvular AF, over 90% of the thrombi are formed in the left atrial appendage[9]. The blood stasis in a fibrillating LAA makes it prone to have thrombus formation. Therefore, the exclusion of LAA in these AF patients should greatly decrease the risk of stroke. Surgical ligation or amputation has been used for many years but with limited evidence regarding its effectiveness[10]. It is usually performed with valve surgery as an added procedure rather than stand-alone procedure. However, the effectiveness of complete exclusion is still a question. Any residual leakage in LAA would actually pose an even higher risk of thrombus formation than a nude LAA.

Percutaneous closure of LAA has been developed since 2002. By closing the LAA, the chance of thrombus formation in patients with AF would be hugely decreased theoretically even without the coverage of anti-coagulation as there will be no place for the thrombus formation. The first device, which was specifically designed for percutaneous LAAO, was called PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) system. It was a self-expanding nitinol frame that was covered by a fabric that was impermeable to blood. The device was placed and occluded the LAA via a transeptal catheter. Preliminary studies showed encouraging results but the manufacturer discontinued the development of the device later on[11].

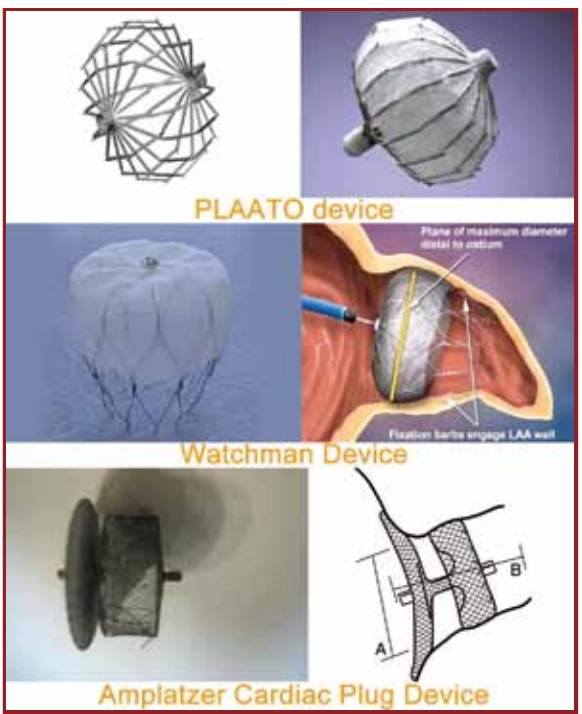


Figure 1. Different percutaneous LAAO devices

After the PLAATO device, there are currently two devices using the same principle available in the

market. They are the WatchmanTM device (Atritech, Boston Scientific, Natick, MA, USA) and Amplatzer cardiac plugTM (AGA, St. Jude Medical, Minneapolis, MN, USA) device, both of them are CE (European Conformity) marked in Europe but are not approved by the US Food and Drug Administration (FDA) for clinical use yet (Figure 1). In addition, Lariat (snare device) (SentreHEART, inc.) closes the LAA by the method of percutaneous ligation is also available and it has FDA approval for suture placement and knot typing in surgical applications. However, it is not FDA approved specifically for stroke reduction in AF yet.

Watchman device

The Watchman device has a self-expanding nitinol frame, which was covered by a fabric that is impermeable to blood[12]. Deployment is usually performed under general anaesthesia with trans-oesophageal echocardiogram guidance via the transeptal catheter and femoral vein (Figure 2). The patient is usually required to take warfarin (unless contra-indicated) for at least 45 days after the procedure with concomitant aspirin 80-325mg daily. Once trans-oeophageal echocardiogram shows no residual leakage at day 45, clopidogrel will replace warfarin for another 6 months.

Figure 2. Watchman device in closing the left atrial appendage

The efficacy and safety of the Watchman device has been evaluated in over 2000 patients in multiple randomised trials and registries with 4800 patient-years of follow-up. The PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF) trial was the first prospective randomised controlled trial (RCT) on LAAO with more than 700 patients with non-valvular AF[13]. The study had a non-inferiority design. Inclusion criteria allowed for patients with paroxysmal, persistent, or permanent AF and all patients had a CHADS2 (Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischaemic Attack) score >1. The study showed that the Watchman device was non-inferior to warfarin in patients at high-risk of thromboembolism regarding the primary end point, a composite of stroke, systemic embolism, and cardiovascular death with a risk ratio of 0.62 (95% CI: 0.35 to 1.25). However, the rate of procedure related complications (composite of major bleeding, pericardial effusion, procedure related stroke, and device embolisation) was relatively high at 8.7%. With the improvement of the device and the effect of the learning curve, CAP (Continued Access Protocol Registry)[14], a prospective registry with 450 patients and PREVAIL (Prospective Randomised Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation vs Long-Term Warfarin Therapy)[15], a prospective RCT with 407 patients later showed similar efficacy in prevention of stroke as shown in PROTECT AF trial but with a much lower complication rate of ~4.1-4.4%. ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology)[16], a prospective registry specially looked into the patients who were contra-indicated for warfarin (the patients with mean CHADS2 score of 2.8); among 150 patients, the study showed 77% relative reduction in the rate of all stroke comparing the expected rate per CHADS2 score. The newly released data of 4 years follow-up in PROTECT AF trial showed that the Watchman device was even superior to warfarin in terms of 40% relative reduction of stroke/ systemic embolism/ cardiovascular death[17]. However, further large-scale studies would be required before reaching such conclusion.

Amplatzer Cardiac Plug (ACP)

The Amplatzer cardiac plug is another device specially designed for LAA closure. There are two generations of the device at the moment, ACP 1 and ACP 2 (Amulet). Both devices are nitinol based and consist of a left atrial disc and a distal plug connected to the disc by a short waist. The distal plug has pairs of hooks to increase the stability within the appendage. The difference between ACP 1 and ACP 2 device is shown in Table 1. There are no RCT data for ACP 1 or 2 in the meantime but there were several registries results using ACP 1 showing promising results[18, 19, 20]. The First-in-man experience using ACP 2 was reported by a group in Montreal, Canada and the report was published in January 2013[21]. Further clinical trials regarding this device are undergoing.

Because of the total length of the ACP device is shorter than the Watchman device, some operators may find the ACP device more advantageous in patients with shorter appendage depths.

Table 1. Summary of the ACP 2 features.

Common features of the ACP 1 and the ACP 2:
Distal lobe which anchors to the body of the LAA
Proximal disc which seals the ostium of the LAA (pacifiereffect)
Connecting waist between lobe and disc
Nitinol mesh and two polyester patches sewn on the lobe and the disc
New features in ACP 2 to facilitate device deployment:
Pre-loaded system
Larger disc diameters
Longer lobe length
Longer waist length
Larger sizes available
New delivery cable with an inner 0.014" wire
New features to minimise complications:
Low-profile end-screw
More stabilising wires on larger devices
Stiffer stabilising wires

Lariat system

Other than the device occlusion technique, percutaneous closure of the LAA by a suturing method has evolved in the market in recent years. The device is approved for the use of suture placement and knot typing in surgery (Figure 3). Closure of the LAA with Lariat involves a percutaneous subxiphoid approach and a pericardial puncture. The LAA is snared with a pre-tie suture loop that is then cinched at the base of the appendage. Once tied off, the appendage shrinks to scar tissue.

However, limited data on the outcomes on LAAO are available by using this device and long- term and larger clinical trials are waiting.

Figure 3. Lariat System.

The 2012 focused update of the European Society of Cardiology (ESC) guidelines for the management of AF has added LAAO as one of the options in patients with a high risk of stroke and contra-indicated for long term anticoagulation (level of evidence B, class II b indication)[22].

In conclusion, percutaneous LAA closure seems as effective as warfarin or even superior to warfarin according to current available data, and comes with a low rate of procedure-related complications. Further clinical trials regarding different devices are underway.

The current indications of LAA closure should be limited to those AF patients who are at high risk of stroke and

1. Have clear contra-indications for anti-coagulation (e.g. history of bleeding) or
2. High risk of bleeding on anti-coagulation (e.g. the elderly, patients at high risk of fall, concomitant long term use of double anti-platelet therapy, anticipated high risk of bleeding calculated from several developed bleeding scores like HAS-BLED score etc).

References

1. LloydJones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004; 110: 1042-6.
2. Fuster, et al. ACC/AHA/ESC Practice Guidelines, Circulation. 2006;114:700-52.
3. Hart, et al. Meta-analysis 28044 pts, Ann Intern Med. 2007;146:857-67.
4. Waldo AL, Becker RC, Tapson VF, Colgan KJ; NABOR Steering Committee. Hospitalised patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. J Am Coll Cardiol. 2005 Nov 1;46(9):1729-36.
5. Gallagher AM, Rietbrock S, Plumb J, et al. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriatepatients receive stroke prophylaxis? J Thromb Haemost 2008; 6: 1500-6.
6. Jeremy S Paikin, Michelle J Haroun, and John W Eikelboom. Dabigatran for stroke prevention in atrial fibrillation: the RE-LY trial. Expert Review of Cardiovascular Therapy, March 2011, Vol. 9, No. 3 , Pages 279-286.
7. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med, 365 (2011), pp. 883–891.
8. Alexander, John H, et.al. Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial. European heart journal (Eur Heart J), 2013.
9. J.L. Blackshear, J.A. Odell. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg, 61 (1996), pp. 755–759.
10. Kanderian AS, Gillinov AM, Pettersson GB, Blackstone E, Klein AL. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. J Am Coll Cardiol. 2008 Sep 9;52(11):924-9.
11. S.H. Ostermayer, M. Reisman, Kramer et al. Percutaneous left atrial appendage transcatheter occlusion (PLAATO system) to prevent stroke in high-risk patients with non-rheumatic atrial fibrillation: results from the international multi-center feasibility trials.J Am Coll Cardiol, 46 (2005), pp. 9–14.
12. Munkholm-Larsen S, Cao C, Yan TD, et al. Percutaneous atrial appendage occlusion for stroke prevention in patients with atrial fibrillation: a systematic review. Heart 2012; 98: 900-7.
13. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet. 2009;374:534-42.
14. Reddy VY et al. Circulation. 2013; 127:720-729.
15. U. Landmesser, D.R. Holmes Jr.Left atrial appendage closure: a percutaneous transcatheter approach for stroke prevention in atrial fibrillation.Eur Heart J, 33 (2012), pp. 698–704.
16. Reddy VY, Möbius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). J Am Coll Cardiol. 2013 Jun 25;61(25):2551-6.
17. Reddy, et al., HRS LBCT 2013.
18. Park JW, Bethencourt A, Sievert H, Santoro G, Meier B, Walsh K, Lopez-Minguez JR, Meerkin D, Valdés M, Ormerod O, Leithäuser B. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. Catheter Cardiovasc Interv. 2011;77:700-6.
19. Lam YY, Yip GW, Yu CM, Chan WW, Cheng BC, Yan BP, Clugston R, Yong G, Gattorna T, Paul V. Left atrial appendage clo-sure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience. Catheter Cardiovasc Interv. 2012;79:794-800.
20. Rodés-Cabau J, Champagne J, Bernier M. Transcatheter closure of the left atrial appendage: initial experience with the Amplatzer cardiac plug device. Catheter Cardiovasc Interv. 2010;76:186-92.
21. Freixa X, Chan JL, Tzikas A, Garceau P, Basmadjian A, Ibrahim R. The Amplatzer™ Cardiac Plug 2 for left atrial appendage occlusion: novel features and first-in-man experience. EuroIntervention. 2013 Jan 22;8(9):1094-8.
22. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33: 2719-47.

Recommend CoaguChek® XS
- for your patients on warfarin

Why recommend INR self-monitoring with CoaguChek® XS?

'Self-monitoring can improve the quality of oral anticoagulant therapy, leading to fewer thromboembolic events and lower mortality.' [1]

Patient Self-Monitoring of INR

- Selected patients monitor their own INR in addition to regular clinic visits

Reliable INR results using CoaguChek® XS:

- On-board control automatically checks strip's integrity
- Calibration according to WHO recommendations

References:
1. Garcia-Alamino JM et al. Cochrane Database of Systematic Reviews, Issue 4, 2010.

CoaguChek®
Because it's my life

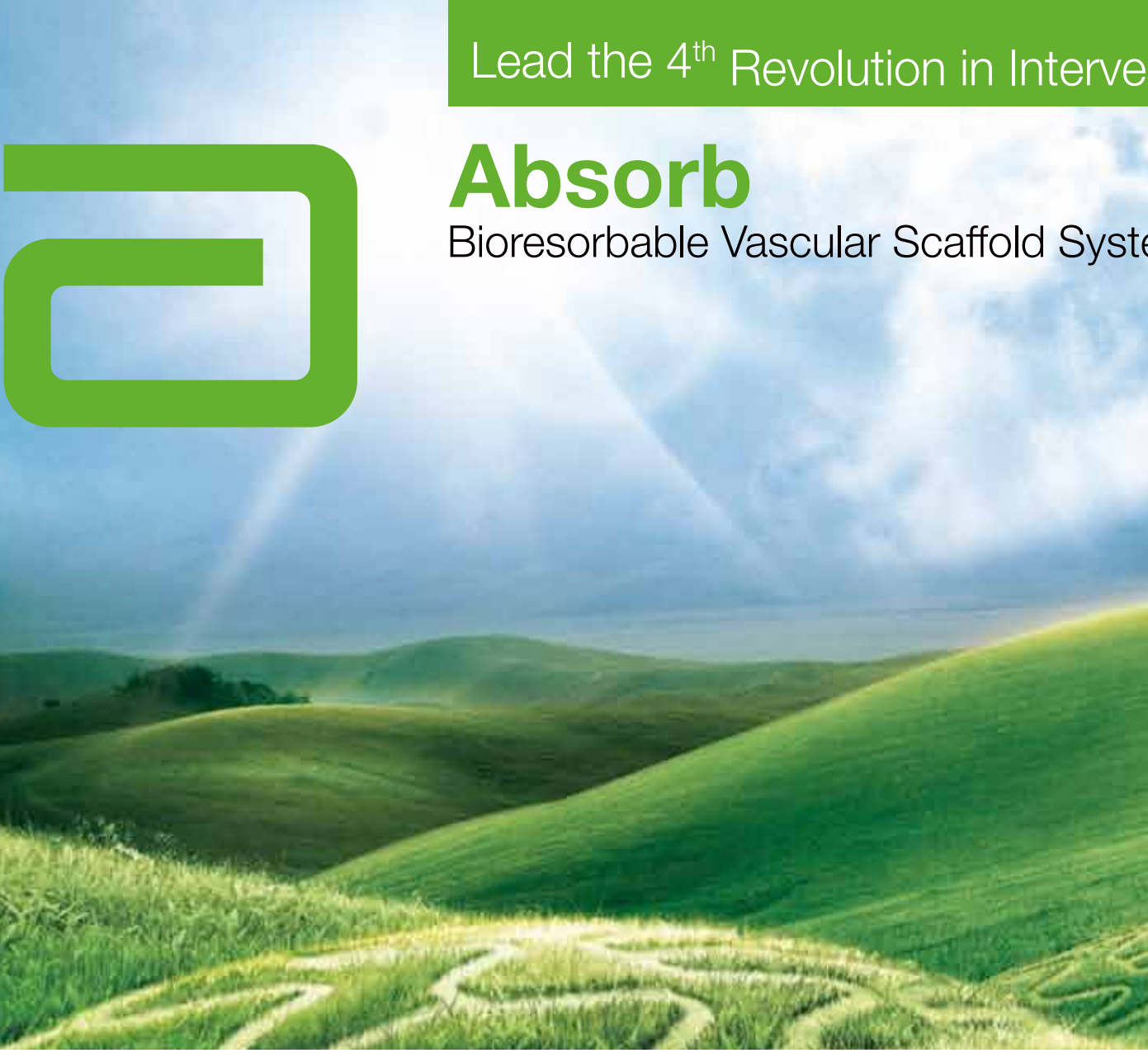
Roche Diagnostics (Hong Kong) Ltd
Tel: 2481 3387 / 9534 6020
Email: hongkong.coaguchek@roche.com
Website: www.coaguchek.com

Roche

Lead the 4th Revolution in Interve

Absorb

Bioresorbable Vascular Scaffold Syste



It's easy to move forward when you leave n

The dream of a bioresorbable scaffold has now become a reality. Absorb of VRT is to restore the vessel to a more natural state, capable of norma promises a bright future for interventional cardiology. Together, we can

*Small platinum markers at scaffold edges remain for fluoroscopic landmarking.

Products intended for use by or under the direction of a physician. Prior to use, it is important to read the package insert thoroughly for inst outside U.S. and Japan only. Please check the regulatory status of the device before distribution in areas where CE marking is not the regul

Restore Freedom

em

nothing behind

o defines a new paradigm – Vascular Reparative Therapy (VRT). The goal
l vascular function to enable long term benefits. Leaving nothing behind*
ead the revolution in patient care.

---

ructions for use, warnings and potential complications associated with the use of this device. Information contained herein is for distribution
ation in force. For more information, visit our web site at www.abbottvascular.com.

Abbott
Vascular

Novel Oral Anticoagulants for Non-Valvular Atrial Fibrillation: Who, When and How?

Dr. Chu-Pak LAU

MD, FRCP, FACC

Specialist in Cardiology
Cardiology Division, Department of Medicine, Queen Mary Hospital

ABSTRACT

The most serious complication of atrial fibrillation (AF) is systemic thromboembolism (SE), of which embolic stroke is most devastating. Approximately 20% of strokes are attributed to AF. Aspirin has a limited role in stroke prevention, and is inferior to vitamin K antagonists (VKAs) such as warfarin. The limitations of warfarin include drug and food interaction, difficulty to achieve and maintain an optimal therapeutic level, and serious haemorrhagic complications such as intracranial haemorrhage (ICH). As a result, novel oral anticoagulation agents (NOACs) which are either thrombin inhibitor (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban and endoxaban) are introduced as alternatives to VKAs. They are at least equally effective as warfarin in reducing SE without increasing the risk of bleeding. Importantly, they all reduce the incidence of ICH compared with warfarin.

Being "novel", it is important to consider their indications, appropriate dosages especially in the presence of renal dysfunction, monitoring and drug interactions, and management during intercurrent illnesses such as surgery and bleeding. In the setting of the acute coronary syndrome (ACS), in which newer antiplatelet agents such as prasugrel or ticagrelor are indicated, careful considerations should be made for using VKAs or NOACs to avoid bleeding complications.

INTRODUCTION

Stroke prevention in patients with AF is one of the most important aims of AF management. About 15-20% of all ischaemic strokes are attributable to AF[1]. Furthermore in 20% of patients without an obvious cause of stroke, AF can be documented using ambulatory monitoring. Due to the high prevalence of AF, appropriate antithrombotic therapy has significant impacts on stroke prevention. Antiplatelet agents and VKAs are traditional agents to prevent stroke in AF, although they are either ineffective (aspirin) or cumbersome to use (VKAs). This article reviews the role of NOACs in non-valvular AF based on literature and current guidelines[2,3], and provides a practical approach to their indications and prescription.

ASSESSING EMBOLIC RISK IN AF

The acronym CHA_2DS_2VASc score is used to assess SE risks in patients with non-valvular AF (Table 1)[4]. This represents the risk factors of Congestive heart failure, Hypertension, Advanced age > 75 years (double), Diabetes, previous Stroke (double), Vascular disease, Age 65-75 years, and female Sex category. With the exception of females under 65 years, antithrombotic therapy should be considered for a score of ≥ 1, as the stroke risk per year outweighs the bleeding risk induced by VKAs (~1%/year). This score has been validated in different populations including the Chinese. However, the score represents a population based assessment, and for an individual with a particular score, the stroke risk can be significantly higher or lower than the average population. In addition, the risk is likely to be different for an individual with the same risk factor with different levels of exposure. For example, the risk is different between recent onset, well controlled hypertension compared to long standing, uncontrolled hypertension, although in either case the score is one. Clinical judgement is appropriate.

In prescribing antithrombotic treatment, the risk of bleeding is increased in concomitant of Hypertension, Abnormal renal or liver function, prior Stroke, prior Bleeding, Labile international normalised ratio (INR), Elderly (>65 years) and the interaction with other Drugs or alcohol, the so called HAD-BLED score. A score ≥ 3 suggests an increased risk of bleeding[2]. However, many of the risk factors for bleeding are modifiable. This score highlights the bleeding risk to be controlled rather than as contraindications to antithrombotic treatment.

Table 1. The component of CHA_2DS_2VASc score and the corresponding yearly rate of systemic embolism according to the score in non-valvular atrial fibrillation. Truly low risk patients are those < 65 years with otherwise lone AF, including the female sex. All other patients are considered at increased risk of thromboembolism[4]. CI = confidence interval

CHA_2DS_2-VASc Criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/transient ischaemic attack /other systemic embolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65 - 74 years	1
Sex category (i.e. female gender)	1

CHA_2DS_2-VASc total score	Rate of Stroke/Other Systemic Embolism (%/year)	(95% CI)
0	0	(0-0)
1	0.6	(0.0-3.4)
2	1.6	(0.3-4.7)
3	3.9	(1.7-7.6)
4	1.9	(0.5-4.9)
5	3.2	(0.7-9.0)
6	3.6	(0.4-12.3)
7	8.0	(1.0-26.0)
8	11.1	(0.3-48.3)
9	100	(2.5-100)

LIMITATIONS OF WARFARIN

VKAs such as warfarin are time-proven anti-thrombotic agents that reduce stroke in both valvular and non-valvular AF, when compared to either placebo or aspirin. However, the therapeutic efficacy is variable as they are liable to interact with many food and medications, and patient compliance is an issue. Patients are often not in the therapeutic range of INR of 2-3. There are data to suggest that INR level is better maintained in Caucasians than in Asians treated with warfarin. An important complication of warfarin is ICH. This is more important for Asians, as shown in a subgroup analysis of the Randomised Evaluation of Long-term Anticoagulant Therapy (RE-LY) study[5]. ICH occurred at 3.06%/year in Asians versus 1.48%/year for non-Asians, even though they had the same baseline stroke risk. Finally, warfarin has a slow onset of action, and bridging with heparin is needed for immediate anticoagulation.

DIFFERENT TYPES OF NOACs

NOACs offer better efficacy, safety, and convenience compared with VKAs. They are either direct thrombin inhibitors (dabigatran, RE-LY study[6]) or oral factor Xa inhibitors (rivaroxaban, ROCKET-AF[7]; apixaban, ARISTOTLE Study[8]; or endoxaban, not commercially available at present). Novel OACs are at least comparable to warfarin in preventing stroke and other SE in non-valvular AF[6,7,8,9](Table 2). Their onset of action is more rapid, typically within 2 hours of a dose, making bridging with heparin unnecessary. There is less drug interaction and variability in efficacy, so that a fixed dose can be given without routine monitoring of anticoagulant effect. In all agents, either haemorrhagic stroke or other ICH were reduced compared with warfarin. Stroke risk was reduced compared with warfarin with dabigatran at 150 mg bd and apixaban at 5 mg bd.

Choice of NOACs

When choosing between novel OACs, factors to consider include patient characteristics, compliance with therapy, tolerability, and cost. The novel OACs are similar in terms of efficacy and safety, and without a head-to-head comparison, it is hard to draw a conclusion on superiority with any one of them over another. Rivaroxaban is given once daily, which may improve compliance. In the RELY-ABLE study[10], 48% of the original RE-LY population were followed up for up to an additional 28 months. This showed continued low yearly rate of stroke/and other SE as the original trial period, and similar low rate of ICH. While this is a cohort, non-randomised subgroup, it does suggest durability of NOACs in preventing stroke in non-valvular AF. Verapamil, amiodarone, quinidine and erythromycin potentiate the effects of dabigatran. Anti-fungal agents such as ketoconazole increase plasma levels with all agents.

NOACs in ASIANS

It is recognised that Asians are less protected from SE by warfarin, and they tend to have more ICH than non-Asians. There are many reasons for these observations, including possibly a lower therapeutic INR level in Asians than what is required for Caucasians, difference in food contents, use of herbal medications that interact with warfarin, and a lower percentage of achieved therapeutic target INR. In a subgroup analysis in the RE-LY study, 15% of the study population are Asians. Despite similar risk scores, SE were higher in Asians than non-Asians with warfarin, which might be due to a higher proportion of Asians recruited having prior stroke (Figure 1A). Dabigatran at either 110 mg bd or 150 mg bd significant reduced SE in Asians to a similar extent as non-Asians. In addition, ICH risks are significantly reduced (Figure 1B). Early reports in abstract form suggest similar outcome

Table 2. Summary of clinical trials involving novel oral anticoagulants versus warfarin for stroke prevention in non-valvular atrial fibrillation.[6,7,8,9] CI = Confidence interval, RR = Relative risk, HR = Hazard ratio.

	Dabigatran			Rivaroxaban		Apixaban	
Median duration on follow up (years)	2.3			1.8		1.9	
$CHADS_2$ (mean)	2.1			3.5		2.1	
Outcome (% per year)							
	Warfarin	Dabigatran 150 mg bd	Dabigatran 110 mg bd	Warfarin	Rivaroxaban	Warfarin	Apixaban
	(n = 6022)	(n = 6076) (RR, 95% CI; P value)	(n = 6015) (RR, 95% CI; P value)	(n = 7133)	(n = 7131) (HR, 95% CI; P value)	(n = 9081)	(n = 9120) (HR, 95% CI; P value)
Stroke/other systemic embolism	1.69	1.11 (0.66, 0.53-0.82; P for superiority <0.001)	1.53 (0.91, 0.74-1.11; P for non-inferiority <0.001)	2.4	2.1 (0.88,0.75-1.03; P for non-inferiority <0.001, P for superiority = 0.12)	1.6	1.27 (0.79,0.66-0.95; P<0.001 for non-inferiority. P=0.01 for superiority)
Ischaemic stroke	1.2	0.92 (0.76, 0.60-0.98; P = 0.03)	1.34 (1.11, 0.89-1.40; P = 0.35)	1.42	1.34 (0.94, 0.75-1.17; P=0.581)	1.05	0.97 (0.92, 0.74-1.13; P=0.42)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14-0.49; P<0.001)	0.12 (0.31, 0.17-0.56; P<0001)	0.44	0.26 (0.59, 0.37-0.93; P=0.024)	0.47	0.24 (0.51, 0.35-0.75; P<0.001)
Major bleeding	3.36	3.11 (0.93, 0.81-1.07; P=0.31)	2.71 (0.80, 0.69-0.93; P=0.003)	3.4	3.6 (P=0.58)	3.09	2.13 (0.69, 0.60-0.80; P<0.001)
Intracranial bleeding	0.74	0.30 (0.40, 0.27-0.60; P<0.001)	0.23 (0.31, 0.20-0.47; P<0.001)	0.7	0.5 (0.67, 0.47-0.93; P=0.02	0.80	0.33 (0.42, 0.30-0.58; P<0.001)
Extracranial bleeding	2.67	2.84 (1.07, 0.92-1.25; P=0.38)	2.51 (0.94, 0.80-1.10; P=0.45)	-	-	-	-
Gastrointestinal bleeding	1.02	1.51 (1.50, 1.19-1.89; P<0.001)	1.12 (1.10, 0.86-1.41; P=0.43)	2.2	3.2 (P<0.001)	0.86	0.76 (0.89, 0.70-1.15; P=0.37)
Myocardial infarction	0.64	0.81 (1.27, 0.94-1.71; P=0.12)	0.82 (1.29, 0.96-1.75; P=0.09)	1.1	0.9 (0.81, 0.63-1.06; P=0.12)	0.61	0.53 (0.88, 0.66-1.17; P=0.37)
Death	4.13	3.64 (0.88, 0.77-1.00; P=0.051)	3.75 (0.91, 0.80-1.03; P=0.13)	2.2	1.9 (0.85, 0.70-1.02; P=0.07)	3.94	3.52 (0.89, 0.80-0.99; P=0.047)
% Discontinuation at the end of follow-up	10.2	15.5	14.5	22.2	23.7	27.5	25.3
% Discontinuation/year	5.1	7.8	7.3	11.7	12.5	15.3	14.1

for Asians and Non-Asians for Apixaban. Taken together, Asians appear to derive similar benefits and perhaps lower risk from NOACs as non-Asians, although there is concern on the optimal dose.

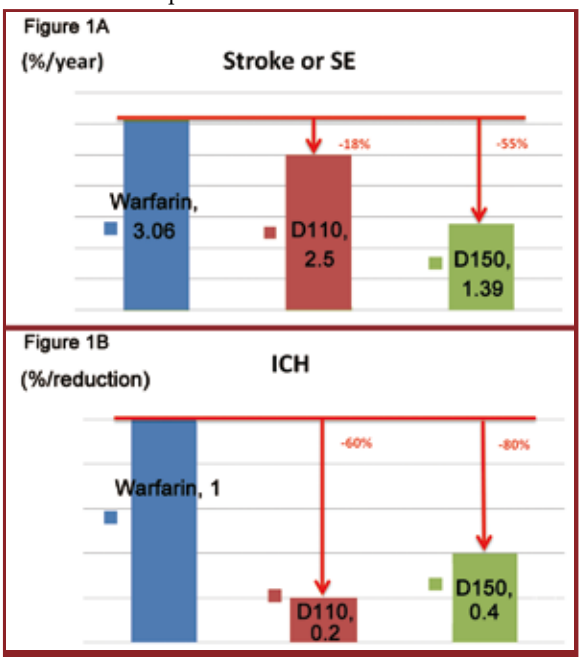


Figure 1. Dabigatran versus warfarin in Asians. (A) Stroke or systemic embolic risk (SE) with warfarin and dabigatran 110 mg bd (D110) or 150 mg bd (D150). The corresponding risks for non-Asians are 1.48%, 1.37% and 1.06%, respectively. (B) Reduction in ICH of dabigatran compared with warfarin, with the warfarin risk set to be 1.[5]

MANAGEMENT OF NOACs IN DIFFERENT CLINICAL SITUATIONS

Over time, a patient may encounter clinical scenarios that may require interruption or dosage modifications of NOACs. There is limited literature on these areas, and the following account represents expert opinions from the European Heart Rhythm Association[3]. These should be treated as references only and the clinician's own judgement based on the patient's clinical condition is important.

Intercurrent Surgery

For elective surgery in patients with normal renal function, NOACs can be withheld for 1 day after the last dose for surgery with minor bleeding risk (e.g. pacemaker implantation, endoscopy with biopsy and angiography), or performed at the trough level of drugs in case of minimal bleeding risk (e.g. dental procedure, cataract or glaucoma intervention). NOACs can be resumed 6-8 hours after haemostasis. For surgery with major bleeding risk, at least 48h interruption of NOACs is required, and resumption of NOACs should be individually determined. Bridging with parental anticoagulants may be considered.

When the creatinine clearance is 30-50 ml/min, dabigatran should be withheld at least 48h and 96h before surgery with minor and major bleeding risks, respectively. For creatinine clearance between 15-30 ml/min, in which apixaban and rivaroxaban can be used, an interruption of at least 36h and 48h should be considered for surgeries with minor and major bleeding risk, respectively. Evaluation of commonly available coagulation tests (aPTT for dabigatran and PT for factor Xa inhibitors) or of specific coagulation tests (dTT for dabigatran or chromogenic assay of Factor Xa) can be used to assess pharmacological waning of anticoagulation effect, although they are not surrogates of clinical bleeding potential.

Bleeding Complications

Unlike VKAs, NOACs have no specific proven antidotes when bleeding complications occur. In addition, there is no easy and accurate rate to monitor reversal of anticoagulation effects. On the other hand, NOACs have shorter half-live than VKAs, and if the patient can be supported during a bleeding episode, their effects will wean off.

In case of an overdose, activated charcoal can be used to reduce absorption. Dialysis can remove dabigatran, but not factor Xa inhibitors which are highly protein bound. During life-threatening bleedings, prothrombin complex concentrate, activated prothrombin complex concentrate or activated factor VII have been tried, although their efficacy has not been well tested.

Renal Dysfunction

VKAs reduce SE risk in patients with renal dysfunction, although haemorrhagic risks are increased. NOACs have different extent of renal elimination, which can affect the prescribed dosage. Dose adjustment or interruption are also required when renal dysfunction occurs (Table 3).

Table 3. Use of novel oral anticoagulants in renal dysfunction[3]

	Dabigatran	Rivaroxaban	Apixaban
Bioavailability	3-7%	66% (100% when taken with food)	50%
% Renally excreted of absorbed dose	80%	35%	27%
CrCl level not recommended	<30 ml/min	<15 ml/min	<15 ml/min
Standard dose	150 mg bd	20 mg Qd	5 mg bd
Dose adjustment	1. CrCl 30-49 ml/min, 150 mg bd or 110 mg bd if high risk of bleeding 2. FDA recommends 75 mg bd if CrCl 15-30 ml/min, or CrCl 30-49 ml/min in presence of drug interaction	CrCl 15-49 ml/min, 15 mg Qd	For CrCl 15-29 ml/min, 2.5 mg bd if creatinine ≥ 1.5 mg/dl and age ≥ 80 yrs or weight ≤ 60 kg or drug interaction

CrCl = Creatinine clearance
FDA = Food and Drug Adminstration

In patients on haemodialysis, NOACs are best avoided because of potential overdose and uncertain effect of haemodialysis on the drug level. VKAs are recommended in this situation. In patients with borderline renal function, dosage adjustment is suggested. Dabigatran, with predominant renal excretion is less preferable to factor Xa inhibitors,

which have major non-renal excretion mechanisms. Notwithstanding, renal function can deteriorate over time or change rapidly due to intercurrent diseases such as dehydration and infection, especially in the elderly. Frequent monitoring of renal function is advisable in these situations.

Cardioversion

In patients with AF > 48 hours duration undergoing cardioversion, oral anticoagulants should be given for ≥ 3 weeks. Alternatively, if a transoesophageal echocardiogram (TEE) shows absence of left atrial thrombi, cardioversion can go ahead immediately. Anticoagulation for at least 4 weeks afterwards is required in both situations, and long term anticoagulation may be required depending on the patient's $CHA_2DS_2VAS_C$ score. There is no prospective study on the use of NOACs for cardioversion, but a subgroup analysis of the RE-LY shows a similar cardioversion related stroke risk with or without TEE guidance[11]. Limited data are also available for some factor Xa inhibitors. As there are no readily available coagulation tests for assessing efficacy of NOACs, good NOACs compliance for the last 3 weeks on a careful history taking is essential. If in doubt, a TEE should be performed.

Haemorrhagic stroke while on NOACs

Similar to VKAs, patients presenting with haemorrhagic stroke while on NOACs pose a clinical dilemma, with the need to stop bleeding immediately but also to prevent further SE. Such patients should be treated as for life-threatening haemorrhage (see above), and neurological therapy should be performed with the advice of a neurologist and neurosurgeon.

Acute Ischaemic Stroke due to AF

When a transient ischaemic attack occurs due to AF related cardioembolism, NOACs can be started as soon as possible. Bridging with heparin will not be required due to the rapid onset of action of NOACs. In the presence of ischaemic stroke due to AF, guidelines for initiation of anticoagulation do not yet include NOACs. Indeed, a recent stroke is an exclusion criterion in major studies on NOACs. Initiation of anticoagulation depends on the infarct size (and the related risk of haemorrhagic transformation) and the risk of recurrent embolism from AF. Should NOACs be used, bridging with heparin will not be needed due to their faster onset of action compared to VKAs. In the presence of an ischaemic stroke while on NOACs, thrombolysis should not be administrated even when the patient presents within the 4.5h time frame from the onset of stroke symptoms.

Coronary Artery Disease

Patients with coronary artery disease (CAD) can have pre-existing or new onset AF. In addition, ACS, whether ST-elevation or non-ST-elevation, dictates the use of dual antiplatelet therapy (DAPT: aspirin and clopidogrel or newer antiplatelet agents) at least for some time. The combination of NOACs in these situations with antiplatelet agents have not been formally evaluated.

Stable CAD and after Chronic Coronary Stenting

These patients have stable disease, and traditional use of aspirin is required for secondary prevention. VKA to achieve an INR of 3-4 is superior to aspirin alone for secondary prevention of reinfarction and stroke in patients with recent myocardial infraction.[12,13] The combination of conventional level VKA (INR 2-2.5) + aspirin increases bleeding risk, and resulted in almost similar outcome as high intensity warfarin. Thus it is recommended that VKAs alone can be used without aspirin in this setting. NOACs are considered similar to VKAs, and thus they are suggested to be used alone in place of VKAs. With drug eluting stents (DES) implanted > 1 year or bare metal stents (BMS) implanted > 1 month, these patients can be regarded as stable CAD, and similar NOACs usage suggested.

Elective Coronary Artery Stenting

It is prudent to withhold a NOAC for 24h to allow its effects to wean off so that conventional parenteral anticoagulants such as heparin can be used during percutaneous coronary intervention (PCI). Consideration should be made for radial artery approach, and to use BMS over DES such that the duration of triple therapy can be shortened. There is a disproportionate increase in bleeding with DAPT when used with VKA, without reducing the risk of ischaemic events. In the WOEST trial[14], triple therapy has been compared to dual therapy (VKA + clopidogrel) in patients undergoing PCI. About 70% of patients were on warfarin for AF, and triple therapy doubles the risk of bleeding and increases mortality compared to VKA + clopidogrel. Thus it is recommended that dual therapy with VKA + clopidogrel may be preferred in the immediate period after stenting (1 month for BMS or 3-6 months for DES). By analogy, a NOAC may be used in place of VKA with clopidogrel alone, although there are no formal data.

Non-ST-elevation ACS

Newer oral antiplatelet agents such as prasugrel and ticagrelor are preferred over clopidogrel, given their more rapid onset of action, less variable pharmacodynamic, and better clinical outcome.[15,16] However, the interactions of NOACs and these antiplatelet agents are unknown. It is recommended to delay the timing of PCI if possible to allow the NOACs to wean off in the circulation (commonly by 24h). A radial approach is recommended. Resumption of NOACs can be considered when the effect of parenteral anticoagulant used during PCI has weaned off. There are no data to recommend switching of NOAC to VKA or vice versa. DAPT is recommended for 1 year after non-ST elevation ACS, but the risk of bleeding with triple therapy is significant. Consideration to shorten the duration of triple therapy is needed, and use of BMS is a consideration. In case of an urgent need for PCI, the timing of the last dose of NOAC and monitoring of NOAC effects may be useful to guide intraoperative parenteral anticoagulation therapy. As with elective stenting, VKA + clopidogrel may be an alternative to triple therapy. As suggested in the guideline[3], if antiplatelet agent is deemed necessary throughout the first year after the acute event, a lower dose of NOAC might be a safer option. It might be a safer option to use VKA and to keep a lower INR level. For patients requiring ticagrelor or prasugrel, even more caution is needed when adding VKA or NOAC.

ST- elevation ACS

Primary PCI is the preferred treatment, as the use of thrombolytics in a patient on NOAC is contraindicated. Due to the need to shorten the door to balloon time, it is not possible to wait for the effects of NOAC to wane, and monitoring is seldom available. Serious consideration for radial rather than femoral approach will minimise access site complications. Bivalirudin is shorter-lasting and has less bleeding risk than heparin, and can be considered. If thrombolysis is the only available treatment, it may be considered if aPTT (dabigatran) or PT (for factor Xa inhibitor) levels do not exceed the upper limit of normal. Additional heparin should be avoided after thrombolysis.

More or Less Therapy?

The above situations in CAD in the presence of AF that dictate antithrombotic treatment are complex. Firstly, there is uncertain risk/benefit ratio of combining VKAs with conventional antiplatelet agents such as aspirin and clopidogrel. Secondly, the multiple possibility of using NOACs with conventional or newer antiplatelet agents. The number of possible combination of VKAs, NOACs, aspirin, clopidogrel and newer antiplatelet agents is striking and perhaps confusing (Table 4). Whether more treatment (as suggested by guideline for ACS) or less treatment (because of bleeding risk) remains a matter of clinical judgement.

Table 4. Combinations of anti-thrombotic treatment in patients with atrial fibrillation and coronary artery disease. There are 32 combinations possible depending on the presentation: stable coronary artery disease, after chronic stenting and acute coronary syndrome.

Warfarin	Dabigatran	Rivaroxaban	Apixaban
Warfarin + Aspirin	Dabigatran + Aspirin	Rivaroxaban + Aspirin	Apixaban + Aspirin
Warfarin + Aspirin + Clopidogrel	Dabigatran + Aspirin + Clopidogrel	Rivaroxaban + Aspirin + Clopidogrel	Apixaban + Aspirin + Clopidogrel
Warfarin + Aspirin + Prasugrel	Dabigatran + Aspirin + Prasugrel	Rivaroxaban + Aspirin + Prasugrel	Apixaban + Aspirin + Prasugrel
Warfarin + Aspirin + Ticagrelor	Dabigatran + Aspirin + Ticagrelor	Rivaroxaban + Aspirin + Ticagrelor	Apixaban + Aspirin + Ticagrelor
Warfarin + Clopidogrel	Dabigatran + Clopidogrel	Rivaroxaban + Clopidogrel	Apixaban + Clopidogrel
Warfarin + Prasugrel	Dabigatran + Prasugrel	Rivaroxaban + Prasugrel	Apixaban + Prasugrel
Warfarin + Ticagrelor	Dabigatran + Ticagrelor	Rivaroxaban + Ticagrelor	Apixaban + Ticagrelor

CONCLUSION

A new paradigm for anti-thrombotic therapy has occurred with NOACs. All reduce the incidence of ICH compared with VKAs, and are at least as effective as VKAs. This is particularly important in Asians who are more susceptible to VKAs associated ICH at the conventional therapeutic INR level than the non-Asians. The efficacy differences between different NOACs are probably much less important than their overall benefits over VKAs. However, they do differ in their pharmacokinetics especially in the presence of renal dysfunction. It is thus important to know an agent well, especially their dosage scheme and drug interaction. This is important especially when dealing with intercurrent clinical scenarios such as a bleeding episode, intercurrent stroke, surgery or ACS. At present, there are no formal studies to guide management in these scenarios, and the "expert" opinions remain opinions only, and should not replace sound clinical judgement.

References

1. Lip GY, Lim HS. Atrial fibrillation and stroke prevention. Lancet Neurol. 2007;6:981-93.
2. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. Europace. 2012;14:1385-413.
3. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013;15:625-51.
4. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263-72.
5. Hori M, Connolly SJ, Zhu J, Liu LS, Lau CP, Pais P, Xavier D, Kim SS, Omar R, Dans AL, Tan RS, Chen JH, Tanomsup S, Watanabe M, Koyanagi M, Ezekowitz MD, Reilly PA, Wallentin L, Yusuf S; RE-LY Investigators. Dabigatran versus warfarin: effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. Stroke. 2013;44:1891-6.
6. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.
7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883-91.
8. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.
9. Lau CP. Stroke prevention in atrial fibrillation: differentiating between oral anticoagulants and antiplatelet agents. Medical Tribune 2013; April: 1-2.
10. Connolly SJ, Wallentin L, Ezekowitz MD, Eikelboom J, Oldgren J, Reilly PA, Brueckmann M, Pogue J, Alings M, Amerena JV, Avezum A, Baumgartner I, Budaj AJ, Chen JH, Dans AL, Darius H, Di Pasquale G, Ferreira J, Flaker GC, Flather MD, Franzosi MG, Golitsyn SP, Halon DA, Heidbuchel H, Hohnloser SH, Huber K, Jansky P, Kamensky G, Keltai M, Kim SS, Lau CP, Le Heuzey JY, Lewis BS, Liu L, Nanas J, Omar R, Pais P, Pedersen KE, Piegas LS, Raev D, Smith PJ, Talajic M, Tan RS, Tanomsup S, Toivonen L, Vinereanu D, Xavier D, Zhu J, Wang SQ, Duffy CO, Themeles E, Yusuf S. The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study. Circulation. 2013;128:237-43.
11. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, Flaker G, Brugada J, Kamensky G, Parekh A, Reilly PA, Yusuf S, Connolly SJ. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation. 2011;123:131-6.
12. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE; Antithrombotics in the Secondary Preventionof Events in Coronary Thrombosis-2 (ASPECT-2) Research Group. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet. 2002;360:109-13.
13. Hurlen M, Abdelnoor M, Smith P, Eriksen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med. 2002;347:969-74.
14. 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.
15. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 ;32:2999-3054.
16. Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen SL, Køber L, Torp-Pedersen C, Gislason GH, Hansen ML. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. Circulation. 2012;126:1185-93.

EXELON® PATCH
(rivastigmine transdermal system)

Defending against decline

ARE YOUR DECLINING ALZHEIMER'S DISEASE PATIENTS **LOSING THEIR INDEPENDENCE?**

HELP PATIENTS COPE WITH PERSONAL HYGIENE **AND OTHER BASIC ACTIVITIES OF DAILY LIFE**

EXELON PATCH 10 cm² showed superior efficacy to placebo over 24 weeks

EXELON PATCH 10 cm² significantly improved **Activities of Daily Living (ADLs),** such as the ability to **groom** and **dress**[1]

ITT-LOCF=Intention to treat–last observation carried forward.

- EXELON PATCH 10 cm² showed superior efficacy to placebo as measured by improvement in the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale and global functioning over 24 weeks ($P<.05$)[2]

EXELON® Patch 5
EXELON® Patch 10

Important note: Before prescribing, please consult full prescribing information.

Presentation: ♦ **Exelon® Patch 5** of 5 cm² contains 9 mg rivastigmine base, *in vivo* release rate of 4.6 mg/24 hr. ♦ **Exelon® Patch 10** of 10 cm² contains 18 mg rivastigmine base, *in vivo* release rate of 9.5 mg/24 hr.

Indication: Alzheimer's Disease Exelon Patch is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

Dosage: ♦ Treatment is started with Exelon Patch 5 once a day. ♦ After a minimum of four weeks of treatment and if well tolerated, dose should be increased to Exelon Patch 10, which is the recommended effective and maintenance dose, as long as therapeutic benefit for the patient exists. ♦ Patients treated on a dose of < 6 mg/day oral rivastigmine can be switched to Exelon Patch 5. ♦ Patients treated on Exelon capsules or oral suspension with a maintenance dose of 6 to 12 mg/day may be switched to Exelon Patch 10. ♦ Treatment should be temporarily interrupted if gastrointestinal adverse effects and/or worsening of existing extrapyramidal symptoms (e.g. tremor) are observed until adverse effects resolve. Patch treatment can be resumed at the same dose if treatment interruption is no more than several days. Otherwise treatment should be re-initiated with Exelon Patch 5.

Method of administration: Rivastigmine transdermal patches should be applied once a day to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. The patch should not be applied to skin that is red, irritated or cut. It is recommended to change the application site daily to avoid potential irritation. The same site should not be used within 14 days. The patch should be pressed down firmly until the edges stick well. Only one patch should be worn at a time and should be replaced by a new one after 24 hrs.

Contraindications: Known hypersensitivity to rivastigmine, other carbamate derivatives, or other ingredients of the formulation.

Precautions/Warnings: ♦ If treatment is interrupted for longer than several days, treatment should be re-initiated with Exelon® Patch 5. Gastrointestinal adverse effects have been observed at initiation of therapy and/or after dose increase. Patients who show signs or symptoms of dehydration due to prolonged vomiting or diarrhoea can be managed with iv fluids and dose reduction or discontinuation if recognized. Patients may lose weight during therapy. ♦ As with other cholinomimetics, extrapyramidal symptoms may be exacerbated during treatment. ♦ As with other cholinergic substances, caution must be taken in patients with sick sinus syndrome, conduction defects (sino-atrial block; atrio-ventricular block), gastroduodenal ulcerative conditions, history of or current respiratory disease, urinary obstruction, and seizures in predisposed patients. ♦ Special Populations: Caution in patients with clinically significant hepatic impairment and in patients with body weight below 50 kg. Not recommended in children. The safety of Exelon Patch is not established in pregnant and breast-feeding women. Rivastigmine is not recommended in children and adolescents (< 18 years).

Interactions: Rivastigmine should not be given concomitantly with other cholinomimetic drugs and might interfere with the activity of anticholinergic medications. As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia.

Adverse reactions: ♦ **Very common:** vomiting, nausea. ♦ **Common:** anorexia, decreased appetite, anxiety, depression, insomnia, dizziness, headache, diarrhoea, dyspepsia, abdominal pain, application site reactions (erythema, pruritus, oedema), fatigue, asthenia, weight decrease. ♦ **Uncommon:** agitation, delirium, hallucinations, cerebrovascular accident, syncope, somnolence, cardiac arrhythmia (e.g. bradycardia, supraventricular extrasystole), gastric ulcers, gastrointestinal haemorrhage, hyperhidrosis, contact dermatitis, malaise. ♦ **Rare:** hypertension, application site hypersensitivity, pruritus, rash, erythema, urticaria, blister, dermatitis allergic. ♦ **Very rare:** tachycardia, atrioventricular block, atrial fibrillation, pancreatitis, fall, seizure. ♦ **Not known:** dehydration, aggression, restlessness, sick sinus syndrome, hepatitis. (PI April 2011 + US PI Aug 2012)

References: 1. Winblad B, Cummings J, Andreasen N, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease—rivastigmine patch versus capsule. Int J Geriatr Psychiatry. 2007;22:456-467.

NOVARTIS
Novartis Pharmaceuticals (HK) Limited
27/F, 1063 King's Road, Quarry Bay, Hong Kong
TEL: +852 2862 5222 FAX: +852 2577 0274

HK-EXE-061836 May2013

Dietary Approaches to Stop Hypertension-DASH Diet

Ms. Ingrid YUNG

Registered Dietitian (Canada)
Hon. Secretary of the Hong Kong Practising Dietitians Union

Ms. Ingrid YUNG

About Hypertension

Based on the guidelines of WHO, hypertension is defined as resting systolic/diastolic pressure persistently higher than 140/90mmHg.

Risk factors for Hypertension

For those who have a family history of high blood pressure, he/ she may have a higher risk of developing hypertension. An unhealthy lifestyle also contributes significantly to high blood pressure. These factors include inadequate fresh fruits and vegetables, excessive sodium intake, a sedentary lifestyle, excessive alcohol consumption, overweight and smoking.

Total fat	27% of calories	Sodium	2300mg *
Saturated fat	6% of calories	potassium	4700mg
Protein	18% of calories	Calcium	1,250mg
Carbohydrate	55% of calories	Magnesium	500mg
Cholesterol	150mg	Fibre	30g

* 1,500mg sodium was a lower goal tested and found to be even better for lowering blood pressure. It was particularly effective for middle-aged and older individuals. African Americans, and those who already had high blood pressure.

Figure 1. Daily Nutrient Goals Used in the National Heart, Lung, and Blood Institute (NHLBI)DASH Studies (for a 2,100 Calorie Eating Plan)[3].

Dietary interventions

The DASH Diet

The DASH diet is clinically-proven to lower hypertension. Studies showed that a diet rich in fruits and vegetables, low fat dairy, whole grain foods, fish, poultry, beans, seeds and relatively low in sodium reduced systolic and diastolic blood pressure by 5.5/3.0mmHg[1]. The DASH diet contains food choices that are high in fibre, potassium, calcium and magnesium (Figure 1), which are associated with lower blood pressure. The DASH diet plan also follows heart healthy guidelines of limiting refined carbohydrate, saturated fat and cholesterol intake, which decrease the incidence of heart failure[2].

The DASH way of Eating

1) Follow DASH Diet Plan

The DASH diet emphasises high fibre whole grains, low fat dairy, lean meats and poultry, vegetables and fruits and food choices high in calcium, magnesium and potassium. To adapt a 2,000 calorie DASH diet, aim to have six to eight servings of whole grains, four to five servings of vegetables, four to five servings of fruits and two to three servings of low fat dairy daily. In order to increase magnesium intake, include nuts, seeds and legumes in the diet four to five times per week[3].

Meal A

Breakfast
- 2 Fried eggs
- 1 bowl of Macaroni Soup with Ham
- 1 sliced Toast with Butter
- 1 cup of coffee

Lunch
- 1 serving of curry beef
- 1 cup of cooked rice
- 1 cup of Iced Hong Kong-style milk tea

Afternoon Tea
- 2 Fried chicken wings
- 1 Sausage
- 1 cup of Iced lemon tea

Dinner
- 1 serving of Stir-fried tomato and sliced beef with tomato sauce
- 1 cup of cooked rice
- 1 cup of Boiled choy sum with sweetened soy sauce
- 1 cup of Iced lemon tea

Meal B

Breakfast
- 1 serving of Tomato and egg whole wheat sandwiches
- 1 cup of hot lemon tea (artificial sweeteners added)

Morning Snack
- 1 cup of yogurt
- 1 Baby banana
- 1.5 oz of nuts/seeds can be added as snack for 3-4 times weekly

Lunch
- Wheat noodles in soup with wonton
- 1 cup of boiled lettuce (no sauce)

Afternoon Tea
- 1 cup of high calcium low fat milk or
- 1 cup of high calcium soy milk
- 1 medium size apple

Dinner
- 3 oz of Steamed grass carp (sweetened soy sauce on the side)
- 1 cup of cooked rice
- 1 cup of boiled choy sum (no soy sauce added)

Figure 2. Diet Comparison: One day intake of a typical Hong Kong person

Meal A is an example of one day diet, which contains excessive sodium, fat, refined sugar and inadequate fibre from fruit and vegetable. In contrast, Meal B follows the principle of the DASH diet, which contains less sodium, higher fibre intake from whole grains products, fruits and vegetables (Figure 2).

Although following a diet is a challenging part for patients, dietitians work as a dietary coach by not only giving out dietary advices, also provide support to patients at different stages of change. Dietitians will conduct a detailed dietetic assessment regarding the patient's medical history, laboratory results, social history and diet history. Based on the collected information, dietitians will be able to recognise the affecting factors and develop an achievable and

individualised treatment plan with patients. In the follow up consultation, dietitians will re-assess the patient's medical and dietary status, identify the possible barriers and modify the treatment plan accordingly.

2) Reduce daily sodium intake

Studies showed with combination of the DASH diet and restricted dietary sodium intake may have a bigger blood pressure lowering power than following the DASH diet alone[4]. For adults aged 19 to 50, our body only requires 1500mg of sodium per day, and the upper limit is 2300mg daily. The WHO recommends that a healthy adult should consume less than 2000mg of sodium daily (i.e. < 5g per day).

Summary

Hypertension can be treated and/or prevented by following a healthy lifestyle, being physically active, drinking in moderation, eliminating smoking, and maintaining a healthy body weight. Proper control of hypertension can reduce the chance of developing future health problems.

References

1. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP et al. A Clinical Trial of the Dietary Patterns on Blood Pressure. N Engl J Med. 1997; 336: 1117-1124.
2. Levitan EB, Wolk A, Mittleman MA. Consistency with the DASH Diet and Incidence of Heart Failure. Arch Intern Med. 2009; 169(9):851-857.
3. US Department of Health and Human services. Your Guide to Lowering Your Blood Pressure With DASH. Rockville, MD: National Heart, Lung, and Blood Institute, National Institutes of Health;2006.
4. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA et al. Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. N Engl J Med. 2001; 344(1): 3-10.

Using Plant Sterols to Lower Cholesterol

Ms. Alice CHEN

Registered Dietitian (Canada), MSc, MBA
Vice-Chairman of the Hong Kong Practising Dietitians Union

What are plant sterols?

Plant sterols are a group of plant-derived sterols that are structurally similar and functionally analogous to cholesterol, and are naturally occurring in plant foods such as soybean, nuts, seeds, legumes and cereals, but only in small amounts[1]. They perform biological functions in plant cells similar to cholesterol in mammalian cells. Available studies suggested that the intake of plant sterol is about 150-400mg/d in a typical Western diet[2].

What do plant sterols do and how do they work?

The presence of plant sterols in the intestine interferes with the absorption of cholesterol via competitive displacement of cholesterol in micellar solubilisation and lowers the cholesterol levels[1]. More cholesterol is removed from the body as a result. The levels of HDL cholesterol and triglycerides are unaffected. Plant sterols are generally minimally absorbable through the gastrointestinal tract[1]. The structures of cholesterol and some common plant sterols, and the mechanism of action of plant sterols are shown in Figure 1a and 1b:

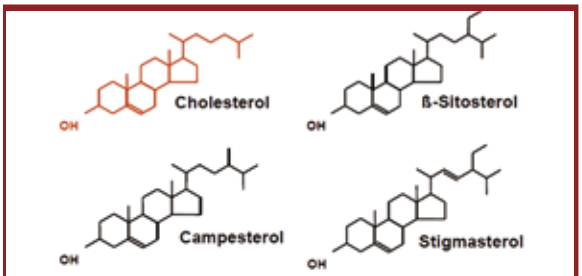


Figure 1a. Structure of cholesterol and common plant sterols. Plant sterols are structural homologues of cholesterol.

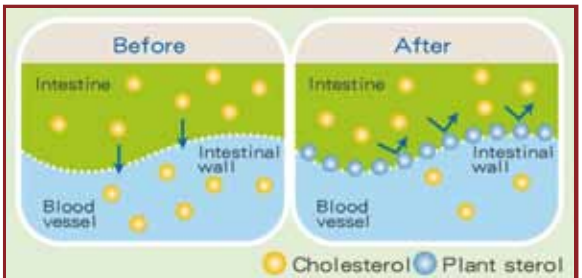


Figure 1b. Mechanism of action of plant sterols. Plant sterols interfere with intestinal cholesterol absorption into the blood stream, and enhance cholesterol removal from the body.

What is the efficacy of plant sterols?

A meta-analysis with data from 41 trials suggested that the intake of *2g/d of plant sterols reduces low-density lipoprotein by 10%*[2] (Figure 2). Dosage higher than 2g/d seems to have little additional impact[2]. Data from available research studies also estimated that long-term use of plant sterols can lower cardiovascular disease by 12-20% in the first 5 years and by 20% over a lifetime[2]. The most recent American Heart Association Diet and Lifestyle Recommendations 2006 for cardiovascular disease risk reduction and the National Cholesterol Education Program Adult Treatment Panel III[3] recommended 2g/d as an effective dosage to lower cholesterol[4]. A recent mata-analysis including 84 randomised controlled trials has re-confirmed the above recommendation[5].

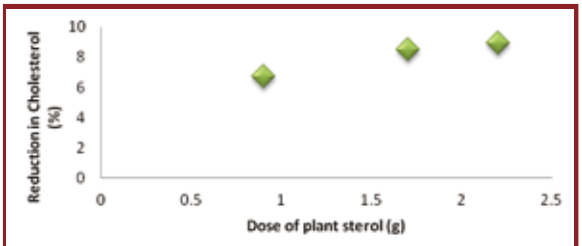


Figure 2. Reduction in low density lipoprotein cholesterol as a function of plant sterol dose (summary of 41 trials) 2.

Who is plant sterols suitable for?

Plant sterols have been evaluated in adults with normal or high cholesterol levels, in children and in patients with type 2 diabetes, with effective results to lower LDL cholesterol[6]. The addition of plant sterols to existing statin, bile acid sequestrant and/or fibratre therapies have been shown to associate with greater reductions in LDL cholesterol than medication alone[6,7]. Plant sterols are proved to be effective, with no negative impact on blood sugar control in patients with diabetes[6].

Due to limited data, plant sterols are not recommended in children less than six years of age, during pregnancy and in breast-feeding women[4].

Plant sterols are well tolerated and recognised as safe4

Over 100 studies have demonstrated the safety and efficacy of plant sterols in lowering cholesterol. Commonly reported adverse effects are primarily gastrointestinal in nature (nausea, dyspepsia, diarrhoea, constipation, flatulence, faeces discolouration, gastro-oesophageal reflux, appetite changes)[6].

The consumption of 1.5g/d or more have been found to reduce serum α-tocopherol by 6%, beta carotene by 20% and lycopene by 7% due to reduced absorption of these fat soluble vitamins[2]. The reduction can be prevented by adding sufficient fruits and vegetables to the diet[2]. Vitamin A and D concentrations are generally not affected by plant sterols[2]. Vitamin K-dependent clotting factors are reported to be unaffected[2]. Plant sterols are found to have few drug interactions[6].

Individuals with a rare autosomal recessive disease sitosterolaemia (which occurs in about 1 in 5 million people) absorb substantial amounts of plant sterols and may have an elevated risk for cardiovascular disease from consuming plant sterols[2]. These individuals should be counselled against of foods containing plant sterols.

Adding plant sterols as part of the cholesterol lowering and/or healthy heart diet to optimise treatment effect

For optimal cholesterol effect, plant sterols should complement a healthy diet low in saturated fat and cholesterol and high in fruits, vegetables, and whole grains[2]. Plant sterols are shown to be effective when combined with other dietary factors including psyllium, fish oil, beta-glucan, or statin drugs[8]. The combination of viscous fibres, soy protein, plant sterols and nuts in the portfolio diet has even been shown to effectively lower cholesterol by up to 35%, similar to the effect achieved with statins[9].

What's the difference between plant sterols and stanols?

Plant sterols have similar structure and cellular function to cholesterol. Plant stanols, on the other hand, are saturated derivatives of sterols. Both decrease intestinal absorption of cholesterol. Meta-analysis showed that there are no statistically or clinically significant differences between plant sterols and plant stanols in their abilities to modify total cholesterol[10].

References

1. Ostlund RE. Phytosterols in Human Nutrition. Ann Rev Nutr 2002;22:533-49.
2. Katan MB, Grundy SM, Jones P et al. Efficacy and Safety of Plant Stanols and Sterols in the Management of Blood Cholesterol Levels. Mayo Clin Proc 2003;78:965-978.
3. Lichtenstein AH, Appel LJ, Brands M et al. AHA Scientific Statement: Diet and Lifestyle Recommendations Revision 2006. Circulation 2006;114:82-96.
4. Malinowski JM and Gehret MM. Phytosterols for Dyslipidemia. Am J Health-Syst Phar 2010;67:1165-73.
5. Simone RMBE, de Jong N, Rompelberg CJM et al. Dose-dependent Cholesterol-lowering Effects of Phytosterol/Phytostanol-enriched Margarine in Statin Users and Statin Non-users under Free-living Conditions. Public Health Nutr 2011;14:1823-32.
6. Jones PJH and AbuMweis SS. Phytosterols as Functional Food Ingredients: Linkages to Cardiovascular Disease and Cancer. Curr Opi in Clin Nutr Met Care 2009;12:147-51.
7. Kendall CWC and Jenkins DJA. A Dietary Portfolio: Maximal Reduction of Low-density Lipoprotein Cholesterol with Diet. Curr Athero Reports 2004;6:492-498.
8. Grundy SM. Stanol Esters as a Component of Maximal Dietary Therapy in the National Cholesterol Education Program Adult Treatment Panel III Report. Am J Cardiol 2005;96:47D-50D.
9. Demonty I, Ras RT, van der Knaap HCM et al. Continuous Dose-response Relationship of the LDL-cholesterol-lowering Effect of Phytosterol Intake. J Nutr 2009;139:271-284.
10. Talati R, Sobieraj DM, Makanji SS et al. The Comparative Efficacy of Plant Sterols and Stanols on Serum Lipids: A Systematic Review and Meta-Analysis. J Am Diet Assoc 2010;110:719-726.

Benecol®

LOWERS FAST

LOWERS
TOTAL AND LDL
CHOLESTEROL
ON AVERAGE
BY 10%*

CLINICALLY
PROVEN
EFFICACY

KEEPS LOW*

Benecol provides fast results and keeps cholesterol at lower level, naturally

Benecol® is a range of functional foods, which complement other lifestyle changes and medical treatment in cholesterol lowering. Benecol contains an unique added ingredient – plant stanol ester. Its efficacy has been proven in more than 70 clinical studies published in well-renowned, peer-reviewed scientific journals, and it is widely recommended in the treatment guidelines.** Benecol yoghurt drinks are now also available in Hong Kong.

RECOMMENDED INTAKE: 1 YOGHURT DRINK/DAY

* The EFSA Journal (2009) 1175, 1-9. Miettinen T et al. N Engl J Med. 1995; 333: 1308-12.
**For further information, please refer to our website

www.benecol.com.hk

Produced by Emmi (Switzerland)
for Raisio Nutrition Ltd. (Finland), www.raisio.com.

Dunhuang Grotto Art

Dr. Patrick TH KO

MD(Alberta), FRCPC, FHKCP, FHKAM(Med), FACC
Specialist in Cardiology

Dr. Patrick TH KO

Photo 1. Mogao Cave Pavillion, Dunhuang

The Mogao Grottoes 莫高窟 (Photo 1) are most famous for their mural paintings and statues in Dunhuang 敦煌, which is an oasis strategically located at a cultural crossroad on the Silk Road in the northern part of Gansu Province. I visited Dunhuang seven years ago and I was highly impressed by the mural paintings and statues of Buddha and Bodhisattvas 菩薩 inside some of the 492 Mogao caves that were built over a span of one thousand years from AD 366 to AD 1368. I was able to have a glimpse of only six grottoes then, and I vowed to return to see more. About two months ago, I had the opportunity to go to Dunhuang again, with a group of about twenty people privileged enough to have Ms Lee Mei Yin, who has an ardent interest in Chinese culture, especially in Dunhuang grotto art. Under her guidance, I was able to learn and appreciate Dunhuang, and I have great pleasure to share with readers what I have learnt during this trip.

Photo 2. Dunhuang at the crossroad along the Silk Road

Dunhuang was designated as a frontier outpost during the Western Han Dynasty (202 BC to AD 8). In 111 BC, Emperor Wudi 漢武帝 established Dunhuang as one of the four towns near upstream Yellow River to guard against Xiongnu 匈奴. This became a meeting place for Chinese from central China to interact and trade with people from neighbouring countries as far as Sogdia (Uzbekistan) and Persia (Iran) (Photo 2).

Mogao Grottoes

A Buddhist monk named Yuzun 樂尊 began to build a grotto as a place for meditation. Many more were built during the Six Dynasties (六朝) (AD 420 to AD 589) and Sui 隋 (AD 589 to AD 617). During the Tang Dynasty (AD 617 to AD 907), Dunhuang became the hub of commerce of the Silk Road and a major religious centre, and Mogao Grottoes became a place for worship and pilgrimage for those that travelled along the Silk Road. After the Tang Dynasty, Dunhuang lost some importance but construction of new caves still continued during Song (AD 970 to AD 1279) and Yuan (AD 1279 to AD 1368). After the Yuan Dynasty, however, much of Central Asia was dominated by Islam and the Silk Road was largely abandoned during the Ming Dynasty (AD 1368 to AD 1644).

Rediscovery of Mogao Grottoes and the Dunhuang Treasures

In 1900, a taoist monk, Wang Yuanlu 王圓祿, allegedly and accidentally discovered a walled-up area behind a side corridor inside cave 16, and after clearing the sand and mud, he was astonished to see in the adjoining cave, now known as the Library Cave, an enormous amount of manuscripts, paintings and calligraphy. Wang asked local officials for funding to refurbish the much rundown state of the grottoes, but in vain. In 1904, the Governor of Gansu ordered him to reseal caves 16 and 17.

In 1907, Aurel Stein, a British Hungarian archaeologist came to Dunhuang. After much negotiation and persuasion, he was able to remove some 7000 manuscripts and 6000 fragments as well as a number of superb paintings for a ridiculously small sum of 130 British Pounds! In 1908, a French expeditionist Paul Pelliot, a multi-linguist who was fluent in Chinese, came and took back to France close to 10,000 items. This was followed by a Japanese expedition led by Otani Kozui in 1911, and a Russian team under Sergei Oldenburg in 1914. Finally in 1924, American expeditionist Langdon

Warner came and removed a number of wall paintings as well as a statue from the Mogao caves. This might have inspired Dan Brown, the author of Da Vinci Code, in which he named the Harvard expert of symbols as Professor Langdon (this being my own conjecture and I have not verified this with Mr Brown himself!)

It has been estimated that roughly one third of the manuscripts and other articles "unearthed" from the Mogao Grottoes are now stored and catalogued in the British Museum, the Quimet Museum, the National Library of Paris, and various Museums in Russia, Japan, the U.S. etc. The Dunhuang Academy under the directorship of Ms Fan Jinshi 范錦詩 is working hard to reconstitute the Library Cave manuscripts digitally, which is a part of the International Dunhuang Project.

Dunhuang Manuscripts

The manuscripts recovered from the Library Cave (cave 17) date back to as early as the 5th century, to the 11th century when it was sealed. This has been touted as the greatest treasure trove of ancient documents ever found. While most of them are writings in Chinese, many of these scrolls are in other languages such as Indian, Tibetan, Uigur, Sanskrit and Sogdian.

In the great majority of these scriptures and scrolls, Buddhism religion is the main theme, but a diversity of interesting secular topics are covered, e.g. Confucian writings, decrees from local governments, literary writings, calligraphy and even judiciary records. Because of the immense significance of the Mogao Grotto cultural relics, the Mogao caves were designated an UNESCO World Heritage site in 1987.

Works of Art and Finds Unearthed from cave 17

The total number of scrolls and highly valuable records of the history and economy of Dunhuang and its vicinity, some dating back to the Han Dynasty, plus other rare finds including a few of the judiciary documents amount to no less than 50,000. These are now stored at the Dunhuang Academy and various museums in China and overseas. Two areas of special interest are worth mentioning, and here I would like to share with readers.

Sogdian Traders

Ever since the Silk Road was established by Zhang Hsin 張騫 in 111 BC during the Han Wudi's reign, traders came from countries west of China as far as Persia (present day Iran) and Sogdia 肅特 (present day Samakand in Uzbekistan). The Sogdian traders proved to be particularly successful. They purchased silk from China and brought back spices and jewellery from the West. Among the goods imported into China were pepper 胡椒, jasmine 茉莉, Huqin 胡琴, etc. Their prefix in Chinese suggests their origin.

Some of the characters and their costumes displayed in the Dunhuang Grottoes reflect foreign influence, Indian and Sogdian for instance.

Aurel Stein accidentally discovered not far away from Dunhuang eight letters written in Sogdian, and in one of them, there was a story explaining the cause of a delay in shipment of goods to Sogdia, which was due to an upheaval of events during the Revolt of the Eight Kings in AD 308 to-AD 316 in the West Jin Dynasty 西晉八王永嘉之亂. The writer of this letter was stranded in Dunhuang and was not able to return home in Samakand!

By the middle of the Tang Dynasty, quite a number of Sogdians lived in central China. Some even adopted Chinese surnames such as An e.g. An Lushan 安祿山, Shi e.g. Shi Siming 史思明, Mi e.g. Mi Fu 米芾 a famous Song Dynasty painter, Shih e.g. 後晉石敬塘 of Five Dynasties, Kang 康 (also a very common Sogdian surname). These surnames did not exist before the Han Dynasty, and probably originated from Sogdian descendants who came and lived in China after the advent of the Silk Road trade.

Dunhuang Flying Dancers

The Dunhunag flying dancer is an icon of Dunhuang. One can see these dancers flying freely and gracefully in many of the grottoes. These flying dancers or flying deities represent the guardian angels of Buddha.

There are eight regiments of guardian angels 天龍八部：Deva 天, Naga 人, Yaksa 夜叉, Gandharva 乾闥婆, Asura 阿修羅, Garuda 迦樓羅, Kimnara 緊那羅, and Mahoraga 摩呼羅迦. Of these, Gandharva and Kimnara are specialists in music and dancing.

Early Period

During the Sixteen Kingdom from Northern Wei 北魏 to Northern Zhou 北周 (AD 265 to-AD 589), flying dancers appeared masculine, with western influence such as Indian and the Middle East (Photo 3). The flying ribbons were wider and tightly stretched, suggesting that they were travelling at a fast speed.

Photo 3. Flying Dancer of the Earlier Period (Six Dynasties)

Middle Period

In Sui 隋, and Tang 唐, dancing assumed a prominent role, and grand performances were depicted on many of the mural paintings. The dancers were feminine and they flew closer to the ground with a slower speed

naturally (Photo 4). The ribbons were longer and more slender, with a curvy tail shaped like the letter "r". Dancers of the Sui Dynasty wore leggings or tights, rather daring even by modern standard, decorated with beaded pearls, probably influenced by the West. Tang Dynasty dancers also appeared on the plump side, and wore necklaces which was a fashion imported from the Middle East. These features enable one to distinguish flying dancers of the Sui and Tang Dynasties from those of the earlier period. Flying dancers of the Five Dynasties 五代, Song 宋, Yuan 元 simply followed the pattern set by the Tang Dynasty.

Photo 4. Flying Dancer of the Tang Dynasty

Examples of Mogao Grotto Art

Early Period 366 AD to 589 AD

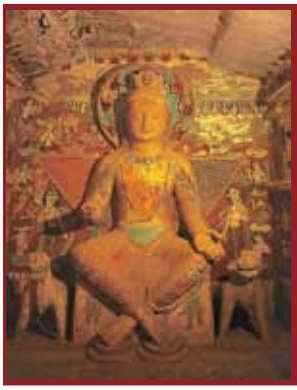


Photo 5. Sakyamuni Buddha in cave 275, early Six Dynasties. Notethe inverted triangle at the back, characteristic of Buddha of the Six Dynasties.

In this period of unrest from AD 265 to AD 420 Northern China was divided into 16 states, while central and southern China was ruled by West and East Jin 西晉, 東晉. Dunhuang was occupied by Liang 前涼, 北涼. One of the early grottoes constructed during this period is cave 275 (Photo 5). The Buddha statue sitting cross-legged and wearing a crown with three facets with an inverted triangle at the back is typical of a Buddha west of China, indicating that the early grotto was designed with Buddhism imported from the west of China. Mural frescos depicted stories 經變圖 of Sakyamuni's 釋迦牟尼 conversion from a princely status to priesthood. While travelling in various states, he saw people suffering from the miseries in life. After much deliberation and soul-searching, he decided to give up his right to be heir to his kingdom, in order to save the souls of mankind.

Sui Dynasty Grotto, cave 420

In the Sui and Tang Dynasties, Buddhism became more and more popular and became the mainstream religion. The Kings and nobles were fervent buddhists. Among the grottoes built during the short-lived Sui Dynasty, Grotto 420 (Photo 6) is most representative. The bodhisattvas standing on each side of the Sakyamuni wore pants with beaded pearls, characteristic of western influence.

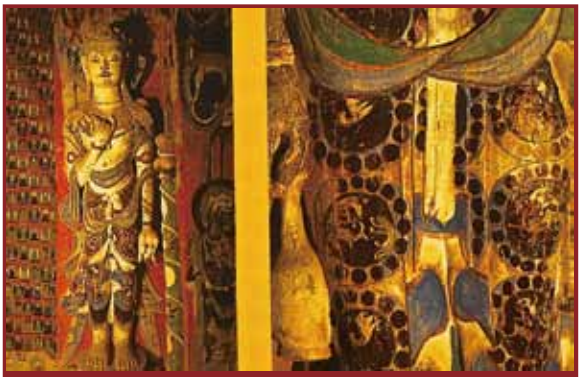


Photo 6. Sui Dynasty Buddha costume showing the beaded pearls, cave 420.

Tang Dynasty Grotto, caves 57 and 45

Tang Taizong's reign was most successful, as he was able to make good use of righteous and talented officials during his famous Zhenguan rule 貞觀之治. He was open-minded and appointed officials based on their talents, and not purely because they were close to him and obeyed him 用人為才, 非用人為親. During this period, economy recovered and China became prosperous. In the latter part of his life, however, he listened to those with pleasing words and turned to ways to prolong life, like Qin Shi Huang 秦始皇, Han Wudi 漢武帝 some 800 years before and many others that followed him, e.g. several emperors in the Ming Dynasty. In AD 649, while looking for immortality, Emperor Taizong died from taking pills made up of stones and metals!

Caves 57 and 45 are fine examples of the grottoes constructed during the early and prosperous parts of the Tang Dynasty. The Sakyamuni Buddha and bodhisattvas were all well-built with slightly plump faces and bodies, and were meticulously dressed, with facial expressions exuding a confident and majestic look! In cave 57 built in early Tang, (AD 705 to AD 781), the artists added famine features to the several bodhisattvas. Their eyes were so beautifully drawn (Photo 7) that attracted the attention of Zhang Da Qian 張大千 who studied Dunhuang art in 1938-1941. He exalted "these are so beautiful that my heart pumps"!

In cave 45 Mid-Tang (AD 705 to AD 781), one can see Buddha sitting in the middle and standing on each side are disciples Ananda 阿難 and Katyayana or Kasyap 迦葉, then bodhisattvas and 力士. These statues were constructed on a rough wooden frame, sculptured with clay and mud, and finished with meticulous and vivid painting and colouring. They look amazingly true to life

in dimension, posture and expression. One could have a glimpse of the opulent fashion of the times by their costumes. For instance, the bodhisattvas wear leggings, miniskirts and a see-through blouse (Photo 8)!

Photo 7. Bodhisattva of the Early Tang Dynasty, cave 57

Photo 8. Disciple Katyayana, Boddhisattva and Warrior in cave 45

Yulin Grotto

The construction of cave No. 3 (Photo 9) dated back to Xi Hsia 西夏 (AD 1032 to AD 1227), with renovations done during Yuan, Ming and Qing. The mural painting was based on Wu Dao Tzi style 吳道子, a famous artist who lived in the Tang Dynasty. The Buddha on each of the Easter, Southern and Northern walls of the cave has "one thousand eyes and one thousand arms". On a vertical wall with uneven surface, drawing of eyes and hands with fine strokes or line drawing 細絲描 is indeed amazing. The thousand eyes of Buddha literally represent the fact that Buddha is aware of the sufferings and wrongdoings of mankind, and the thousand hands means that Buddha is ready to lend a hand to all those in need, according, to Buddhism teaching. The landscape painting 山水畫 in the background was probably the works of Song Dynasty artists. It was pure pleasure for me to have the opportunity to see this mural paintings in cave 3, which alone was worth the trip.

Photo 9 Mural Painting of Xi Hsia 西厦 Dynasty Yulin cave 3

Epilogue

My trip to Dunhuang in September 2013 was simply wonderful. I was one of the fortunate few who were able to visit Dunhuang under the guidance of an expert Lee Mei Yin 李美賢老師 whose knowledge of Dunhuang art is truly amazing! The group was also fortunate enough to meet with the President of the Dunhuang Academy, Ms Fan Jinshi 范錦詩. She has been the third President of the Academy since 1998, and like her predecessors Chang Shuhong 常書鴻, 1st President of the Academy from1944-1982 and Duan Wenjie 段文杰 2nd President 1982 to 1998, she has been working extremely hard, and her selfless dedication towards the restoration and preservation of the Dunhuang Grottoes is admirable. President Fan and her staff are currently working hard to protect and preserve Dunhuang Grottoes and to document by digitalisation techniques not only the remaining Dunhuang relics in China, but hopefully also the ones that are now stored in overseas museums. Another project is recording by digital-videos all the 45,000 square metres of mural paintings and more than 2000 statues inside the caves in Dunhuang and its vicinity.

I salute to all those who did wonders for ten centuries, from the 4th to the 14th, and those who are still working hard, striving towards the creation, construction and preservation of Dunhuang in the past, present and the future!

References

General reference and photos are excerpted from the following:-

1. The Caves of Dunhuang 敦煌石窟 by FanJinshi Dunhuang Academy 2010 London Edition (H.K.) Ltd
2. Jiemi Duhuang 解密敦煌 by Hu Gingtong, Luo Qinghua Gansu People's Publishers Jan 2010
3. China Dunhuang 中國敦煌 by Fan Jinshi Gansu Art Publishers June 2010
4. Harvard Art Museums, some murals and a statue removed from Dunhuang by Langdon Warner
www. Harvardartmususeums.org/art/search=mogao

Financial Dinner Seminar for Member Societies

A financial dinner seminar was held at the Hong Kong Bankers Club in the evening of 23 September 2013 for our member societies, with support from UOB Kay Hian Hong Kong which is a stalwart in the securities trading and investments for Asian financial markets.

This informative seminar was delivered by two experienced Chartered Financial Analysts, Mr. Chi-wai LAM and Mr. Mun-hon THAM, and was of interest especially with the present economic scene. In the topics of "Growing your net worth in this uncertain investment climate" and "Yield chasing-a dead end alley" respectively, they gave our attended members and guests a valuable update and information in improving investment decisions. We would like to take this opportunity to express our gratitude to UOB Kay Hian Hong Kong for co-organising the seminar.

The Federation Presidents and Editors' Dinner 2013

The Federation Presidents and Editors' Dinner 2013 was successfully held on 16 September 2013 at the Hong Kong Club. It was a great occasion to meet the presidents of the member societies and editors of the Hong Kong Medical Diary for reunion and fraternity.

During the Dinner, the Federation's Executive Committee updated our work and activities throughout the year. The representatives from our member societies gave us comments and suggestions on the Federation's work to which our EXCO very much appreciated. Souvenirs were presented to the editors of the Medical Diary in expressing our heartfelt thanks for their dedication and support in ensuring our Diary a continuing success. We are honoured to have Dr. Wing-man KO, Secretary for Food and Health & Prof. Sophia CHAN, Under Secretary of Food and Health joined the dinner and delivered speeches which were absolutely the highlights of the event.

Our special thanks go to the Meetings and Exhibitions Hong Kong of the Hong Kong Tourism Board as the supporting organisation of the Dinner. The evening was made most memorable with the delightful harp performance by the talented MUI Family from the Hong Kong Harp Chamber.

The Federation Presidents and Editors' Dinner 2013

THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG
香港醫學組織聯會

The Federation Annual Dinner 2013

31st December, 2013 (TUE)

Run Run Shaw Hall
The Hong Kong Academy of Medicine Jockey Club Building

Annabelle Louie
雷安娜

Suzan Guterres
蘇姍

Dr. David Fang Jin Sheng
方津生醫生

Alex Lee Chi Kong
李志剛

Roger Fung Kar Chun
馮家俊

Fantastic New Year's Eve on Federation Cruise

- String Quartet
- Magician's Show
- Portrait Shooting & Instant Fun Photo
- Music Table & BINGO gifts
- 1 FREE for a Table of 12
  Exclusive offer for Member Societies

★ Fabulous Raffles
Cruise Packages
Danube River
Alaska
Brunei & Sabah

Book your tickets now ($1,200 HKD per person)
Call the Federation Secretariat on 2527-8898 to reserve your tables early !
Booking form can be downloaded from website: http://www.fmshk.org

WYETH MAMA® | Wyeth® Materna®

Planning, pregnancy to lactation
Nurture life with professionalism

Wyeth® Maternal Portfolio

Support the nutrition needs from planning, pregnancy to lactation

Wyeth® Materna®

- Contains 23 vitamins and minerals
- Folic acid supports fetal neurodevelopment[1]
- Vitamin D helps calcium absorption and bone health[2]
- Iodine helps fetal brain development[3]

WYETH® MAMA™

- Provides balanced nutritional support throughout planning, pregnancy and lactation
- High calcium and relatively low fat*

WYETH MAMA™ ALGAE OIL DHA

- 200mg DHA in each softgel, 1 softgel can satisfy the daily recommended intake for pregnant and lactating women by international expert groups[4,5]
- High purity and free from oceanic contamination[6,7,8]
- Easy to be utilized by the human body[9]

References
1. Obican SG, Finnell RH, Mills JL, et al. Folic acid in early pregnancy: a public health success story. FASEB J. 2010;24(11):4157-4174. 2. Mulligan ML, Felton SK, Riek AE, et al. Implications of vitamin D deficiency in pregnancy and lactation. Am J Obstet Gynecol. 2010;202 (5):429.e1-9. 3. Murcia M, Rebagliato M, Iniguez C, et al. Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age. Am J Epidemiol. 2011;173(7):804-814. 4. Koletzko B, Lien E, Agostoni C, et al. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. J Perinat Med. 2008;36(1):5-14. 5. FAO/WHO. Fats and fatty acids in human nutrition: Report of an expert consultation. FAO Food Nutr Pap. 2010;91:1-166. 6. Adarme-Vega TC, Lim DK, Timmins M, et al. Microalgal biofactories: a promising approach towards sustainable omega-3 fatty acid production. Microb Cell Fact. 2012 Jul 25;11:96. 7. GRAS notice GRN000137. U.S. Food and Drug Administration. Available at: http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=grasListing&id=137 accessed date 23Aug2013. 8. Wen XX, Li JP, Hou WW, et al. Microalgal docosahexaenoic acid: a new functional food additive. Food Science. 2010 Jun;31(21):446-450.

* Per serving fat content in Wyeth Mama is about ½ of that in whole fat milk. (US Department of Agriculture. USDA National Nutrient Database for Standard Reference, Release 24, 2012.NDB No. 01211)

Nutritional needs may vary among individuals. Your patient may require different types of nutrition products according to her needs

Wyeth (Hong Kong) Holding Company Limited
12/F., Lincoln House, Taikoo Place, 979 King's Road, Island East, Hong Kong
Tel: (852) 2599 8888

MEPNUSAT-AUG-13

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
★ RSCP Volleyball Tournament 2013 ★ HKMA Tennis Tournament 2013 **1**	★ HKMA Kowloon City Community Network - New Asthma Insights & its Management ★ Hong Kong Urological Association **2**	★ FMSHK Officers' Meeting ★ HKMA Council Meting **3**	★ HKMA Central, Western & Southern Community Network - Diagnosis of Asthma: Review & Update **4**	★ HKMA Kowloon East Community Network - Non-Alcoholic Fatty Liver Disease ★ HKMA Hong Kong East Community Network - Injection Therapy for Various Painful Conditions ★ Ntegrative Management of Skin Secretions and Seborrhoea **5**	**6**	**7**
★ International Scientific Congress- Manpower needs in medicine: moving with the times ★ HKMA Tennis Tournament 2013 **8**	★ International Scientific Congress- Manpower needs in medicine: moving with the times **9**	★ International Scientific Congress- Manpower needs in medicine: moving with the times **10**	★ Hong Kong Neurosurgical Society Monthly Academic Meeting –ECIC Bypass for Athero-Occlusive Disease: Is It an Evidenced Based Option? ★ HKMA Shatin Doctors Network – Workshop on Practical Assessment and Management of LUTS **11**	★ HKMA New Territories West Community Network - Picky Eating and its Consequences ★ HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2013 – The Child is not Responding to Sounds ★ RSCP Annual General Meeting **12**	**13**	★ HKMA CME – Refresher Course for Health Care Providers 2013/2014 **14**
★ HKMA Tennis Tournament 2013 **15**	**16**	**17**	★ HKMA Central, Western & Southern Community Network - Overcome the Challenge in Management of AF patients **18**	★ HKMA New Territories West Community Network - Do Patient Characteristics Influence Choice of DPP-4 Inhibitor? ★ HKMA Kowloon East Community Network – Final Session of the Certificate Course for GPs 2013: Update on Management of Glaucoma ★ FMSHK Executive Committee Meeting **19**	**20**	**21**
★ HKMA Tennis Tournament 2013 **22**	**23**	**24**	**25**	**26**	**27**	**28**
29	**30**	★ FMSHK Annual Dinner 2013 ★ HKMA Annual Ball 2013 **31**				

Date / Time	Function	Enquiry / Remarks
1 SUN 6:00 pm	**RSCP Volleyball Tournament 2013** Organiser: The Hong Kong Medical Association, Chairman: Dr. CHEONG Shao Nean, Philip, Speaker: , Venue: Siu Sai Wan Sports Centre	Ms. Dorothy KWOK Tel: 2527 8285
8:00 pm	**HKMA Tennis Tournament 2013** Organiser: The Hong Kong Medical Association, Chairman: Dr. CHIN Chu Wah, Speaker: , Venue: Kowloon Tong Club	Ms. Dorothy KWOK Tel: 2527 8285
2 MON 1:00 pm	**HKMA Kowloon City Community Network - New Asthma Insights & its Management** Organiser: HKMA Kowloon City Community Network, Chairman: Dr. CHIN Chu Wah, Speaker: Dr. LO Chi Wai, Venue: Spotlight Recreation Club (博藝會), 4/F, Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon	Ms. Candice TONG Tel: 2527 8285
7:30 pm	**Hong Kong Urological Association** Organiser: Hong Kong Urological Association, Chairman: Dr Ho Sze Ho Brian, Speaker: Dr Cheng Kun Chung Bryan, Venue: Multi-disciplinary Simulation and Skills Centre, 4/F, Block F, QEH	Ms. Tammy HUNG Tel: 9609 6064 1 CME point
3 TUE 8:00 pm	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
8:00 pm	**HKMA Council Meting** Organiser: The Hong Kong Medical Association, Chairman: Dr. TSE Hung Hing, Venue: HKMA Head Office (5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong)	Ms. Christine WONG Tel: 2527 8285
4 WED 1:00 pm	**HKMA Central, Western & Southern Community Network - Diagnosis of Asthma: Review & Update** Organiser: HKMA Central, Western & Southern Community Network, Chairman: Dr. YIK Ping Yin, Speaker: Dr. WONG King Yan, Matthew, Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME point
5 THU 1:00 pm	**HKMA Kowloon East Community Network - Non-Alcoholic Fatty Liver Disease** Organiser: HKMA Kowloon East Community Network, Chairman: Dr. AU Ka Kui, Gary, Speaker: Dr. CHAU Tai Nin, Venue: Lei Garden Restaurant (利苑酒家),Shop no. L5-8, apm, Kwun Tong,No. 418 Kwun Tong Road, Kwun Tong, Kowloon	Miss Hana YEUNG Tel: 2527 8285 1 CME point
1:00 pm	**HKMA Hong Kong East Community Network - Injection Therapy for Various Painful Conditions** Organiser: HKMA Hong Kong East Community Network, Chairman: Dr. LAM See Yui, Joseph, Speaker: Dr. LAW Yee Cheong, Venue: HKMA Head Office (5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong)	Ms. Candice TONG Tel: 2527 8285
7:00 pm	**Ntegrative Management of Skin Secretions and Seborrhoea** Organiser: Association for Integrative Aesthetic Medicine, Chairmen: Dr. HAU Kwun Cheung, Dr. CHAN Kam Tim, Michael, Speakers: Dr. LOO King Fan, Steven, Dr. TAI Yuk Ping Cheung & Dr. CHAN Kam Tim, Michael, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central	Ms. P SUEN Tel: 3575 8600
8 SUN *(9,10)*	**International Scientific Congress- Manpower needs in medicine: moving with the times** Organiser: Hong Kong Academy of Medicine, Venue: Academy Building	Secretariat Tel: 2871 8787
8:00 pm	**HKMA Tennis Tournament 2013** Organiser: The Hong Kong Medical Association, Chairman: Dr. CHIN Chu Wah, Venue: Kowloon Tong Club	Ms. Dorothy KWOK Tel: 2527 8285
11 WED 7:30 am	**Hong Kong Neurosurgical Society Monthly Academic Meeting –ECIC Bypass for Athero-Occlusive Disease: Is It an Evidenced Based Option?** Organiser: Hong Kong Neurosurgical Society, Chairman: Dr. FOK Kam Fuk, Speaker: Dr. LAM Siu Kei, Samuel, Venue: Seminar Room, Ground Floor, Block A, Queen Elizabeth Hospital	Dr. Gilberto LEUNG Tel: 2255 3368 1.5 CME points
1:00 pm	**HKMA Shatin Doctors Network – Workshop on Practical Assessment and Management of LUTS** Organiser: HKMA Shatin Doctors Network, Chairman: Dr. MAK Wing Kin, Speaker: Prof. NG Chi Fai, Venue: Jasmine Room, 2/F, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Sharon LAM Tel: 3189 8787 1 CME point
12 THU 1:00 pm	**HKMA New Territories West Community Network - Picky Eating and its Consequences** Organiser: HKMA New Territories West Community Network, Chairman: Dr. LEE Huen, Speaker: Mr. David CHAN, Venue: Plentiful Delight Banquet (元朗喜尚嘉喜酒家),1/F., Ho Shun Tai Building,10 Sai Ching Street, Yuen Long	Miss Hana YEUNG Tel: 2527 8285 1 CME point
1:00 pm	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2013 – The Child is not Responding to Sounds** Organiser: Hong Kong Medical Association Hong Kong Sanatorium & Hospital, Speaker: Dr. Au Kin Kwok, Dennis, Venue: HKMA Central Premises	HKMA CME Department Tel: 2527 8285 Fax: 2865 0943 1 CME point
7:00 pm	**RSCP Annual General Meeting**	
14 SAT 2:15 pm	**HKMA CME – Refresher Course for Health Care Providers 2013/2014** Organisers: Hong Kong Medical Association, HK College of Family Physicians & HA-Our Lady of Maryknoll Hospital, Speaker: Dr. Tee Man Fai, Lawrence, Venue: Our Lady of Maryknoll Hospital	Ms. Clara Tsang Tel: 2354 2440 2 CME points
15 SUN 8:00 pm	**HKMA Tennis Tournament 2013** Organiser: The Hong Kong Medical Association, Chairman: Dr. CHIN Chu Wah, Venue: Kowloon Tong Club	Ms. Dorothy KWOK Tel: 2527 8285
18 WED 1:00 pm	**HKMA Central, Western & Southern Community Network - Overcome the Challenge in Management of AF patients** Organiser: HKMA Central, Western & Southern Community Network, Chairman: Dr. POON Man Kay, Speaker: Dr. TSE Tak Sun, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 Fax: 2865 0943 1 CME point
19 THU 1:00 pm	**HKMA New Territories West Community Network - Do Patient Characteristics Influence Choice of DPP-4 Inhibitor?** Organiser: HKMA New Territories West Community Network, Speaker: Dr. TAM Kwok Kuen, Vincent, Venue: Plentiful Delight Banquet (元朗喜尚嘉喜酒家),1/F., Ho Shun Tai Building,10 Sai Ching Street, Yuen Long	Miss Hana YEUNG Tel: 2527 8285 Fax: 2865 0943 1 CME point
1:00 pm	**HKMA Kowloon East Community Network – Final Session of the Certificate Course for GPs 2013: Update on Management of Glaucoma** Organisers: HA-United Christian Hospital, HK College of Family Physicians, HKMA-KLN East Community Network, Chairman: Dr. Gary AU, Speaker: Dr. SO Fei, Sophia, Venue: East Ocean Seafood Restaurant, Tseung Kwan O	Ms. Cordy WONG Tel: 3513 3087 1 CME point
8:00 pm	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
22 SUN 8:00 pm	**HKMA Tennis Tournament 2013** Organiser: The Hong Kong Medical Association, Chairman: Dr. CHIN Chu Wah, Venue: Kowloon Tong Club	Ms. Dorothy KWOK Tel: 2527 8285
31 TUE 7:00 pm	**FMSHK Annual Dinner 2013** Organiser: The Federation of Medical Societies of Hong Kong, Venue: Run Run Shaw Hall, the Hong Kong Academy of Medicine Jockey Club Building	Ms. Nancy CHAN Tel: 2527 8898
8:00 pm	**HKMA Annual Ball 2013** Organiser: The Hong Kong Medical Association, Venue: Grand Ballroom, Conrad Hong Kong	Ms. Candy YUEN Tel: 2527 8285

優雅健®
EVISTA®
raloxifene HCl™

健乳健骨
保護1+1

全球唯一[3]
提供雙重保護
關心您的骨骼及乳房健康
請即向您的醫生查詢

每日只需一粒，有效減少骨質流失和增加骨質密度[1]
醫學研究証實，更能減低乳房高風險問題超過8成[2]

HK/CH/EVI/06/06-2013

Takeda

優雅會熱線：2856 1223

武田藥品(香港)有限公司
Takeda Pharmaceuticals (Hong Kong) Ltd.

優雅健乃醫生處方藥物，請依從醫生指示持續服用，不能自行停藥。如有疑問，請向醫生或藥劑師查詢

香港銅鑼灣禮頓道38號東區電訊大廈23及24樓 電話: 2133 9800 傳真: 2856 2728 網頁: www.takeda.com

參考資料: 1. Evista Prescribing Information, Hong Kong, April, 2013. 2. Cauley JA., et al. Breast Cancer Research and Treatment 65: 125—134, 2001. 3. Jaime KJ et al. Arq Bras Endocrinol Metabol. 2010 March ; 54(2): 200—205.