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INDICATIONS: First-line treatment of hypertension and first-line treatment of myocardial ischemia, whether due to fixed obstruction (stable angina and/or non-sustained ventricular tachycardia and/or ventricular fibrillation and/or ventricular arrhythmias) and/or unspecified ventricular tachycardia and/or unspecified ventricular arrhythmias. NORVASC® is also indicated for the treatment of amlodipine besylate in patients with hypercholesterolemia, including patients with atherosclerotic vascular disease. NORVASC® is also indicated for the treatment of amlodipine besylate in patients with hypercholesterolemia, including patients with atherosclerotic vascular disease.

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WARNINGS & PRECAUTIONS: Patients with heart failure or impaired hepatic function should be used with caution. NORVASC® is contraindicated in patients with known sensitivity to amlodipine besylate.

INTERACTIONS: None known. NORVASC® has not been shown to be effective in patients with hepatic impairment.

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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
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 prevention 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.
Cardiovascular disease can be alarming.
Let Nebilet lower the pressure.

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

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

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 transcathester 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.

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.

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).

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 reduced. In 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 sequela. 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.
Conclusions
Despite the advances of modern anti-hypertensives, many patients still fail to achieve a target blood pressure despite good drug compliance and lifestyle 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

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)

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Name (block letters):____________________________ HKMA No.: __________________
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Contact Tel No.:________________________________ MCHK No.: __________
(for reference only)

Answers to November 2013 Issue

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

Mandibular Condylar Fracture – A Review of Management and Case Reports

PRACTICE MANAGEMENT FOR PRIVATE MEDICAL PRACTICES
February 10 to April 14, 2014 (3-month short course)

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

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<tr>
<th>Date</th>
<th>Lecture Topic</th>
<th>Guest Experts</th>
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<td>10 Feb 2014</td>
<td>Overview of the private sector - Hong Kong's</td>
<td>Dr. Nelson Wong</td>
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<td>and Southwest Asia perspectives</td>
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<td>17 Feb 2014</td>
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<td>24 Feb 2014</td>
<td>Business continuity, operations plan and Workflow</td>
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<td>Dr. Ronlee Hui</td>
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<td>24 Mar 2014</td>
<td>Manpower planning, professional development and training</td>
<td>Dr. Bilian Chan</td>
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<tr>
<td>31 Mar 2014</td>
<td>Supply chain and resources management</td>
<td>Dr. Bennet Fung</td>
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<td>07 Apr 2014</td>
<td>Clinical governance</td>
<td>Dr. Ares Leung</td>
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<td>14 Apr 2014</td>
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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 overseas 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), MRCPG (UK), Dip Med (CUHK)

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

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

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

Dr. Nelson WONG
LRCP (London), MRCS (England), MBBS (London), MRCP (UK), FIHM (With Distinction)

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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

Introduction

After Dr. Andreas Gruentzig performed the first Percutaneous Coronary Intervention (PCI) with a balloon catheter in 1977, 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 safety of PCI. However, the inherent limitations and potential complications of permanent coronary stenting still pose an important challenge for cardiologists. 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. 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.

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.

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 Pharm.), 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/cm². 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 CO² and H2O. The blood vessels can then resume the normal ability to flex, contract and pulsate with response to

Table 1: Current limitations of permanent metallic stents

<table>
<thead>
<tr>
<th>chronic inflammatory response</th>
<th>stent thrombosis</th>
<th>prolonged dual antiplatelets</th>
<th>Re-intervention or CABG difficult</th>
<th>Limit imaging modalities</th>
</tr>
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</table>

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.
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; Abbott 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.\(^{23}\)

<table>
<thead>
<tr>
<th>ABSORB EXTEND : Clinical Outcomes at 6 and 12 Months</th>
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<th>6 months (N=512)</th>
<th>12 months (N=512)</th>
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<tr>
<td>Cardiac Death</td>
<td>%</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>%</td>
<td>2.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Ischaemia driven TLR</td>
<td>%</td>
<td>0.6</td>
<td>1.8</td>
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<tr>
<td>Hierarchical MACE</td>
<td>%</td>
<td>2.9</td>
<td>4.3</td>
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<tr>
<td>Hierarchical TVF</td>
<td>%</td>
<td>3.3</td>
<td>4.9</td>
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<tr>
<td>Scaffold thrombosis</td>
<td>%</td>
<td>0.6</td>
<td>0.8</td>
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</tbody>
</table>

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, multicentre 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 Infarction 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-scaffold 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.

DE Solve Novolimus Eluting Bioresorbable Coronary Scaffold System
DE Solve is another PLLA-based ultrathin polymeric scaffold (Elixir Medical Corporation) and the drug sirolimus is used to inhibit neointimal hyperplasia. DE Solve 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 DE Solve 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

DE Solve 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 DE Solve 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.

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Update on Transcatheter Aortic Valve Implantation (TAVI)

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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, 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; 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. Since the first review of the topic by our group in this Diary, 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 SAPIEN 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 tri-leaflet 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. Small valve 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 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. 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). As such, the applicability of these scores in patient selection for TAVI has been questioned. Despite these limitations, patient enrolment in TAVI trials has been determined by an EuroSCORE >15% or an STS score >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. 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-foot 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., 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.

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. More rigorous clinical results are now available from the landmark randomised PARTNER trials.

The Edwards SAPIEN 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. 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. 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. 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. 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). 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. 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 SAPIEN 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. 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)24. 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 CoreValve has 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, 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.45 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.46 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.

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 Transcather 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 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. 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 but evidence is accumulating and there are several ongoing 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. 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, 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.

References
Left Atrial Appendage Occlusion (LAAO) In Atrial Fibrillation

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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 studies3. 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 warfarin4. In a study of 41,900 patients with chronic AF, only 70% of patients treated with warfarin remained on the therapy at 1 year5.

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 warfarin6,7,8. 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 appendage9. 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 effectiveness10. 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 on11.

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 tying 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 blood12. 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-oesophageal echocardiogram shows no residual leakage at day 45, clopidogrel will replace warfarin (unless contra-indicated) for another 6 months.

**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 results18, 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 201321. 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.

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

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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. 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, and provides a practical approach to their indications and prescription.

ASSESSING EMBOLIC RISK IN AF

The acronym CHA2DS2-VASc score is used to assess SE risks in patients with non-valvular AF (Table 1). 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. 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>
<thead>
<tr>
<th>CHA2DS2-VASc Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/left ventricular dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack/other systemic embolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female gender)</td>
<td>1</td>
</tr>
</tbody>
</table>

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. 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 CHA2DS2-VASc 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. CI = confidence interval

<table>
<thead>
<tr>
<th>CHA2DS2-VASc total score</th>
<th>Rate of Stroke/Other Systemic Embolism (%/year)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>(0.0-0.0)</td>
</tr>
<tr>
<td>1</td>
<td>0.6</td>
<td>(0.3-4.3)</td>
</tr>
<tr>
<td>2</td>
<td>1.6</td>
<td>(0.3-4.7)</td>
</tr>
<tr>
<td>3</td>
<td>3.9</td>
<td>(1.7-7.6)</td>
</tr>
<tr>
<td>4</td>
<td>1.9</td>
<td>(0.5-4.9)</td>
</tr>
<tr>
<td>5</td>
<td>3.2</td>
<td>(0.7-9.0)</td>
</tr>
<tr>
<td>6</td>
<td>3.6</td>
<td>(0.4-12.3)</td>
</tr>
<tr>
<td>7</td>
<td>8.0</td>
<td>(1.0-26.0)</td>
</tr>
<tr>
<td>8</td>
<td>11.1</td>
<td>(0.3-48.3)</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>(2.5-100)</td>
</tr>
</tbody>
</table>
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. 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) or oral factor Xa inhibitors (rivaroxaban, ROCKET-AF; apixaban, ARISTOTLE Study; or endoxaban, not commercially available at present). Novel OACs are at least comparable 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 might improve compliance. In the RELY-ABLE study, 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.

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 might improve compliance. In the RELY-ABLE study, 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 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).

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

<table>
<thead>
<tr>
<th>Outcome (% per year)</th>
<th>Warfarin (n = 6022)</th>
<th>Dabigatran 150 mg bd (n = 6076)</th>
<th>Dabigatran 110 mg bd (n = 6015)</th>
<th>Warfarin (n = 7133)</th>
<th>Rivaroxaban (n = 7131)</th>
<th>Warfarin (n = 9081)</th>
<th>Apixaban (n = 9120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/other systemic embolism</td>
<td>2.3 (RR, 95% CI; P value)</td>
<td>1.9 (RR, 95% CI; P value)</td>
<td>1.8 (RR, 95% CI; P value)</td>
<td>2.4 (RR, 95% CI; P value)</td>
<td>2.1 (RR, 95% CI; P value)</td>
<td>1.6 (RR, 95% CI; P value)</td>
<td>1.27 (RR, 95% CI; P value)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1.11 (0.66, 0.53-0.82; P for superiority &lt;0.001)</td>
<td>1.53 (0.91, 0.74-1.11; P for non-inferiority &lt;0.001)</td>
<td>2.4 (RR, 95% CI; P value)</td>
<td>2.1 (RR, 95% CI; P value)</td>
<td>1.42 (RR, 95% CI; P value)</td>
<td>1.05 (RR, 95% CI; P value)</td>
<td>0.97 (RR, 95% CI; P value)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>0.10 (0.26, 0.14-0.49; P&lt;0.001)</td>
<td>0.12 (0.31, 0.17-0.56; P=0.001)</td>
<td>0.44 (RR, 95% CI; P=0.024)</td>
<td>0.26 (0.59, 0.37-0.93; P=0.001)</td>
<td>0.47 (RR, 95% CI; P=0.001)</td>
<td>0.24 (0.51, 0.33-0.75; P=0.01)</td>
<td>2.13 (RR, 95% CI; P=0.001)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.36 (RR, 95% CI; P=0.001)</td>
<td>2.71 (RR, 95% CI; P=0.000)</td>
<td>0.7 (RR, 95% CI; P=0.001)</td>
<td>0.5 (RR, 95% CI; P=0.02)</td>
<td>0.80 (RR, 95% CI; P=0.001)</td>
<td>0.33 (RR, 95% CI; P=0.58)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.74 (RR, 95% CI; P=0.001)</td>
<td>0.23 (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>2.67 (RR, 95% CI; P=0.001)</td>
<td>2.51 (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
<td>- (RR, 95% CI; P=0.001)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.02 (RR, 95% CI; P=0.001)</td>
<td>1.12 (RR, 95% CI; P=0.001)</td>
<td>2.2 (RR, 95% CI; P=0.001)</td>
<td>2.3 (RR, 95% CI; P=0.001)</td>
<td>0.86 (RR, 95% CI; P=0.001)</td>
<td>0.76 (RR, 95% CI; P=0.001)</td>
<td>0.76 (RR, 95% CI; P=0.001)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.64 (RR, 95% CI; P=0.001)</td>
<td>0.82 (RR, 95% CI; P=0.001)</td>
<td>2.2 (RR, 95% CI; P=0.001)</td>
<td>2.9 (RR, 95% CI; P=0.001)</td>
<td>1.1 (RR, 95% CI; P=0.001)</td>
<td>0.53 (RR, 95% CI; P=0.001)</td>
<td>0.53 (RR, 95% CI; P=0.001)</td>
</tr>
<tr>
<td>Death</td>
<td>4.13 (RR, 95% CI; P=0.001)</td>
<td>3.75 (RR, 95% CI; P=0.001)</td>
<td>2.2 (RR, 95% CI; P=0.001)</td>
<td>1.9 (RR, 95% CI; P=0.001)</td>
<td>2.2 (RR, 95% CI; P=0.001)</td>
<td>3.94 (RR, 95% CI; P=0.001)</td>
<td>3.52 (RR, 95% CI; P=0.001)</td>
</tr>
<tr>
<td>% Discontinuation at the end of follow-up</td>
<td>10.2</td>
<td>15.5</td>
<td>14.5</td>
<td>14.5</td>
<td>23.7</td>
<td>27.5</td>
<td>25.3</td>
</tr>
<tr>
<td>% Discontinuation/year</td>
<td>5.1</td>
<td>7.8</td>
<td>7.3</td>
<td>11.7</td>
<td>12.5</td>
<td>15.3</td>
<td>14.1</td>
</tr>
</tbody>
</table>
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.

**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. 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-life 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**

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Bioavailability</th>
<th>% Renally excreted of absorbed dose</th>
<th>CrCl level not recommended</th>
<th>Standard dose</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>3-7%</td>
<td>80% (+100% when taken with food)</td>
<td>&lt;30 ml/min</td>
<td>150 mg bd</td>
<td>1. FDA recommends 75 mg bd if CrCl 15-30 ml/min or CrCl 30-49 ml/min in presence of drug interaction</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>66% (100% when taken with food)</td>
<td>35%</td>
<td>&lt;15 ml/min</td>
<td>2 mg Qd</td>
<td>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</td>
</tr>
<tr>
<td>Apixaban</td>
<td>50%</td>
<td>27%</td>
<td>&lt;15 ml/min</td>
<td>5 mg bd</td>
<td></td>
</tr>
</tbody>
</table>

CrCl = Creatinine clearance
FDA = Food and Drug Administration

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 CHA2DS2-VASC 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. 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 during cardioversion, initiation of anticoagulation do not yet include NOACs. Indeed, a recent stroke is an exclusion criterion in major trials. There is no data to recommend switching of NOAC to VKA. If a NOAC may be used in place of VKA with clopidogrel 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 CHA2DS2-VASC 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. 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.

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 infarction. 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 wear 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, 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. 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, 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 antplatelet agents such as aspirin and clopidogrel. Secondly, the multiple possibility of using NOACs with conventional or newer antplatelet agents. The number of possible combination of VKAs, NOACs, aspirin, clopidogrel and newer antplatelet agents is striking and perhaps confusing (Table 4). Whether there is less 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.

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin + Aspirin</td>
<td>Dabigatran + Aspirin</td>
<td>Rivaroxaban + Aspirin</td>
<td>Apixaban + Aspirin</td>
</tr>
<tr>
<td>Warfarin + Clopidogrel</td>
<td>Dabigatran + Aspirin</td>
<td>Rivaroxaban + Aspirin</td>
<td>Apixaban + Aspirin</td>
</tr>
<tr>
<td>Warfarin + Prasugrel</td>
<td>Dabigatran + Aspirin</td>
<td>Rivaroxaban + Aspirin</td>
<td>Apixaban + Aspirin</td>
</tr>
<tr>
<td>Warfarin + Ticagrelor</td>
<td>Dabigatran + Aspirin</td>
<td>Rivaroxaban + Aspirin</td>
<td>Apixaban + Aspirin</td>
</tr>
<tr>
<td>Warfarin + Prasugrel</td>
<td>Dabigatran + Ticagrelor</td>
<td>Rivaroxaban + Ticagrelor</td>
<td>Apixaban + Ticagrelor</td>
</tr>
<tr>
<td>Warfarin + Ticagrelor</td>
<td>Dabigatran + Ticagrelor</td>
<td>Rivaroxaban + Ticagrelor</td>
<td>Apixaban + Ticagrelor</td>
</tr>
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</table>

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

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.

**HTT/LTC**=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).

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

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**Exelon® Patch 5**

**Exelon® Patch 10**

**Presentation:**
- **Exelon® Patch 5 cm²** contains 9 mg rivastigmine base, in a 24 hr release rate of 4.8 mg/24 hr.
- **Exelon® Patch 10 cm²** contains 18 mg rivastigmine base, in a 24 hr release rate of 9.6 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 rivastigmine 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 carboxiimide 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 after dose increase. Patients who show signs or symptoms of dehydration due to prolonged vomiting or diarrhea can be managed with IV fluids and dose reduction or discontinuation if recognized. Patients may lose weight during therapy. As with other cholinesterase inhibitors, 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-aural block, atio-ventricular block), gastrointestinal ulcerative conditions, history of or current respiratory disease, urinary obstruction, and sepsis in predisposed patients. Special Populations: Caution in patients with clinically significant hepatic impairment and patients with body weight below 50 kg. Not recommended in children. The safety of Exelon Patch is not established in pregnant and breastfeeding women. Rivastigmine is not recommended in children and adolescents (< 18 years).

**Interactions:** Rivastigmine should not be given concurrently with other cholinomimetic drugs and might interfere with the activity of anti-cholinergic medications. As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-induced muscle relaxants during anesthesia.

**Adverse reactions:**
- **Very common:** vomiting, nausea.
- **Common:** anorexia, decreased appetite, anxiety, depression, insomnia, dizziness, headache, diarrhea, dyspepsia, abdominal pain, palpitation, somnolence, cardiac arrhythmia (e.g., bradycardia, supraventricular extrasystole), gastrointestinal symptoms, gastrointestinal haemorrhage, urinary tract symptoms, contact dermatitis, malaise.
- **Rare:** hypertension, application site hypersensitivity, pruritus, rash, urticaria, angioedema, asthma, common cold.

**References:**

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**Novartis**

Novartis Pharmaceuticals (Hong Kong) Limited

2/F, 1093 King's Road, Quarry Bay, Hong Kong

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FAX: +852 2577 0274
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.

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. 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.

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.

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.

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 amounts1. 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 diet2.

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 levels1. 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 tract1. The structures of cholesterol and some common plant sterols, and the mechanism of action of plant sterols are shown in Figure 1a and 1b:

References

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 impact3. 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 lifetime2. 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 III1 recommended 2g/d as an effective dosage to lower cholesterol4. A recent meta-analysis including 84 randomised controlled trials has re-confirmed the above recommendation5.

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

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 cholesterol6. 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 alone6,7. Plant sterols are proved to be effective, with no negative impact on blood sugar control in patients with diabetes8.

Due to limited data, plant sterols are not recommended in children less than six years of age, during pregnancy and in breast-feeding women9.

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-esophageal reflex, 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 vitamins3. The reduction can be prevented by adding sufficient fruits and vegetables to the diet2. Vitamin A and D concentrations are generally not affected by plant sterols2. Vitamin K-dependent clotting factors are reported to be unaffected2. Plant sterols are found to have few drug interactions6.

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 sterols2. 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 grains2. Plant sterols are shown to be effective when combined with other dietary factors including psyllium, fish oil, beta-glucan, or statin drugs8. 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 statins9.

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 cholesterol10.

References

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.

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Dunhuang Grotto Art

Dr. Patrick TH KO
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Specialist in Cardiology

Dunhuang was designated as a frontier outpost during the Western Han Dynasty (202 BC to AD 8). In 111 BC, Emperor Wu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 楽尊 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 on 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 named 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 向晉八王永嘉之亂. 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. 後晋石敬瑭 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 Dunhuang 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 。</s>
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.

Examples of Mogao Grotto Art

Early Period 366 AD to 589 AD

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 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.

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 御 廷. 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)!

**Yulin Grotto**

The construction of cave No. 3 (Photo 9) dated back to Xi Hsia (AD 1032 to AD 1227), with renovations done during Yuan, Ming and Qing. The mural painting was based on Wu Dao Tzi style, 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.

**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 from 1944-1982 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:-
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
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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 Annual Dinner 2013

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References:

* Per serving fat content in Wyeth MAMA is about 1/2 that of whole fat milk (US Department of Agriculture. USDA National Nutrient Database for Standard Reference, Release 24, 2012, NSD No. 01211). Nutritional needs may vary among individuals. Your patient may require different types of nutrition products according to her needs.

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**Events:***
- RSCP Volleyball Tournament 2013
- HKMA Tennis Tournament 2013
- HKMA Kowloon City Community Network - New Asthma Insights & its Management
- HKMA Council Meeting
- HKMA Central, Western & Southern Community Network - Diagnosis of Asthma: Review & Update
- HKMA Kowloon East Community Network - Non-Alcoholic Fatty Liver Disease
- HKMA Hong Kong East Community Network - Injection Therapy for Various Painful Conditions
- Neglective Management of Skin Secretions and Seborrhoea
- HKMA Tennis Tournament 2013
- International Scientific Congress - Manpower needs in medicine: moving with the times
- International Scientific Congress - Manpower needs in medicine: moving with the times
- International Scientific Congress - Manpower needs in medicine: moving with the times
- 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
- HKMA CME – Refresher Course for Health Care Providers 2013/2014
- HKMA Tennis Tournament 2013
- HKMA Kowloon City Community Network - New Asthma Insights & its Management
- HKMA Central, Western & Southern Community Network - Overcome the Challenge in Management of AF patients
- HKMA New Territories West Community Network - Do Patient Characteristics Influence Choice of DPP-4 Inhibitor?...
<table>
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<tr>
<th>Date / Time</th>
<th>Function</th>
<th>Enquiry / Remarks</th>
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<tbody>
<tr>
<td><strong>1 SUN</strong></td>
<td><strong>6:00 pm</strong></td>
<td>RSCP Volleyball Tournament 2013 Organiser: The Hong Kong Medical Association, Chairman: Dr. CHEONG Shao Nean, Philip, Speaker, Venue: Stu Sai Sai Sports Centre</td>
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<tr>
<td><strong>8:00 pm</strong></td>
<td>HKMA Tennis Tournament 2013 Organiser: The Hong Kong Medical Association, Chairman: Dr. CHIN Chu Wah, Speaker, Venue: Kowloon Tong Club</td>
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<td><strong>2 MON</strong></td>
<td><strong>1:00 pm</strong></td>
<td>HKMA Kowloon City Community - New Asthma Insights &amp; its Management Organiser: HKMA Kowloon City Community Network, Chairman: Dr. CHIN Chu Wah, Speaker: Dr. LO Chi Wai, Venue: Spotlight Recreation Club (博樂會), 4/F, Screen World, Site 8, Whampoa Garden, Hung hom, Kowloon</td>
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<tr>
<td><strong>7:30 pm</strong></td>
<td>Hong Kong Urological Association Organiser: Hong Kong Urological Association, Chairman: Dr Ho Sze Ho Brian, Speaker: Dr Cheng Kwan Chung, Venue: Multi-disciplinary Simulation and Skills Centre, 4/F, Block F, QEII</td>
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<td><strong>3 TUE</strong></td>
<td><strong>8:00 pm</strong></td>
<td>FMSHK Officers’ Meeting Organiser: The Federation of Medical Societies of Hong Kong, Venue: Gallop, 2/F, Hong Kong Jockey Club House, Shan Kwong Road, Happy Valley, Hong Kong</td>
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<td><strong>8:00 pm</strong></td>
<td>HKMA Council Meeting Organiser: The Medical Hong Kong Association, Chairman: Dr. TSE Hung Hing, Venue: HKMA Head Office (5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong)</td>
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<td><strong>4 WED</strong></td>
<td><strong>1:00 pm</strong></td>
<td>HKMA Central, Western &amp; Southern Community Network - Review &amp; Update Organiser: HKMA Central, Western &amp; Southern Community Network, Chairman: Dr. YIK Ping Yin, Speaker: Dr. WONG King Yan, Matthew, Venue: HKMA Central Premises, Dr. Li Shui Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong</td>
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<td><strong>10:00 pm</strong></td>
<td>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 (利景閣), Shop no. L5-B, 8th, Kwan Tong, No. 418 Kwan Tong Road, Kwan Tong, Kowloon</td>
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<td><strong>5 THU</strong></td>
<td><strong>1:00 pm</strong></td>
<td>HKMA Hong Kong East Community Network - Injection Therapy for Various Painful Conditions Organiser: HKMA Hong Kong East Community Network, Chairman: Dr. LAM Sze Yui, Joseph, Speaker: Dr. LAW Yee Cheong, Venue: HKMA Head Office (5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong)</td>
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<td><strong>7:30 pm</strong></td>
<td>Negative Management of Skin Secretions and Seborrhoea Organiser: Association for Integrative Aesthetic Medicine, Chairman: Dr. HAU Kwun Cheung, Dr. CHAN Kam Tim, Michael, Speakers: Dr. LOO King Fan, Samuel, Dr. TAI Yuk Ping, Chong &amp; Dr. CHAN Kam Tim, Michael, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shui Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central</td>
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<tr>
<td><strong>8 SUN</strong></td>
<td><strong>8:00 pm</strong></td>
<td>International Scientific Congress - Manpower needs in medicine: moving with the times Organiser: Hong Kong Academy of Medicine, Venue: Academy Building</td>
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<td><strong>9.10 SUN</strong></td>
<td><strong>8:00 pm</strong></td>
<td>HKMA Tennis Tournament 2013 Organiser: The Hong Kong Medical Association, Chairman: Dr. CHIN Chu Wah, Venue: Kowloon Tong Club</td>
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<tr>
<td><strong>11 WED</strong></td>
<td><strong>7:30 am</strong></td>
<td>Hong Kong Neurosurgical Society Monthly Academic Meeting – ECIC Bypass for Acute Ischemic Stroke: Is it an Evidence Based Option? Organiser: Hong Kong Neurosurgical Society, Chairman: Dr. FOK Kam Fuk, Speaker: Dr. TAM Kwok Kuen, Dennis, Venue: Seminar Room, Ground Floor, Block A, Queen Elizabeth Hospital</td>
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<tr>
<td><strong>1:00 pm</strong></td>
<td>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 Fak Hok Ting Street, Shatin</td>
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<td><strong>12 THU</strong></td>
<td><strong>1:00 pm</strong></td>
<td>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 (元朗尚嘉喜酒家), 1/F, Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long</td>
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<td><strong>19:00 pm</strong></td>
<td>HKMA Structured CME Programme with Hong Kong Sanatorium &amp; Hospital Year 2013 – The Child is not Responding to Sounds Organiser: Hong Kong Medical Association, Hong Kong Sanatorium &amp; Hospital, Speaker: Dr. Au Kin Kwok, Dennis, Venue: HKMA Central Premises</td>
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<tr>
<td><strong>7:00 pm</strong></td>
<td>RSCP Annual General Meeting Organiser: RSCP, HKMA, HKCA, Venue: Kowloon Tong Club</td>
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<td><strong>14 SAT</strong></td>
<td><strong>2:15 pm</strong></td>
<td>HKMA CME – Refresher Course for Health Care Providers 2013/2014 Organisers: Hong Kong Medical Association, HK College of Family Physicians, Chairmen: Dr. CHAN Kam Tim, Michael, Speaker: Dr. TAM Kwok Kuen, Dennis, Venue: Academy Building</td>
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<tr>
<td><strong>15 SUN</strong></td>
<td><strong>8:00 pm</strong></td>
<td>HKMA Tennis Tournament 2013 Organiser: The Hong Kong Medical Association, Chairman: Dr. CHIN Chu Wah, Venue: Kowloon Tong Club</td>
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<td><strong>18 WED</strong></td>
<td><strong>1:00 pm</strong></td>
<td>HKMA Central, Western &amp; Southern Community Network - Overcome the Challenge in Management of AF patients Organiser: HKMA Central, Western &amp; Southern Community Network, Chairman: Dr. POON Man Kay, Speaker: Dr. TSE Tak Sun, Venue: The Hong Kong Medical Association Central Premises, Dr. Li Shui Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong</td>
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<td><strong>1:00 pm</strong></td>
<td>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 (元朗尚嘉喜酒家), 1/F, Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long</td>
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<td><strong>10:00 am</strong></td>
<td>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</td>
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<td><strong>8:00 pm</strong></td>
<td>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</td>
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<td><strong>22 SUN</strong></td>
<td><strong>8:00 pm</strong></td>
<td>HKMA Tennis Tournament 2013 Organiser: The Hong Kong Medical Association, Chairman: Dr. CHIN Chu Wah, Venue: Kowloon Tong Club</td>
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<tr>
<td><strong>31 TUE</strong></td>
<td><strong>7:00 pm</strong></td>
<td>FMSHK Annual Dinner 2013 Organiser: The Hong Kong Medical Association, Venue: Grand Ballroom, Conrad Hong Kong</td>
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<td><strong>8:00 pm</strong></td>
<td>HKMA Annual Ball 2013 Organiser: The Hong Kong Medical Association, Venue: Grand Ballroom, Conrad Hong Kong</td>
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- Proven CV outcomes evidence from landmark trials 1-9
- Efficacious LDL-C lowering 10,11
- Well established renal safety profile in CKD patients 12,13
- NO dosage adjustment in patients with renal impairment 10,14

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