www.fmshk.org

THE HONG KONG MEDICAL DIARY

香 港 醫 訊

VOL.20 NO.12 December 2015

Cardiology

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

BRINTELLIX TAKES CARE OF MORE THAN MOOD

- Brintellix is a new antidepressant with **Multimodal Activity**[1,4]
- Brintellix is efficacious in treating all the symptoms of depression (assessed by MADRS) across a range of patients[2-5]
- Brintellix also significantly improves cognitive performance in depressed patients and reduces the cognitive symptoms of depression[2,9] that affect most patients[6]
  - **These include: concentration difficulties, poor attention, problems with memory and difficulty planning**[6-8]
- Brintellix is well tolerated[4,5,10-12]
- Patients (18-65 yrs) can start, stay and stop on Brintellix 10 mg once daily[4]

References:

1. Bang-Andersen B et al. J Med Chem. 2011; 54(9): 3206-3221. 2. Katona C et al. Int Clin Psychopharmacol. 2012; 27(4): 215-223. 3. Dragheim M, Nielsen R. A randomized, double-blind, study of vortioxetine versus agomelatine in adults with major depressive disorder (MDD) switched after inadequate response to SSRI or SNRI treatment. Poster presented at the 53rd NCDEU meeting, May 28-31, 2013, Hollywood, Florida, USA. 4. Brintellix. Summary of Product Characteristics. 2013. 5. Alvarez E et al. Int J Neuropsychopharmacol. 2012; 15(5): 589-600.. 6. Conradi HJ et al. Psychol Med. 2011; 41: 1165-1174. 7. Hammar A, Ardal G. Front Hum Neurosci. 2009; 3: 26. 8. Marazziti D et al. Eur J Pharmacol. 2010; 626(1): 83-86. 9. McIntyre R, et al. Randomized, double-blind, placebo-controlled study of the efficacy of vortioxetine on cognitive function in adult patients with major depressive disorder (MDD). Poster presented at the 52nd Annual Meeting of the American College of Neuropsychopharmacology (ACNP), December 8-12, 2013, Hollywood, Florida, USA.. 10. Baldwin DS et al. Eur Neuropsychopharmacol. 2012; 22(7): 482-491. 11. Boulenger JP et al. J Psychopharmacol. 2012; 26(11): 1408-1416. 12. Henigsberg N et al. J Clin Psychiatry. 2012; 73(7): 953-959.

Lundbeck

Contents

Scan the QR-code
To read more about
The Federation of Medical
Societies of Hong Kong

Disclaimer

The Cover Shot

Adjacent coves along Dorset coast of England. The outline together with the sea water colour looks like a heart shape from this view. Coves are formed by perfect match of rock strata, river flow and tectonic movements --- just like heart and brain health need concerted risk factors control at the right time.

Dr Kin-lun TSANG
Specialist in Neurology

Published by
The Federation of Medical Societies of Hong Kong

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

Editorial

Dr Bernard BL WONG

MBBS (HK); MRCP (UK); FRCP (Edin); FRCP, RCPS. (Glasg), FHKCP (HK); FHKAM (MEDICINE); DGM (IRELAND); DCH (LONDON)
Specialist in Cardiology

Editor

Dr Bernard BL WONG

I would like to express my thanks to the editorial board and the Federation of the Medical Societies of Hong Kong for once again inviting me to join the family of Hong Kong Medical Diary as editor of this cardiology issue.

This is a great honour for me and my elite team of cardiologists and neurologist. Over the last three and a half years, due to the powerful drive of the free market and the magnificent advances in medical and interventional technologies, numerous important landmark papers, statements and guidelines have been published. Beneficial and practical "changes" to our cardiovascular preventive, medical and interventional guidelines and daily practice continue to be made on a regular basis.

In this issue, once again we have a marvelous team of practical, innovative, experienced, energetic and famous cardiologists and neurologist. Over the last twenty years, all of them, as my dearest friends and mentors, have taught me a huge amount. They are Dr. Chan Charn Fai, Dr. Leung Tat Chi Godwin, Dr. So Yui Chi, Dr. Tsang Kin Lun Alan, Dr. Wong Wai Lun Warren and Dr. Yip Shing Biu Alex.

This issue will cover practical topics of interest to frontline doctors in their daily practice. From the disease relationship between the heart and the brain to dangerous ECG changes, from lipid lowering medical therapeutics to cardiovascular intervention and from heart failure to novel oral anticoagulant management, our aim is to make lives easier, to simplify and update confusing and difficult international statements and guidelines, and to rewrite and summarize them in easy and simple points for our dearest frontline family practice and non-cardiology colleagues.

In the midst of this global financial downturn, terrorism activities, regional military conflicts and mounting social pressure in the Hong Kong Society, if this cardiology issue of the Hong Kong Medical Diary can be of any help to you or your patients in living a healthier, easier or happier life, then our simple wish is fulfilled.

I wish you and your family a Merry Christmas and prosperous, healthy and happy New Year 2016 !

"Nothing in the world can take the place of persistence.
Talent will not; nothing is more common than unsuccessful men with talent.
Genius will not; unrewarded genius is almost a proverb.
Education will not; the world is full of educated derelicts.
Persistence and determination alone are omnipotent."

Ray Kroc (1902-1984),
Founder and Ex-Chairman of McDonalds, who started the miraculous standardized franchise business when he was a fifty year-old milk-shake salesman in 1954'

幸福貸款 - 個人稅務貸款

- 以本行銀行賬戶提取貸款及還款尊享兩個月利息回贈
- 貸款額高達HK$2,000,000或月薪12倍（以較低者為準）
- 豁免提早償還費用，靈活自主
- 14天內免費退還貸款承諾，讓您更安心

查詢詳情，歡迎親臨堅道分行
或致電2973 0219與王小姐聯絡

* 實際年利率乃根據《銀行營運守則》所載之指引及以12個月還款期計算，並已包括兩個月利息回贈（如適用）之優惠。此息率只適用於個別情況，而最終獲批核之息率將視乎貸款額、信貸評級及其他相關審批結果而有所調整。
- 以上優惠須受有關之條款及細則所約束。有關詳情，請參閱宣傳單張上的條款及細則或向本行職員查詢。
- 本行有權隨時更改以上利率及修訂有關貸款條款而毋須另行通知。如有任何爭議，本行保留最終之決定權。

ICBC 工银亚洲

www.icbcasia.com

Use of Direct Oral Anticoagulants and Reversal Agents in Patients with Non-valvular Atrial Fibrillation

Dr Tsan-fai CHAN
MBBS (HK), MRCP (UK), HHKAM (med), FHKCP , FRCP (Glasg)
Specialist in Cardiology

Patients with atrial fibrillation are at increased risk of thromboembolism and stroke. Prescription of oral anticoagulants has been shown to reduce the thromboembolic risk. The availability of clinical scores provides a guide when choosing which subgroup of patients with non-valvular atrial fibrillation will benefit from oral anticoagulants. Traditionally prescribed warfarin is limited by its narrow therapeutic index, potential drug/food interactions and the need for frequent blood checking to monitor clotting profile. At present, the main disadvantage of direct oral anticoagulants is the lack of a reversal agent in the event of significant clinical bleeding. Nonetheless a new reversal agent for one of the direct oral anticoagulants, digabatran, has recently been approved by the Food and Drug Administration (FDA), and has made a significant impact on the management of patients prescribed digabatran who suffer significant clinical bleeding or urgently require surgery.

Atrial fibrillation increases the risk of stroke in patients with or without valvular heart disease. In patients with valvular heart disease, namely mitral stenosis, warfarin is the only anticoagulant indicated for thromboembolism prevention. For patients with non-valvular atrial fibrillation, utilization of the CHA2DS2Vas score[1] guides the use of oral anticoagulants.

C = congestive heart failure (1 point)
H =hypertension (1 point)
A = Age > 75 (2 points) Age = 65- 74 (1 point)
D= Diabetes (1 point)
S= stroke / Transient ischemic attack / Thromboembolism (2 points)
Va=Aortic vascular disease (1 point)
S = Female (1 point)

In patients who score ≥ 2, thromboembolism prevention is indicated in the form of an oral anticoagulant.

Warfarin is the traditional choice but has several disadvantages. First, it has a narrow therapeutic index. It loses its therapeutic efficacy if the achieved INR is too low (< 1.5). The risk of bleeding is high if the INR is too high (> 4). There are substantial risks associated with internal bleeding, namely gastrointestinal and intracranial bleeding.

Secondly, there are potential drug / food interactions with warfarin therapy. Despite education, many patients do not comply with the warfarin diet. Many Chinese elderly still perceive herbal medications/ supplements to be harmless and concomitant warfarin therapy a potential threat. Finally, because of the narrow therapeutic index, frequent blood sampling is required to monitor INR.

The development and approval of direct oral anticoagulants as a therapeutic agent in non-valvular atrial fibrillation has enabled the problems with warfarin to be avoided. Four such agents are available and currently marketed in Hong Kong.

Dabigatran is a thrombin (factor II) inhibitor and the first direct oral anticoagulant available. The remaining three are factor Xa inhibitors: apixapan, edoxaban and rivaroxaban. Edoxaban is not yet marketed in Hong Kong but will soon be available.

All of these oral anticoagulants have advantages over warfarin, including a more rapid onset of action, a wider therapeutic window and less hemorrhagic complications[2]. They can be prescribed at a fixed dose without the need for blood level monitoring. The potential for drug/ food interactions is also much less compared with warfarin. Although direct comparisons have not been made, these new agents have been proven to be no less effective than dose-adjusted warfarin for prevention and treatment of thromboembolism.

A reduced dose regimen is available for dabigatran and apixaban that enables them to be prescribed to moderate patients with moderate renal impairment, but both agents need to be taken as a bd dose. Rivaroxaban can be taken as a single daily dose so compliance is improved.

Despite the advantages of direct oral anticoagulants over warfarin, the lack of specific reversal agents available for market use is a potential clinical concern. This applies particularly when a patient has severe clinical bleeding or when the patient requires rapid reversal of anticoagulant effect if urgent surgery is required. The cost for direct oral anticoagulants compared with warfarin is also much higher.

In patients prescribed warfarin therapy, the anticoagulant effect can be reversed by fresh frozen plasma or intravenous vitamin K.

Reversal agents for direct anticoagulants
Idarucizumab (Praxbind) is a humanized monoclonal anti-body fragment with high affinity for dabigatran that selectively and immediately reverses its anticoagulant

effect. It has a binding affinity that is around 350 x higher than dabigatran to thrombin and it binds free and thrombin-bound dabigatran[3]. It competitively inhibits the effect of dabigatran on thrombin. In a clinical study[4] the anticoagulant effect of dabigatran was completely reversed in 88- 98 % of patients after a bolus intravenous dose of 5 g Praxbind and there was immediate onset of action without any evidence of drug related adverse events or immunogenic reactions. It is indicated in patients prescribed dabigatran who develop serious bleeding or need for urgent surgery.

Praxbind was approved by the FDA in October 2015 for clinical use and should be available for clinical use in Hong Kong when this article is published.

In the case of other factor Xa antagonists, a reversal agent andexanet alpha, a recombinant factor Xa variant that specifically binds the Xa inhibitors, is in clinical development[5]. This agent also lacks coagulant activity and and will hopefully be available for clinical use in 1 -2 years.

In addition to these competitive inhibitors, a non-specific reversal agent that binds to the direct oral anticoagulant by electrostatic interactions, PER977, is also in clinical development[6].

In conclusion, the availability of direct oral anticoagulants improves the safety of patients who require oral anticoagulants. The novel reversal agent for dabigatran (Praxbind) will be of clinical benefit.

References

1. January CT etal American College of Cardiology / American Heart Association. Task Force on Practice Guidelines, 2014 AHA/ ACC/HRS guideline for the management of patients with AF : a report of the American College of Cardiology / American Heart association Task Force on Guidelines and the Heart rhythm society. J Am Coll Cardiol. 2014 Dec., 2 ,64 (21) : e1- 76
2. Chai-Adisaksophia C et al The impact of bleeding complications in patients receiving target specific oral anticoagulants : a systematic review and meta-analysis. Blood 2014 : 124 : 2450-8
3. Schiele F et al. A specific anti-dote for dabigatran : functional and structural characterization. Blood 2313 : 1 25 : 3554- 6
4. Idarucizumab for dabigatran reversal . Charles V Pollack et al June 22, 2025. New England Journal of medicine
5. Lu G et al. A specific antidote for reversal of anticoagulant by direct and indirect inhibitors of coagulation factor Xa. Nat med. 2013 : 19 : 446-51.
6. Ansell JE et al. Use of PER 977 to reverse the anticoagulant effect of edoxaban. New Eng J med 2014 ; 371 : 2141-2

- Decrease frequency of angina attacks[3,4]
- Reduce severity of angina[5]
- Improve quality of life[5] with increased exercise duration[3,6]

Discover Ranexa®. The Innovative Agent for Symptomatic Treatment In Chronic Stable Angina.[1,7]

Ranexa
ranolazine

References: 1. Hasenfuss G, Maier LS. Cir Res Cardiol 2005;97:222-226. 2. Venkatachalam K, et al. J Am Coll Cardiol 2009; 3: 1301-1309. 3. Chaitman BR, et al. JAMA 2004;291:309-316. 4. Stone PH, et al. J Am Coll Cardiol 2006;48:566-575. 5. Mehlsen J, et al. Drugs R D 2011;11:267-273. 6. Chaitman BR, et al. J Am Coll Cardiol 2004;43:1375-1382. 7. Belardinelli L, et al. Eur Heart J Suppl 2004;6(Suppl B):B3-17.

PRINCESS CRUISES
come back new

Final 50th Anniversary Promotion

Selected Singapore & Japan Sailings
on balcony or above staterooms

- Enjoy **50% Off** Discount
- Free Upper Berths

- Promotion ends at 31December2015 -

- Non-refundable deposit promotion.
- Do not combine with any other offer.

PRINCESS CRUISES

Scan here to learn more details!

Don't hesitate to come onboard with your loved ones!

Singapore

3/4 Days Malaysia
Sapphire Princess - 11Dec*, 14Dec2015

Singapore | Penang, Malaysia | Langkawi, Malaysia | Kuala Lumpur (Port Kelang), Malaysia | Singapore

Balcony	Mini Suite	Suite
~~HKD6,233up~~	~~HKD8,417up~~	~~HKD13,253up~~
HKD2,723up	HKD3,893up	HKD6,623up

* This is a 3days sailing and will not call to Langkawi, Malaysia.

7 Days Vietnam & Thailand
Sapphire Princess - 7Feb2016

Singapore | Ko Samui, Thailand | Bangkok (Laem Chabang), Thailand | Ho Chi Minh City (Phu My), Vietnam | Singapore

Balcony	Mini Suite	Suite
~~HKD12,863up~~	~~HKD15,203up~~	~~HKD23,393up~~
HKD6,428up	HKD7,598up	HKD11,693up

Japan

8 Days Taiwan & Kyushu
Diamond Princess - 8May2016

Kobe, Japan | Kagoshima, Japan | Taipei (Keelung), Taiwan | Kaohsiung, Taiwan | Hualien, Taiwan | Kobe, Japan

Balcony	Mini Suite	Suite
~~HKD15,593up~~	~~HKD21,053up~~	~~HKD36,263up~~
HKD7,793up	HKD10,523up	HKD18,135up

11 Days Circle Hokkaido
Diamond Princess - 30May2016

Kobe, Japan | Hakodate, Japan | Sapporo (Muroran), Japan | Kushiro, Japan | Shiretoko Peninsula (Scenic Cruising), Japan | Korsakov, Russia | Otaru, Japan | Aomori, Japan | Kobe, Japan

Balcony	Mini Suite	Suite
~~HKD22,223up~~	~~HKD29,633up~~	~~HKD50,303up~~
HKD11,111up	HKD14,816up	HKD25,151up



PRINCESS CRUISES
come back new

2952 8079
www.princess.com

Suite 1207, Tower 1, The Gateway, Harbour City
25 Canton Road, Kowloon, Hong Kong

Choices of Coronary Artery Stent

Dr Godwin TC LEUNG

FRCP, FACC
Specialist in Cardiology

Dr Godwin TC LEUNG

Percutaneous coronary intervention (PCI) has become one of the most frequently performed therapeutic procedures in medicine. Drug eluting stents (DES) with controlled release of antiproliferative agents have reduced the risk of restenosis and repeat revascularization, compared with the bare metal stent (BMS). Nonetheless DES have their own limitations, including risk of late stent thrombosis. The development of late adverse events may be related to impaired endothelialization, stent fracture, neoatherosclerosis and chronic inflammatory response to the metallic material or the non-absorbable polymer. Patents are required to take dual anti-platelet therapy (DAPT) for a prolonged period of time (usually for at least 12 months) after DES implantation to prevent stent thrombosis and therefore are at increased risk of bleeding complications. New platforms and drugs for DES that are aimed at improving safety and efficacy have been developed. A few recent clinical trials on the use of DES are reviewed in this article.

Patients at high risk of bleeding

Patients at high risk of bleeding who undergo PCI often receive BMS followed by 1 month of DAPT or a second-generation DES with a shortened course of DAPT. This also applies to patients who have elective non-cardiac surgery that requires interruption of DAPT within 12 months of PCI. A polymer-free and carrier-free drug-coated stent has been developed that transfers umirolimus (also known as biolimus A9), a highly lipophilic sirolimus analogue, into the vessel wall over a period of 1 month. A study has been published recently on the use of this type of DES involving 2466 patients[1]. In this randomized, double-blind trial, this type of DES was compared with a very similar BMS in patients with a high risk of bleeding who underwent PCI. All patients received just 1 month of DAPT. At 390 days, the primary safety end point (composite of cardiac death, myocardial infarction, or stent thrombosis) had occurred in 112 patients (9.4%) in the DES group and in 154 patients (12.9%) in the BMS group (risk difference, −3.6 percentage points; 95% confidence interval [CI], −6.1 to −1.0; hazard ratio, 0.71; 95% CI, 0.56 to 0.91; P<0.001 for non-inferiority and P=0.005 for superiority). During the same time period, clinically driven target-lesion revascularization was required in 59 patients (5.1%) in the DES group and in 113 patients (9.8%) in the BMS group (risk difference, −4.8 percentage points; 95% CI, −6.9 to −2.6; hazard ratio, 0.50; 95% CI, 0.37 to 0.69; P<0.001). In conclusion, among patients at high risk of bleeding who underwent PCI, a polymer-free umirolimus-coated stent was superior to a BMS with respect to the primary safety and efficacy end points when used with a 1-month course of DAPT.

Bioresorbable Vascular Scaffolds

Stents that are fully bioresorbable have been developed to provide mechanical support and drug-delivery functions, followed by complete bioresorption over several years. The use of BVS may prevent many of the limitations of metallic stents and the artery has the potential to restore its native vasomotor function. Because these novel devices are not metallic stents and are expected to leave no permanent material within the vessel, they have been termed "bioresorbable vascular scaffolds". The first fully absorbable scaffold (Absorb Bioresorbable Vascular Scaffold, BVS) is made of Poly-L-lactic acid (PLLA), a biocompatible material commonly used in medical implants such as resorbable sutures. The anti-proliferative drug used is everolimus. The scaffold is hydrolyzed and degraded into lactic acid and further metabolized into carbon dioxide and water. It can be completely resorbed after 2 to 3 years. The ABSORB III study has shown that treatment of noncomplex obstructive coronary artery disease with BVS was non-inferior to second generation DES, with respect to target-lesion failure at 1 year[2]. This large, multicenter, randomized trial enrolled 2008 patients with stable or unstable angina to receive a BVS or an everolimus-eluting cobalt–chromium stent. Target-lesion failure at 1 year occurred in 7.8% of patients in the BVS group and in 6.1% of patients in the DES group (difference, 1.7 percentage points; 95% confidence interval, −0.5 to 3.9; P=0.007 for non-inferiority and P=0.16 for superiority). There was no significant difference between the BVS group and the DES group in rate of cardiac death (0.6% and 0.1%, respectively; P=0.29), target-vessel myocardial infarction (6.0% and 4.6%, respectively; P=0.18), or ischemia-driven target-lesion revascularization (3.0% and 2.5%, respectively; P=0.50). Device thrombosis within 1 year occurred in 1.5% of patients in the BVS group and in 0.7% of patients in the DES group (P=0.13).

Patients with Diabetes Mellitus

Patients with diabetes mellitus (DM) have a higher risk of restenosis and repeat revascularization. The choice of DES in the treatment of patients with DM and coronary artery disease who are undergoing PCI has been debated. Previous studies that compared paclitaxel-eluting stents(PES) with stents eluting sirolimus or its analogues (everolimus or zotarolimus) produced contradictory results, ranging from equivalence between stent types to superiority of everolimus-eluting stents

(EES). A recent study involved 1830 patients with DM and coronary artery disease who underwent PCI and received either a PES or an EES[3]. The primary end point was target-vessel failure, defined as a composite of cardiac death, target-vessel myocardial infarction, or ischemia-driven target-vessel revascularization at 1-year follow-up. At 1 year, PES did not meet the criterion for non-inferiority to EES with respect to the primary end point (rate of target-vessel failure, 5.6% vs. 2.9%; risk difference, 2.7 percentage points [95% confidence interval, 0.8 to 4.5]; relative risk, 1.89 [95% confidence interval, 1.20 to 2.99]; P=0.38 for non-inferiority). There was a significantly higher 1-year rate in the PES group than in the EES group of target-vessel failure (P=0.005), spontaneous myocardial infarction (3.2% vs. 1.2%, P=0.004), stent thrombosis (2.1% vs. 0.4%, P=0.002), target-vessel revascularization (3.4% vs. 1.2%, P=0.002), and target-lesion revascularization (3.4% vs. 1.2%, P=0.002). In summary, in patients with DM and coronary artery disease who underwent PCI, PES were not non-inferior to EES, and resulted in higher rates of target-vessel failure, myocardial infarction, stent thrombosis, and target-vessel revascularization at 1 year.

Dual therapy stent

The dual therapy stent (DTS) is designed to repair vessel injury, regenerate the endothelium and foster natural vessel healing by accelerating endothelial coverage and controlling neo-intimal proliferation through a combination of luminal endothelial progenitor cell (EPC) capture technology and abluminal sirolimus drug elution, delivered from a bioresorbable polymer. The stent comprises a luminal CD 34 antibody surface coating that captures EPCs circulating in the blood to the stent to form an endothelial layer that provides protection against thrombosis and modulates restenosis. In the randomized REMEDEE study (Randomized study to Evaluate the safety and effectiveness of an abluminal sirolimus coated bio-engineered Stent trial)[4] , the DTS showed similar angiographic and clinical outcomes to the paclitaxel-eluting stent (PES). The DTS was found to be non-inferior to the PES in 9-month angiographic in-stent late lumen loss, 0.39 ± 0.45 mm versus 0.44 ± 0.56 mm (p noninferiority = 0.0012). At 12 months, the occurrence of major adverse cardiac events was 8.9% in the DTS group and 10.2% in the PES group (p = 0.80) with no difference in mortality, occurrence of myocardial infarction, or target lesion revascularization. No stent thrombosis was reported in either group. One-year clinical outcome from the one-thousand patient REMEDEE Registry was presented during the annual Transcatheter Cardiovascular Therapeutics annual meeting this year. The REMEDEE Registry is designed to evaluate the DTS for the treatment of coronary lesions in the routine clinical care setting. The registry's primary endpoint of one-year target lesion failure was reported as 5.7%, The individual cardiac event rates reported were 1.7% cardiac death, 0.7% myocardial infarction, and 4.4% ischemia driven target lesion revascularization. The registry also showed a very low stent thrombosis rate of 0.6%. There was no incidence of late stent thrombosis; all thrombotic events occurred within the first 9 days of implantation.

Conclusion

Coronary stents are an essential component of PCI. This article has only reviewed a few clinical trials and is by no means exhaustive. In addition, many new coronary stents with new design are being developed. There is no doubt that improvement in stent technology and drugs will continue and will benefit more high risk patients, such as those with DM or high risk of bleeding. Limitations of coronary stents will be resolved and patients and doctors will have more choices.

References

1. Urban P, Meredith IT, Abizard A, et al. Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk. N Eng J Med 2015;DOI:10.1056/NEJMoa1503943
2. Ellis S, Kereiakes D, Metzger DC, et al. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. N Eng J Med 2015;DOI:10.1056/NEJMoa1509038.
3. Kaul U, Bangalore S, Seth A, et al. Paclitaxel-Eluting versus Everolimus-Eluting Coronary Stents in Diabetes. N Eng J Med 2015;373:1709-1719.
4. Haude M, Lee SW, Worthley SG, et al. The REMEDEE trial: a randomized comparison of a combination sirolimus-eluting endothelial progenitor cell capture stent with a paclitaxel-eluting stent. JACC Cardiovasc Interv. 2013 Apr;6(4):334-43

ECG Abnormalities – Fatal Encounter

Dr Yui-chi SO

MBBS (HK) MRCP (UK.,IRE).FRCP(Edin).FACC.FHKCP
Cardiologist

Dr Yui-chi SO

Hundreds of ECGs are performed every month and historically, the vast majority have been considered normal. Nonetheless with developments in knowledge, many ECGs are now considered not quite so "benign". This article hopes to enlighten the reader about the "abnormalities" that are now detected.

PR interval

Prolonged – If the PR interval exceeds 200 ms , it is considered to indicate Primary Heart Block. A progressive increase in PR interval is termed Type IIa Wenkebach heart block. In the absence of hemodynamic compromise, reassurance and observation is all that is required. It commonly presents in the very young patient, especially athletes, and the elderly where vagal tone is high.
Shortened – PR interval <120 ms. It is important to determine the presence of delta wave. An ECG in Wolff-Parkinsion White syndrome will show a shortened PR interval as the atrial pulse travels down the fast track of accessory pathway.
Previously, a term known as fast accelerated atriohisian tract causing a short PR interval was known as Lown-Ganong-Levine syndrome. It was considered benign although some questioned its existence.
Another common cause of short PR is junctional rhythm that may have an isorhythmic P-QRS phenomenon.

QT interval

Prolonged – a QTc interval that exceeds 460 ms is considered prolonged and is due to prolonged myocyte repolarization: for males 350-450 ms and for females 360-460 ms. QTc = QT/ (RR/1000) square root. Prolonged QT predisposes the patient to Torsades de Pointes, as evidenced by a long-short-long sequence. It may cause VF and ultimately sudden cardiac death. At least ten distinct types of mutations including Na, K and Ca channel ions across the cell membrane have been identified. The QT interval usually shows dynamic change i.e .normal in one ECG but maybe prolonged in another.

The average age at presentation is 30 yrs old.
High risk cases include patients with:-
1. Hx of aborted sudden cardiac death
2. QTc >530 ms
3. Syncopy
4. Family history of sudden cardiac death.
5. Symptoms presenting in the first year of life.

One specific form of long QT is **Brugada Sx**:-
Transmission is autosomal dominant and the most common type is due to Na channel SCN5A mutation. SCNA5A mutations account for 20-30 % of clinically diagnosed cases of Brugada Sx. ECG is characterized by a raised ST segment in the right precordial leads. Type 1 ECG is diagnostic with 2 mm ST segment coved shaped elevations. Type 2-3 is saddle shaped with or without ST segment elevation. It is thought to be due to a transient outward K current that is greater in the epicardium than the endocardium. Fever can inactivate SCN5A that may cause VF.
Provocative tests can be performed using Na blocking agents such as :- Procainamide 10 mg/kg IV over 10 min; or Fleicnide 2 mg/kg IV over 10 min. If intravenous access is unavailable, a single oral dose of Fleicanide 400 mg can be given.
Treatment:-
β blocker; ICD implantation; Left sympathetic ganglia denervation.

Short QT

A QTc interval <360 ms should be considered abnormal. The prevalence of QT <320 ms is 0.08% and the prevalence <340 ms is 0.3%. It is usually inherited with a high incidence of VF during childhood. It is usually due to a gain in function of K channels and is more common in men.
Treatment is ICD implantation.

Early Repolarization Syndrome:-

Tall T waves that are usually detected in the precordial leads of the young is generally benign. It is considered to be early repolarization if there is J point elevation > 2mm in more than two contiguous leads.

J point is due to a transient outward current in the epicardium but not the endocardium. Prominence of the J wave and resultant VF are bradycardia dependent. High risk individuals are those with J point elevation over inferior, lateral and even global leads. ST segment elevation with a horizontal and descending trend has a poor prognosis. All these features predispose the patient to idiopathic VF. The incidence of asymptomatic young adults with early repolarization is estimated to be 1:3000 in the general population. Among survivors of idiopathic VF, early repolarization is six times more frequent than in a control group. Surviving patients with early repolarization have double the chance of recurrent VF.

CPVT Catecholamine Polymorphic VT:-

This is another form of life threatening polymorphic VT that may be encountered during treadmill testing. The patient has a normal ECG at rest but stress testing reveals polymorphic VT and bidirectional VT can also be seen. It is genetically determined and occurs in the presence of normal heart structure and normal QTc. It is related to chromosome 1 with mutation of the cardiac ryanodine receptor gene (RyR2) that controls Ca ion influx.

The mean age of onset is 8 years old although the first syncopy may not present until adulthood. > 60 % of patients experience their firstt syncopy or cardiac arrest by age 20. It can cause sudden cardiac arrest and VF in young adults. Some presentations may be mistaken for epilepsy since prolonged time of hemodynamic compromise may cause twitching. DAD-triggered activity is thought to be the underlying mechanism.

Treatment:-

Emergency treatment involves an IV push of β blocker and later consideration of ICD implantation.

QRS Duration:-

A duration the exceeds 120 ms for the QRS complex is considered abnormal. The electrical impulse either goes through the bundle branches with block or just goes through the ventricular myocytes without going through the bundle branch-Purkinjie system. i.e. VT circuit.

T wave Morphology

Many different forms of T wave change are encountered, most of which are considered "non- specific". T wave has diverse morphology due to numerous causes:- structural; genetic; metabolic; autonomic; psychological; drug induced. Therefore the T wave may demonstrate dynamic changes in the same patient! The duration of the T wave signifies ventricular repolarization and corresponds to closure of the aortic valve. One variant of T wave that may have pathological significance is the "hyperacute T wave with peak" in the presence of myocardial infarction or long QT Sx. All other forms of T wave are rather "non-specific" and should be interpreted in the context of the whole clinical picture.

U wave

This follows the T wave during the normal relaxation phase of cardiac muscle and begins with the second heart sound. It is usually positive and seldom exceeds 0.2 mV. The T-U interval is rate independent. The origin of the U wave is controversial. It has been speculated to be stretch induced DAD during diastole. It is also non-specific when detected. Nonetheless it never merges with the T wave, thus a coved or bifid T wave is T wave, not U wave, pathology. Negative U wave may signify underlying cardiac pathology or drug toxicity eg. Digoxin.

Conclusion

When interpreting an ECG, care should be taken to examine the intervals and compare serial changes to identify any difference. When the ECG is highly suspicious of arrhythmia, closely supervised treadmill testing may be conducted to detect any significant dynamic interval changes that are VT/VF induced. Further consultation with an electrophysiolgist may be necessary in doubtful cases since a **structurally normal heart may not be as "normal" as it appears**!

References

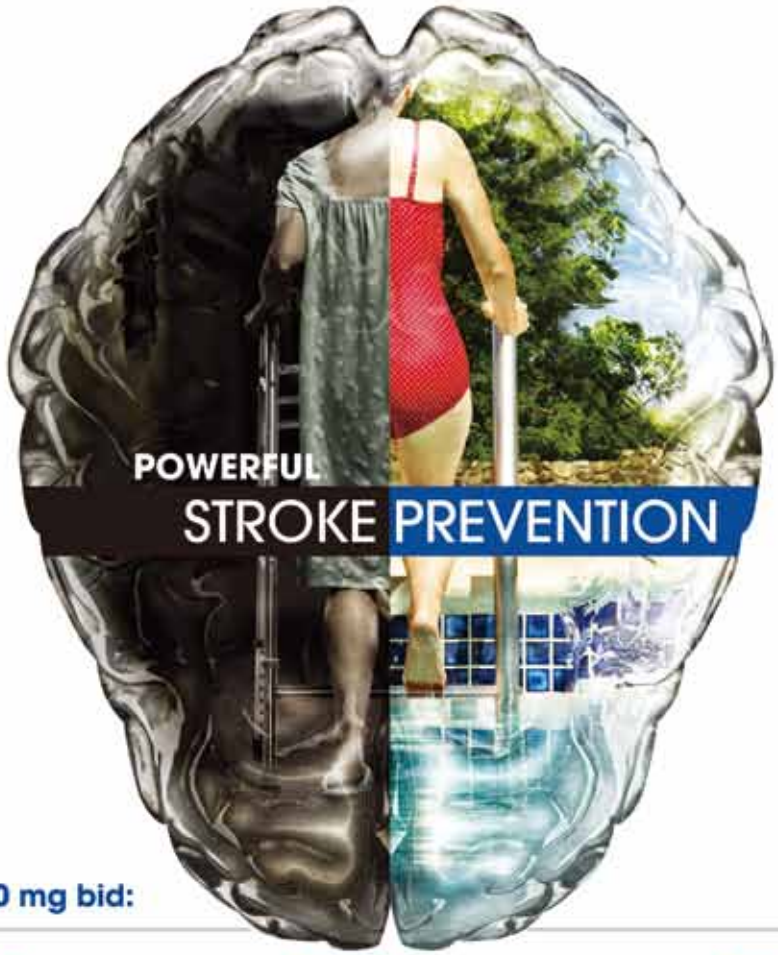
1. Topilski I, Ross R,Third author required? et al. The morphology of the QT interval predicts TdP during acquired bradyarrhythmias. J Am.Coll.Cardiol. 2007;49(3):320-328
2. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA. 2004-292(11):1341-1344
3. Anttonen O, Junttila MJ, Naury P, et al. Differences in 12 lead ECG between symptomatic and asymptomatic subjects with short QT interval. Heart Rhythm. 2009;6(2):267-271
4. Brugada P, Brugada J. RBBB, persistent ST segment elevation and sudden cardiac death: a distinct clinical and ECG Sx. A multicenter report. J. Am. Coll. Cardiol. 1992;20 (6):1391-1396.
5. First letter missing? ang K, Asinger RW, Marriott HJL. ST – segment elevation in conditions other than AMI. N. Engl.J.Med 2003;349(22):2128-2135
6. Tikkanen JT, Anttonen O, Junttila MJ, et al. Long term outcome associted with early repolarization on ECG. N. Engl. J.Med.2009;361(260:2529-2537
7. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N. Engl. J.Med.2008;358(19):2016-2023
8. Ylanen K, PoutanenT, Hippala A, Swan H, Korpi M. Catecholaminergic polymorphic VT. Eur.J. Pediatr 2010;169(5):535-542.
9. Kreating MT. The long QT Sx. A review of recent molecular genetic and physiological discoveries. Medicine (Baltimore).1996;75(1):1-5.
10. Prori SG. Inherited arrhythmogenic diseases: the complexity beyond monogenetic disorders. Circ.Res. 2004;94(2):140-145.

PRADAXA®

THE ONLY ANTICOAGULANT

NO INR monitoring[1]

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



PRADAXA 150 mg bid:

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

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

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

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

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

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

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

Pradaxa® 百達生®
dabigatran etexilate

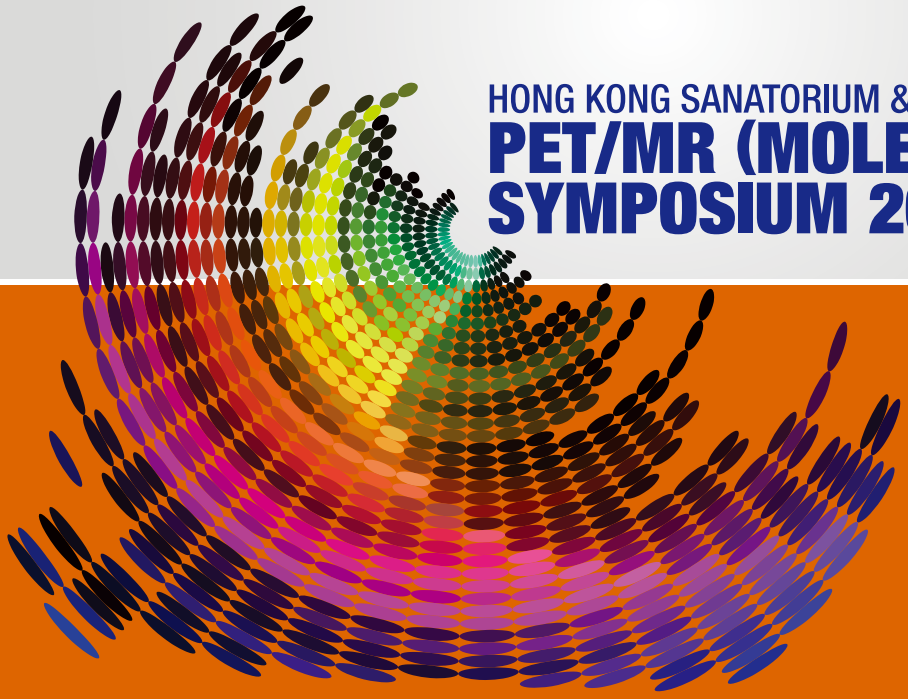
Simply superior stroke prevention

Boehringer Ingelheim

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

www.pradaxa.com

PRA-04-2013-03



HONG KONG SANATORIUM & HOSPITAL

PET/MR (MOLECULAR MR) SYMPOSIUM 2015

DATE 15 December 2015 (Tuesday)
TIME 18:00 – 22:30
VENUE Ballroom, JW Marriott Hotel Hong Kong

PROGRAMME

18:00	Cocktail	
19:00	Introduction	
19:05 – 19:40	**PET/MR Clinical Use in Whole-body Oncology**	Prof. PD Dr. med. Lale UMUTLU Vice Chair, Department of Diagnostic and Interventional Radiology and Neuroradiology University Hospital Essen, Germany
19:40 – 20:15	**Application of the mMR to Pediatrics and the Neurosciences**	Prof. Robert C MCKINSTRY, MD, PhD, FACR. Professor of Radiology and Pediatrics, Washington University in St. Louis, USA
20:15 – 20:30	Q&A	
20:30 – 22:30	Dinner	

Chairpersons:
- Dr. Gladys LO, Head, Department of Diagnostic & Interventional Radiology
- Dr. Garrett HO, Department of Nuclear Medicine & Positron Emission Tomography

FOR MEDICAL PRACTITIONERS ONLY CME Accreditation by Various Colleges (Pending)

ENQUIRIES (852) 2835 3460 / 2835 3461

ONLINE REGISTRATION www.hksh-hospital.com/petmr-registration

REGISTRATION IS ON A FIRST COME, FIRST SERVED BASIS

SPONSORED BY SIEMENS HEALTHCARE SIEMENS

What is the Optimal Duration for Dual Anti-Platelet Therapy (DAPT) ?

Dr Warren WL WONG

MBChB (CUHK), FRCP (Edin), FHKCP, FHKAM (Medicine), MPH (Johns Hopkins)

Consultant, Specialist in Cardiology

Dr Warren WL WONG

Introduction

Dual Anti-Platelet Therapy (DAPT) is prescribed in acute coronary syndrome and for patients undergoing percutaneous coronary intervention. The optimal duration of such therapy is nonetheless unclear. It is generally believed that the shortest duration possible is ideal since the risk of bleeding is minimised. The important factors that determine length of therapy have not been determined.

International guidelines advise continuation of DAPT for 12 months following ACS ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and stable angina, based on randomized clinical trial data. Thus 12 months of DAPT as a minimum is advised based on quite solid and evidence-based data.[1,2]

What did the trials tell us?

The CURE trial in 2001[3] showed that clopidogrel for 3 to 12 months was beneficial in patients with acute coronary syndrome without ST elevation but there was an increased risk of bleeding. TRITON[4] in 2007 extended the study to 15 months in patients with ACS scheduled to undergo PCI, and showed that prasugrel reduced ischemic events but also increased the risk of bleeding, including fatal bleeding. There was no effect on overall mortality. PLATO[5] in 2009 advised up to 12 months therapy, and compared ticagrelor with clopidogrel. In patients with ACS, ticagrelor reduced mortality from vascular causes, myocardial infarction or stroke but increased the rate of non-procedure related bleeding.

Physicians thus have to balance the risks and benefits of therapy, especially with the more potent drugs since longer duration of DAPT equates to a higher risk of bleeding.

When bleeding occurs, it is more common and of larger magnitude early on during the treatment period. If a patient has a major gastrointestinal bleed because of gastric ulcer, it is more likely to occur soon after commencement of DAPT. The risk of bleeding generally recedes over time. If a patient does not have a bleeding episode during the first 12 months, the risk of bleeding thereafter should be less. Nonetheless it is difficult to predict the likelihood of bleeding in subsequent months when a patient is first prescribed DAPT.

The CHARISMA trial in 2006 suggested that clopidogrel was beneficial in patients with symptomatic atherothrombosis but harmful in those with multiple risk factors.[6] Overall, there was no difference in the reduction in myocardial infarction, stroke or death from cardiovascular causes. It is one of the few trials where therapy has continued beyond 12 months, with a median of 28 months. Bleeding risk was low for clopidogrel and the incremental risk over the low baseline risk with aspirin was rather small after about 6 to 9 months. This was encouraging if continuation of DAPT was planned. Although the risk associated with clopidogrel appears to be low, it may not be so for the more potent prasugrel or ticagrelor.

TRILOGY ACS in 2012 showed that among patients with unstable angina or myocardial infarction without ST elevation, prasugrel had no difference in the effect and bleeding when compared with clopidogrel with a treatment up to 30 months (median follow up of 17 months).[7]

In CHARISMA, the overall trial was neutral or negative, but in the subgroup of patients with prior ischemic events, there appeared to be some benefit in those with prior STEMI or NSTEMI. All these indirect subgroup data support a potential additional benefit of treatment longer than a year in patients with ACS or high risk of thrombosis.

The PEGASUS trial in 2015 studied the potential benefits and bleeding risks of ticagrelor.[8] With a median follow up of 33 months, it showed that in patients with myocardial infarction more than 1 year ago, ticagrelor reduced the risk of cardiovascular death, myocardial infarction and stroke, but increased the risk of major bleeding. In the study, high risks patients included those aged ≥ 50 years, diabetics, and those with a prior myocardial infarct > 1 year ago, multi-vessel CAD or renal impairment with CrCl < 60ml/min. Patients with a higher bleeding risk were excluded and included those with bleeding disorder, history if ischemic stroke or haemorrhage, CNS tumor or vascular abnormality, recent GI bleed or major surgery, on dialysis or with severe liver disease.

Some medium sized trials have examined different treatment durations for DAPT. The major limitation of all these trials is that they were underpowered. None found a benefit of continuing DAPT in stable patients with stents, and all identified an increased risk of bleeding with the risk of major bleeding doubled in some cases. Another limitation was the different definitions of bleeding although even those that applied

the Bleeding Academic Research Consortium (BARC) definition reported a doubling in the rate of BARC-defined bleeding.

The DAPT trial is an important study. It studied the effect of extended DAPT for a further 18 months beyond the standard 12 months treatment in patients with coronary stenting. There was a reduction in stent thrombosis, major cardiovascular and cerebrovascular events, but once again, an increased risk of bleeding.[9]

So in high risk patients with ACS, extended DAPT may offer clinical benefit although the consequence is an excessive risk of bleeding. In patients who undergo PCI, the stent is another determinant of benefit in extended dual antiplatelet therapy. It is clear that second-generation drug-eluting stents (DES) have a much lower rate of stent thrombosis than first-generation DES, and probably also a lower rate of stent thrombosis than bare metal stents (BMS).

The EXAMINATION trial in 2014 showed that in the setting of STEMI with a second-generation DES, there was less stent thrombosis after 2 years follow-up compared with that with BMS.[10]

For stable patients in the OPTIMIZE trial, patients were randomized to second-generation DES with either 3 or 12 months of DAPT. With more than 3000 patients, it showed that 3 months of DAPT was not inferior to 12 months and there was no significant increase in risk of stent thrombosis.[11] It provided some reassurance in the event DAPT is stopped prematurely, for example patients who develop bleeding or who require urgent surgery. It provided some rationale and at least some guidance on the safety parameters for early discontinuation or interruption of DAPT.

The PARIS registry in 2013 had more than 5000 patients.[12] It showed that DAPT discontinuation mattered most when it was within 30 days, and even worse when stopped within 7 days. Nonetheless when treatment was stopped on the doctor's recommendation, it did not appear to be associated with any adverse outcomes.

Discussion

There are many different factors that can modify the benefit to risk ratio. If a patient has stable angina and single-vessel disease with a single DES, the risk of stent thrombosis with a second-generation DES is quite low, and the rate of ischemic events is also low, provided other risk factors are well controlled. Such a patient would have very different long-term potential risks and benefits from DAPT when compared with, for example a DM patient with a large STEMI who continues to smoke.

More trials are needed to determine whether DAPT can be shortened with the use of bio-absorbable stents. For the current second-generation DES, registry data and some randomized clinical trials suggest that shorter duration of DAPT is not necessarily associated with a catastrophic outcome and does not lead to excessive ischemic or thrombotic events.

It is also unclear whether treatment is targeted at just the coronary lesion with the stent, or the whole vascular tree. The longer trials like CHARISMA, TRILOGY ACS, and the PEGASUS suggested possible long-term benefit, perhaps indicating that we are treating the entire patient.

For an extended course of DAPT, clopidogrel and aspirin can be used: it is cheaper and they can be combined into one tablet that may improve drug compliance. The safety profile from the CHARISMA showed that there was some excess bleeding risk although it did not appear excessive. Ticagrelor can also be used, especially when different dosages are required such as 60mg BD and 90mg BD, and more evidence is becoming available about the safety and efficacy of its prolonged use.

For PCI patients, extended DAPT can be prescribed for those who receive intracoronary radiation or brachytherapy for restenosis, as well as those with complex stenting procedures and lots of overlapping or bifurcation stents, especially first-generation DES. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) can be used to assess opposition and avoid mechanical problems such as under-deployed stents that may increase the risk of stent thrombosis.

It is important to realize what guidelines want to achieve: a uniform approach to a certain disease. But there are so many factors to consider. At times, the physician must look beyond the overall trial and realize there are different subsets and subgroups. In reality, patients have many kinds of ischemic and bleeding risks that may not have been well-represented in the trials.

Conclusion:

It is vital that physicians continue to interpret trial data cautiously, with treatment decisions made on an individual patient basis. It is almost impossible to find a one-size-fit-all guideline if the best benefit to risk ratio is to be achieved for individual patients. To achieve the largest benefit to risk ratio, the patient's bleeding risk must be assessed as well as their thrombotic risk. Other risk factors of atherosclerotic disease such as blood pressure, Hba1c, LDL must also be under optimal control and the need for smoking cessation must be reinforced. For PCI patients, stents should be correctly sized, and properly deployed with good opposition. Left main, triple vessel disease, bifurcation lesion, and suboptimal revascularization may indicate a higher thrombotic risk and influence the decision for prolongation of DAPT. Clinical symptom and functional assessment, such as stress MRI-heart, can also be used to assess any residual ischemia before stopping DAPT.

References

1. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Kolh P, et al. Guidelines on Myocardial Revascularization. Eur Heart J. 2010;20:2501-2555.
2. 2.Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124:e574-e651.

3. Mehta S, Yusuf S, Peters RJ, et al; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358:527-533.
4. Wiviott S, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001-2015.
5. Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045-1057.
6. Bhatt DL, Fox KA, Hacke W, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354:1706-1717.
7. Roe MT, Armstrong PW, Fox KA, et al; TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med. 2012;367:1297-1309.
8. Prevention of Cardiovascular Events (eg, Death From Heart or Vascular Disease, Heart Attack, or Stroke) in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS). NCT01225562.
9. Randomized, Open Label Trial of 6 Months Versus 12 Months DAPT After Drug-Eluting Stent in STEMI (DAPT-STEMI). NCT01459627.
10. Pfisterer M, Bertel O, Bonetti PO, et al; BASKET-PROVE Investigators. Drug-eluting or bare-metal stents for large coronary vessel stenting? The BASKET-PROVE (PROspective Validation Examination) trial: study protocol and design. Am Heart J. 2008;155:609-614.
11. Feres F, Costa RA, Abizaid A, et al; for the OPTIMIZE Trial Investigators. Three vs Twelve Months of Dual Antiplatelet Therapy After Zotarolimus-Eluting Stents: The OPTIMIZE Randomized Trial. JAMA. 2013 Oct 31.
12. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet. 2013;382:1714-1722

Classified Advertisement

Please contact the Federation Secretariat at **2527 8898** for placement of classified advertisement.

Vascular Cognitive Impairment

Dr Kin-lun TSANG

Specialist in Neurology

Dr Kin-lun TSANG

A recent paper reported that after a single stroke there is continuous cognitive decline that may accelerate in the long term.[1] This reiterates the close relationship between vascular disease and dementia. A cure for dementia is unlikely to have been found by 2025 and its prevalence will double every 20 years.[2] It is high time to promote brain health that shares many vascular risk factors. Subclinical brain MRI markers of vascular damage are frequently encountered and have been attracting attention for risk factor stratification and early intervention.

Vascular cognitive impairment (VCI) is any cognitive defect associated with cerebrovascular injury. It is an "umbrella" term that encompasses milder forms and various patterns including the long-used vascular dementia. Often there is widespread involvement of periventricular white matter. Clinically, psychomotor slowing, executive dysfunction and memory deficits are more prominent. The memory deficits in VCI affect memory retrieval more than encoding. Mood disturbances, including depression, apathy and pseudobulbar affect are common in the early course of VCI.

Lesions of VCI include subclinical brain infarcts (SBIs), cerebral microbleeds (CMBs) and white matter hyperintensities (WMHs), collectively known as small vessel disease (SVD) (Fig. 1). MRI reports often quote "multiple subcortical T2-hyperintesities which are suggestive of microvascular ischaemia" in asymptomatic patients. This should not immediately be cause for alarm because the number of lesions may be small and may just be age-related changes. Studies are ongoing to objectively define the cut-off number or volume of lesions.

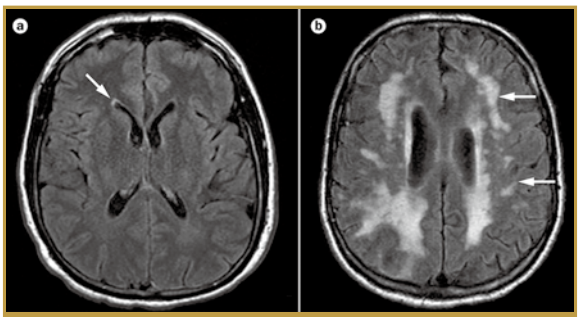


Figure 1.
(a) Mild WMH (arrow) next to lateral ventricle, otherwise brain parenchyma is normal. (b) The periventricular WMHs are confluent and lacunar infarcts (arrows) are present. This represents severe SVD. Abbreviations: WMH: white matter hyperintensity; SVD: small vessel disease

VCI and Alzheimer's disease (AD) have generally been considered two non-overlapping diseases. It is an oversimplification to say that both VCI and AD are diseases of older people and commonly occur by coincidence. A key hypothesis proposes that AD and SVD either co-exist in individuals or interact in a pathological process. Interestingly, CMBs are commonly found in 20 to 30% of patients with AD.[3] Distribution of CMBs in AD is similar to that in sporadic cerebral amyloid angiopathy (CAA), suggesting that CMBs in AD are more likely to be related to CAA. CAA is small vascular damage characterized by vascular deposition of β-amyloid protein and is almost uniform, being found at autopsy in more than 90% of AD cases. It is possible that the intriguing process that may link SVD with AD is CAA, for which CMB is an increasingly important neuroimaging marker.[4] Although the mechanisms by which CMBs might influence cognitive decline remain unclear, CMBs have been speculated to cause direct structural damage to surrounding brain tissue, leading to disruption of frontal-subcortical circuits and nearby neurons. Alternatively they may have an indirect effect including arteriolar narrowing causing hypoperfusion and micro-ischaemic damage. It is unknown whether CMBs are a general neuroimaging marker of small vessel disease or have little influence on cognitive function. In short, there is clearly a need to thoroughly explore CMBs that may be the pathogenic link between VCI and AD.

Dementia has a very long prodrome period which pathological process is ongoing before clinical symptoms appear. Thus risk factors should have an effect at middle age or earlier. Two studies have examined such a relationship. A prospective UK cohort study involved 7,830 adults aged 35–55 years at baseline who underwent a series of cognitive assessments starting 12 years later.[5] It showed that both the Framingham general cardiovascular disease risk score and the Framingham stroke risk score were related to decline in reasoning, verbal fluency, vocabulary and global cognition, but not memory. Another study was performed in Finland and was a double-blind randomised controlled trial of 1,260 individuals aged 60–77 years who were recruited from previous national surveys.[6] Inclusion criteria were CAIDE (Cardiovascular Risk Factors, Aging and Dementia), Dementia Risk Score of at least 6 points and cognition at a mean level or slightly lower than expected for age. Individuals were randomly assigned in a 1:1 ratio to a 2 year multi-domain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). A neuropsychological test battery was used for assessment. Results showed that

multi-domain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population although the p value was not markedly significant.

Both the above mentioned Framingham risk and CAIDE scores can easily be found in the web and are free. The CAIDE dementia and Framingham risk scores predict cognitive decline in late middle age. Nonetheless the Framingham risk score may be superior to the dementia risk score when used in primary prevention to assess risk of cognitive decline and target modifiable risk factors.

The risk factors are well known as they are common to heart disease. The key aim should be to shift our preventive health focus to the broader concept of promoting brain health, encompassing stroke and dementia, as well as VCI, functional impairment, and age-related cognitive decline. Interventions to improve heart health will greatly benefit brain health. The ageing population and the shifting demographics highlight the need for continued aggressive efforts to target traditional and emerging vascular risk factors, with the goal of improving brain health globally.

At the 2014 Dementia Awareness Week in London, The Blackfriars Consensus Statement was launched.[7] It states that the scientific evidence for dementia risk reduction is evolving rapidly and is now sufficient to justify action that incorporates dementia risk reduction in health policies and raises a wider awareness about which factors can reduce the risk of developing dementia. It is intended to help raise awareness among policy makers and the wider healthcare workforce as well as the public that dementia is amenable to risk reduction in similar ways to other non-communicable diseases. In other words, effective public health policies to tackle the major chronic disease risk factors of smoking, physical inactivity, alcohol and poor diet across the population will help reduce the risk of dementia in later life. It strengthens the case for action to create the physical and economic environments that will support people to lead healthier lives; for example, transport plans and investment that promote more walking and exercise as part of everyday life. We need to start to "think brain, think heart" as brain health is inexorably linked to heart health. We can add healthy years to our lives by reducing risks earlier on.

Adopting the same concept, the Department of Medicine and Therapeutics at The Chinese University of Hong Kong (CUHK) has conducted a screening programme between 2012 and 2015 that reveals that one-third of 800 older adults aged 65 or above in the community suffer from moderate to severe brain small vessel disease (SVD). Among the severe SVD patients, those with minor stroke will have a 3.4 times higher risk of developing dementia over 3 years.

Studies conducted by CUHK and other international groups show that those with high blood pressure, blood sugar and lipid level as well as smoking habit are at higher risk of SVD.[8] A simple but essential integrated healthy lifestyle should include (Fig. 2):

- Monitoring and controlling blood pressure, blood sugar and lipid levels
- Stopping smoking
- Maintaining a healthy weight
- Reducing excessive alcohol consumption
- Carrying out physical exercises and mental activities such as reading, using a computer or playing games (such as board games) regularly
- Maintaining an active social life (e.g. joining elderly centres or interest classes and participating in volunteer work, etc.)

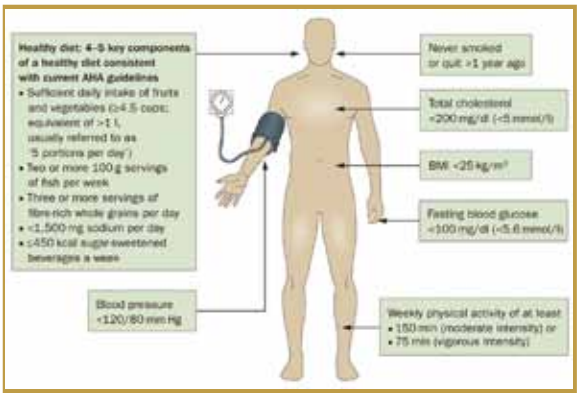


Figure 2.
Healthy lifestyle to minimize vascular risk and cognitive decline.

References

1. Levine DA, Galecki AT et al. Trajectory of cognitive decline after incident stroke. JAMA. 2015;314(1):41-51.
2. Zha AM, Kelley BJ. Vascular cognitive impairment, part 1 & 2. Practical Neurology. 2015;Jan:24-30 and Mar:13-15.
3. Gong L, Liu XY, Fang M. Recent progress on small vessel disease with cognitive impairment. Int J Clin Exp Med. 2015;8(5):7701-09.
4. De Reuck JL. The significance of small cerebral bleeds in neurodegenerative dementia syndromes. Aging Dis. 2012;3(4):307-12.
5. Kaffashian S, Dugravot A et al. Midlife stroke risk and cognitive decline: a 10-year follow-up of the Whitehall II cohort study. Alzheimers Dement. 2013;9(5):572-79.
6. Ngandu T, Lehtisalo J et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk eldely people (FINGER): a randomized controlled trial. Lancet. 2015;385(9984):2255-63.
7. Patel K, Deanfield J, Mwatsama M. The Blackfriars Consensus on brain health and dementia. Lancet. 2014;383(9931):1805-06.
8. Mok V, Kim JS. Prevention and management of cerebral small vessel disease. J Stroke. 2015;17(2):111-22.

Benecol®

LOWERS FAST

LOWERS
TOTAL AND LDL
CHOLESTEROL
ON AVERAGE
BY 10%*

CLINICALLY
PROVEN
EFFICACY

KEEPS LOW*

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

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

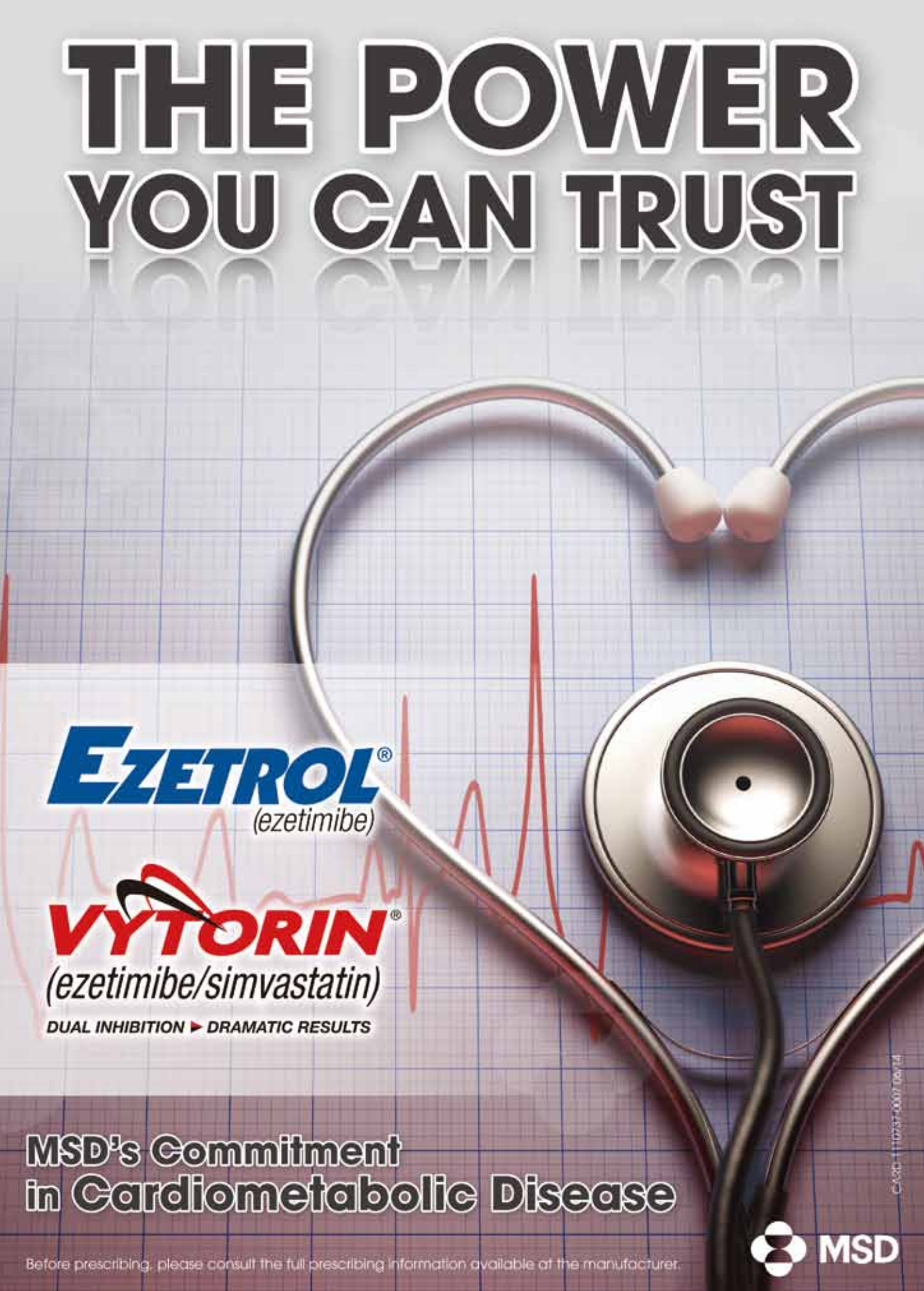
RECOMMENDED INTAKE: 1 YOGHURT DRINK/DAY

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

www.benecol.com.hk

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

THE POWER YOU CAN TRUST



EZETROL®
(ezetimibe)

VYTORIN®
(ezetimibe/simvastatin)

DUAL INHIBITION ► DRAMATIC RESULTS

MSD's Commitment in Cardiometabolic Disease

Before prescribing, please consult the full prescribing information available at the manufacturer.

MSD

CA-NP-1110737-0007 06/14

sanofi-aventis Ho
Units 706-710, Level 7, Core
Tel : (852) 2506 8333 Fax :
Website: www.sanofi-aventis.

SANOFI CV

ONCE-A-DAY Plavix (clopidogrel bisulfate) 75 mg tablets

APROVEL (irbesartan) Tablets 150 mg 300 mg

MULTAQ dronedarone

CLEXANE Enoxaparin sodium

TRITACE Ramipril

ong Kong Limited
C, Cyberport 3, 100 Cyberport Road, Hong Kong
(852) 2506 2537
hk

HK,DRO,14.05.01

SANOFI

HYPERCHOLESTEROLEMIA - A GUIDE TO CLINICAL PRACTICE 2015

~ An Update with Implications of Recent Clinical Trials & Medical Management with a Special Focus on New and Advanced Medications

Dr Bernard BL WONG

MBBS (HK); MRCP (UK); FRCP (Edin); FRCP, RCPS. (Glasg),
FHKCP (HK); FHKAM (MEDICINE); DGM (IRELAND); DCH (LONDON)
Specialist in Cardiology

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 December 2015.

Statins are the new aspirin
~ Heart Protection Study (HPS) Investigators 2001'

STATIN - a near perfect class of drugs

Statins, HMG-CoA reductase (rate-limiting enzyme in liver cholesterol synthesis) inhibitors, are one of the most powerful medical innovations of the 20th century. They very effectively modify the lipid profile:

LDL 18 – 60% (dose dependent)
HDL 5-15%
TG -37% (Table 1)

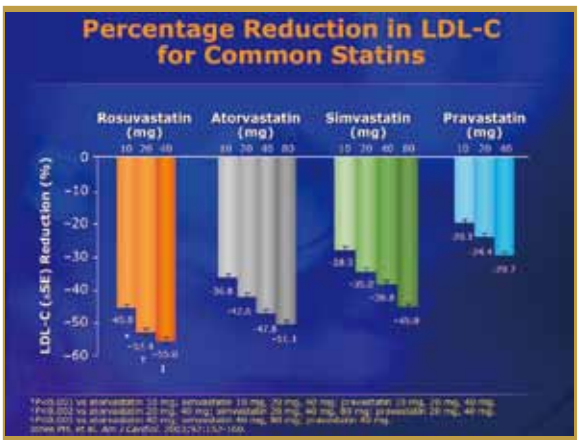


Figure 1 Data from STELLAR Trial

Table 1

Mega-Studies	Drugs	Year	Number of Subjects	1°/2°	LDL-reduction mmol/L	MI/CHD Death reduction	Total Mortality reduction
4-S[10]	Zocor (Simvastatin) 10-40mg	1994	4444	2°	4.9 → 3.14 36%↓	34%	30%
WOSCOPS[11]	Pravachol (Pravastatin) 40mg	1995	6596	1°	5.0 →3.7 26%↓	31%	22
CARE[12]	Pravachol (Pravastatin) 40mg	1996	4159	2°	3.6 → 2.6 28%↓	24%	9% (NS)
AFCAPS/ TEXCAPS[13]	Mevacor (Lovastatin) 20-40mg	1998	6605	1°	3.9 → 2.9 26%↓	25%	+3% (NS)
LIPIDS[14]	Pravachol (Pravastatin) 40mg	1998	9014	2°	3.9 → 2.9 25%↓	24%	22%

Table Legend
4-S:
Scandinavian Simvastatin Survival Study
WOSCOPS: West of Scotland Coronary Prevention Study
CARE: Cholesterol and Recurrent Events
AFCAPS/TEXCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study
LIPIDS: Long-Term Intervention with Pravastatin in Ischemic Disease
1°: Primary Prevention
2°: Secondary Prevention
NS: Non-Significant
MI: Myocardial Infarction
CHD: Coronary Heart Disease

In addition to biochemical lipid profile improvement, statins also achieve a powerful evidence based "Hard End-Point" improvement in morbidity and mortality. (Table 1), (Table 2)

Table 2

Mega-Studies	Drugs	Year	Number of Subjects	1°/2°	LDL-reduction mmol/L	MI/CHD Death reduction	Total Mortality reduction
HPS	Zocor (Simvastatin) 40mg	2002	20,536	1°-2°	3.4→2.4 29%↓	27%	13%
PROSPER	Pravachol (Pravastatin) 40mg	2002	5,804	1°-2°	3.8→2.8 27%↓	19%	3% (NS)
ASCOT-LLA	Lipitor (Atovastatin) 10mg	2003	10,305	1°	3.5→2.4 29%↓	36%	13% (NS)
PROVE IT – TIMI 22	Lipitor 80mg vs Pravachol (Pravastatin) 40mg	2004	4,160	2° <10days from Acute Coronary Syndrome	2.75 Lipitor → 1.61(51%↓) Pravachol → 2.47(22%↓) 18%	18%	28% (NS)

Regardless of,
- which trial you are referring to,
- whether it is on primary or secondary prevention,
- or morbidity or mortality

a statin can give your patient a 20~30% improvement in lipid profile & cardiovascular morbidity/mortality

Nonetheless although minimal, statins are not without contraindications or adverse effects (especially at higher doses)

Statin treatment is contraindicated in,
- active liver disease
- unexplained, persistent elevation of liver enzymes
- pregnant or lactating women

Common side-effects (generally more frequent with higher dosages) include:
- gastrointestinal discomfort 9%
- myalgia 2%
- ALT/AST (>3X upper limit, persist for 2 weeks) 0.1-0.9%
- Discontinuation due to various reasons 3.6%

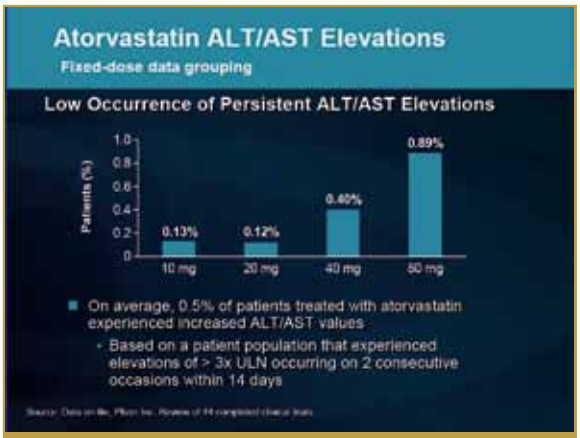


Figure 2 Only ~ 0.5% of patients develop persistent Liver Function Derangement

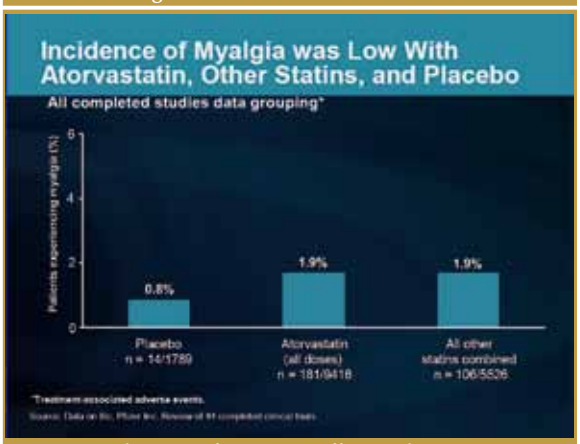


Figure 3 Only ~ 2% of patients suffer myalgia

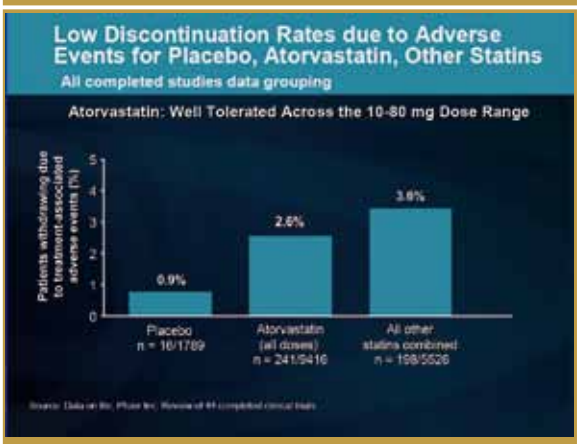


Figure 4 Only ~ 3% discontinue therapy due to adverse events

Statins may be considered a near perfect class of drugs. They are efficient, effective and life-saving with few side effects. They have been meticulously studied by numerous mega-trials, with virtually no fatal adverse events and have a very reasonable price.

Nonetheless statins are *not quite perfect* for the following reasons,

- Gastrointestinal discomfort, myalgia and liver enzyme elevation is not uncommon at higher doses
- Myopathy and rhabdomyolysis have been seen with each statin (only a few reported cases for each statin over the world in the past decade)
- The risk of myopathy increases when statins are used concomitantly with niacin, fibrates and pharmacological agents that share the cytochrome P450 system (cyclosporon, itraconazole, ketoconazole, macrolide antibiotics erythromycin and clarithromycin, amiodarone and verapamil.)
- Price is reasonable, but not inexpensive especially at high doses
- LDL goals are frequently not attained (in 64% of patients) despite repeat dose increases i.e. "*Rule of Six*"(Figure 5), (Figure 6)

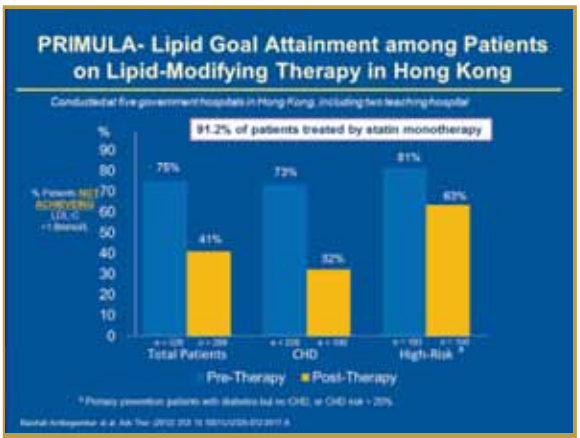


Figure 5 Only ~ 40% of the HK high risk and CHD patients achieved the LDL target

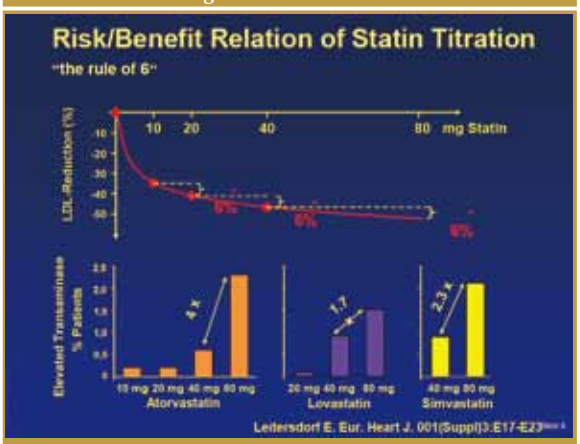


Figure 6 "Rule of Six"

In the author's experience, **statins** make lipid lowering treatment much easier and more effective. Over 95% of patients are happy with their improved lipid profile and no side-effects after just one month of treatment. For the physician, the remarkable improvement in prognosis is very rewarding.

Each man is the architect of his own destiny.
~ Appius Claudius Caecus 340 - 273B.C.

Atorvastatin (Lipitor), a very good example of how a statin helps

Pharmacology:
Atorvastatin (Lipitor) is a synthetic lipid lowering agent – statin, that is a competitive inhibitor of HMGCoA reductase.

Recommended dosage:
10 - 80mg PO, once a day

Potency:
Atorvastatin (Lipitor) is one of the most potent statins and reduces:

- Total cholesterol: 30 - 46%
- LDL 41–61%
- TG 14 - 33%

and increases:

- HDL 5.1 – 8.7%

Side-effect profile:
Like most statins, Atorvastatin (Lipitor) is very safe at various dosages

- Liver transaminases > 3 times ULN (upper limit of normal):
  - 10mg 0.2%
  - 20mg 0.2%
  - 40mg 0.6%
  - 80mg 2.3%
- Creatine Phosphokinase > 10X
  - 0.1%
- Rhabdomyolysis

Table 3 Atorvastatin (Lipitor) vs Rhabdomyolysis

Trial	Rhabdomyolysis
MIRACLE	0%
CARDS	0%
ASAP	0%
ASCOT	Only 1 non-fatal case (out of 5, 168 patients) with multiple confounding febrile illness and alcohol abuse

In the author's experience, the most common side-effect is myalgia (3-5%). Nonetheless myalgia was well tolerated by over 95% of affected patients and treatment with Atorvastatin (Lipitor) continued and was unremarkable.

Statins have a broad spectrum of use with substantial evidence of benefit.
Primary Prevention:-

<u>ASCOT – LLA Trial (Figure 7 & 8)</u>
(Anglo-Scandinavian cardiac Outcomes Trial Lipid Lowering Arm) 2003'

Table 3 Atorvastatin (Lipitor) vs Rhabdomyolysis

- Atorvastatin (Lipitor) 10mg QD vs Placebo
- 10, 3 05 patients
- 3. 3 years follow-up
- Hypertensive patients with total cholesterol ≤ 6.5mmol/L and ≥ 3 additional CV risk factors. (Note: this is a very common patient profile for a family doctor)

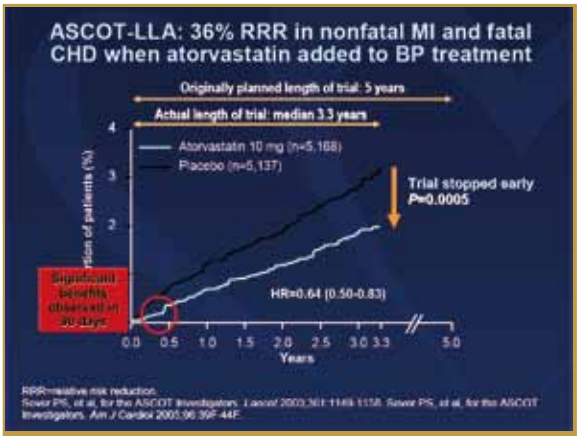


Figure 7 ASCOT – LLA
~ Atorvastatin (Lipitor) 10mg o.d. reduced the incidence of non-fatal and fatal CHD by 36%

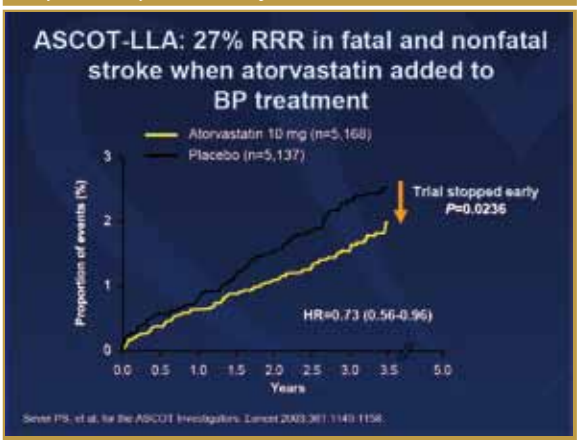


Figure 8 ASCOT – LLA Study
~ Atorvastatin (Lipitor) 10mg o.d. reduced the incidence of non-fatal and fatal stroke by 27%

High risk primary prevention (Patient with diabetes mellitus):-

CARDS (Figure 9)
(Collaborative Atorvastatin Diabetes Study) 2004'

- Atorvastatin (Lipitor) 10mg QD vs Placebo
- 2, 838 patients
- 3.7 years follow-up
- Type II Diabetes with LDL ≤ 4.14mmol/L and TG ≤ 6.78mmol/L plus, one CV risk factor (hypertension, retinopathy, micro / macroalbuminuria, or smoker)

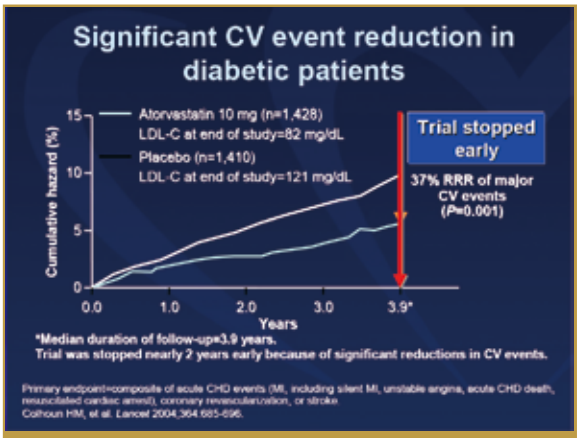


Figure 9 CARDS Study
~ Lipitor 10mg reduced major CV events by 37%

Secondary prevention:-

Low risk secondary prevention (Patient with coronary artery disease)

REVERSAL (Figure 10)
(Reversal of atherosclerosis with aggressive lipid lowering) 2002'

- Atorvastatin (Lipitor) 80mg vs Pravachol (Pravastatin) 40mg
- 654 patients
- Coronary artery disease with coronary angiogram indicated
- Coronary atherosclerosis (total plaque volume) measured by intravascular ultrasound (IVUS), our current gold-standard.
- 18 months of follow-up

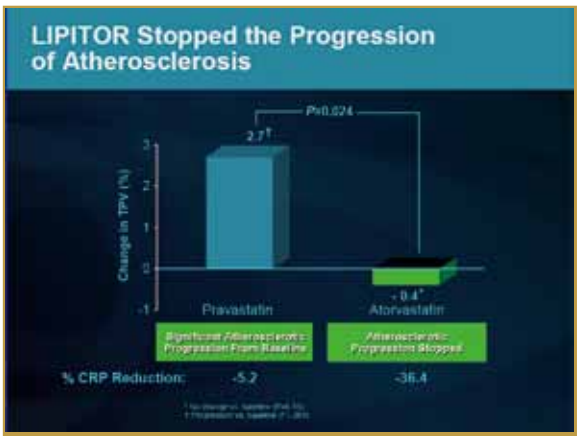


Figure 10 REVERSAL Study
~ Atorvastatin (Lipitor) 80mg showed significant halting of plaque progression and CRP reduction vs Pravachol (Pravastatin) 40mg QD

Moderate risk secondary prevention (patient with myocardial ischemia or infarction)
MIRACL
(Myocardial-Ischemia Reduction with Aggressive Cholesterol Lowering) 2002'

- Atorvastatin (Lipitor) 80mg vs Placebo
- 3, 086 patients
- 16 weeks follow-up
- Myocardial ischemia or infarction in the previous 1-4 days
- Atorvastatin (Lipitor) reduced by 16% (P = 0.048) the combined endpoint of
  - all cause death,
  - non-fatal myocardial infarction,
  - resuscitated cardiac arrest and
  - worsening angina with objective evidence and urgent hospitalization.

High risk secondary prevention (Patient with ACS - acute coronary syndrome)
PROVE IT – TIMI 22 (Figure 11)
(Pravastatin or atorvastatin Evaluation and Infection Therapy
– Thrombolysis in Myocardial Infarction 22) 2004'

- Atorvastatin (Lipitor) 80mg QD vs Pravachol (pravastatin) 40mg QD
- 4, 160 patients
- 2 years follow-up
- < 10 days of ACS - Acute Coronary Syndrome (Myocardial infarction & Unstable angina)[19]

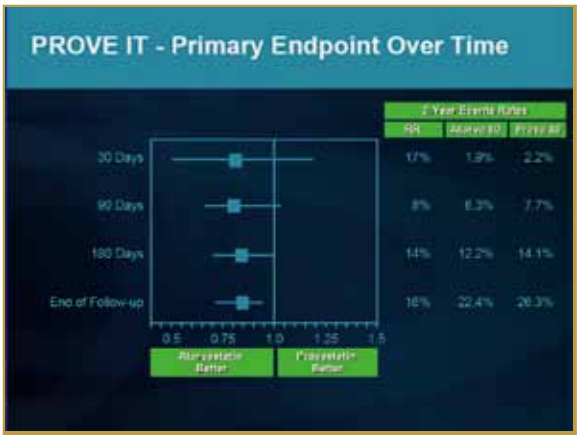


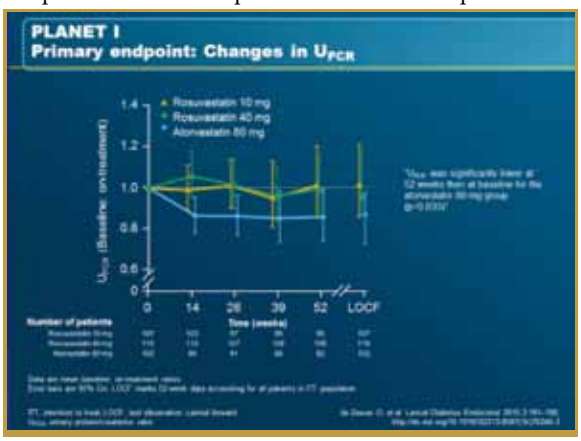
Figure 11. PROVE IT – TIMI 22
Atorvastatin (Lipitor) 80mg QD reduced 16% more all cause mortality and major CV events compared with Pravachol 40mg

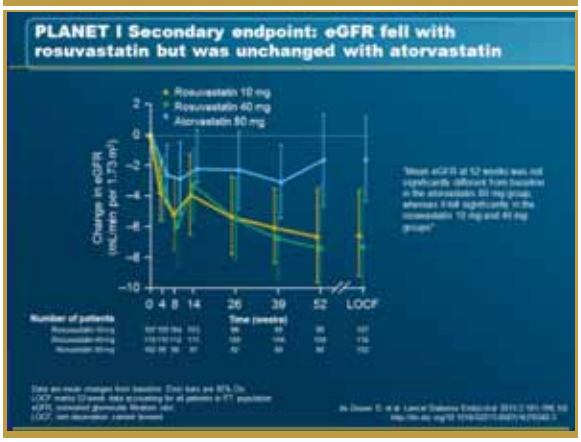
Renal protection for patients with DM and proteinuria

- Planet I (Prospective Evaluation of Proteinuria and Renal Function in Diabetes Patients with Progressive Renal Disease) Study[35]
  - Type I or Type II patients age > 18 years old with proteinuria (urine protein : creatinine ratio(Upcr) 500-5000mg/g)
  - Atorvastatin (Lipitor) 80mg vs Rosuvastatin (Crestor) 10mg vs Rosuvastatin (Crestor)40mg
  - 353 patients, follow-up for 52 weeks

	Atorvastatin 80mg	Rosuvastatin 10mg	Rosuvastatin 40mg
Protein : creatinine ratio (Upcr) Baseline vs 52 weeks	0.87 (p=0.033)	1.02 (p=0.83)	0.96 P= 0.53)
Change in eGFRml/ min per1.73m2 baseline : 52 weeks	-1.61 P=0.21	-3.70 P= 0.0098	-7.29 P=0.0002

- Atorvastatin (Lipitor) offers a significant renal protection effect in patients with DM and proteinuria





The above data is evidence that Atorvastatin (Lipitor) is a very good statin. It

- Is easy to use, once-a-day oral tablet
- Achieves very potent lowering of LDL
- Significantly reduces morbidity and mortality across a broad spectrum of patients:-
  - Primary prevention,
  - High risk primary prevention (Diabetic patients),
  - Secondary prevention,
  - Moderate risk secondary prevention and
  - Secondary prevention with very high risk
- Provides significant renal protection for DM patients with proteinuria
- Is very safe
- Well tolerated
- and provides value for money

It is no surprise that Atorvastatin- Lipitor is one of the most commonly used statins in the world.

"上醫醫未病之病，中醫醫欲病之病，下醫醫已病之病"
~扁鵲 (401-310BC)

Rosuvastatin (Crestor) – a very potent statin with strong data supporting primary prevention

Rosuvastatin (Crestor) has been marketed in Hong Kong since 2000 and is the newest statin. It has been shown to be highly effective in reducing LDL by up to 63%. To date, Crestor is the most potent LDL lowering statin. Rosuvastatin (Crestor) 10mg enables significantly more patients to achieve their LDL target, thereby reducing the need to titrate to higher doses. It produces a significant increase in HDL and decrease in TG across the dose range. (Figure 1) (Figure 14)[26]

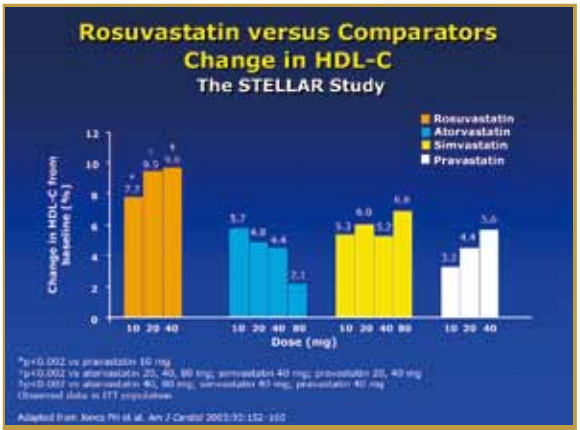


Figure 14

Rosuvastatin (Crestor) enjoys a good overall tolerability profile, comparable with other statins on the market:

- < 3% rate of withdrawals due to adverse events (Figure 15)
- adverse events usually mild and transient
- with 10-40mg dose, rhabdomyolysis is very rare (< 0.01%) (Figure 16)
- favorable benefit-risk profile.

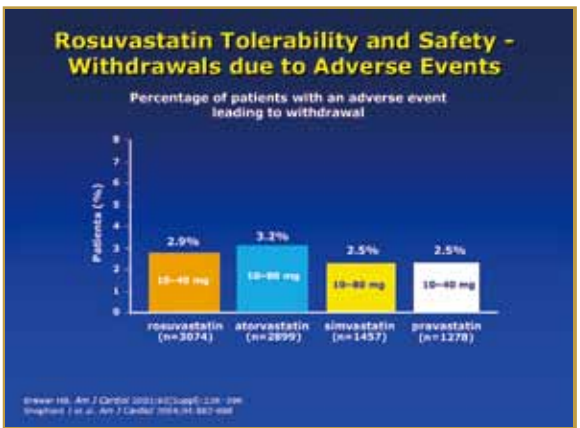


Figure 15

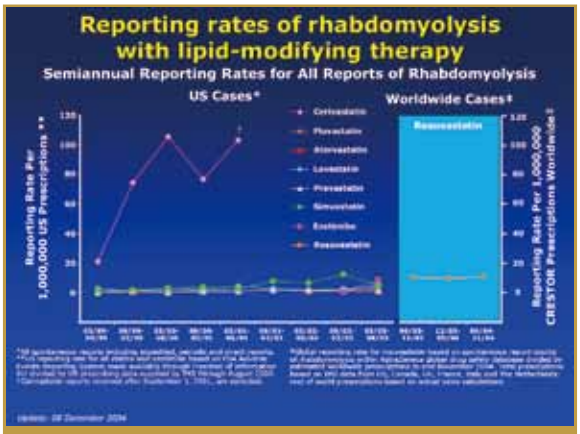


Figure 16

There have been two major breakthroughs for mankind from Crestor

The first human study on regression of atheroma:-

ASTEROID 2006'[27]

- A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound –Derived coronary atheroma burden
- 507 patients
- Follow-up 24 months
- Patients with angiographic coronary stenosis > 25%
- Crestor 40mg vs placebo
- LDL reduction down to 1.56mmol/
- Intravascular ultrasound measurement of coronary atheroma volume revealed the following:
- 0.79% median reduction in percent atheroma volume over the entire coronary vessel and
- 9.1% median reduction in atheroma volume in the 10mm section of coronary vessel with heaviest plaque burden P< 0.001
- → For the first time since the discovery 94 years ago (by Herrick J.B. in 1912) of atheroma as the cause of coronary artery disease, the size of these atheromatous plaques can be regressed.

The first human study on "successfully treating normal people" with no medical or vascular disease:-

JUPITER - Nov. 2008'[28]

- Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)
- 17, 802 patients
- Mean follow-up 1.9 years, (proposed 4 years, pre-mature termination because of the unforeseeable overwhelming positive results)
- Men ≥ 55 years, women ≥ 65 years, LDL < 3.4mmol/L, TG < 5.7mmol/L, with High-Sensitive CRP (hs-CRP) ≥ 2mg/l and no cardiovascular or cerebrovascular disease.
- Crestor 20mg QD vs placebo
- 44% reduction in the hard composite end-point -- cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, unstable angina or arterial revascularization (p< 0.00001) (Figure 17)
- 20% reduction in total mortality (P = 0.02) (Figure 18)

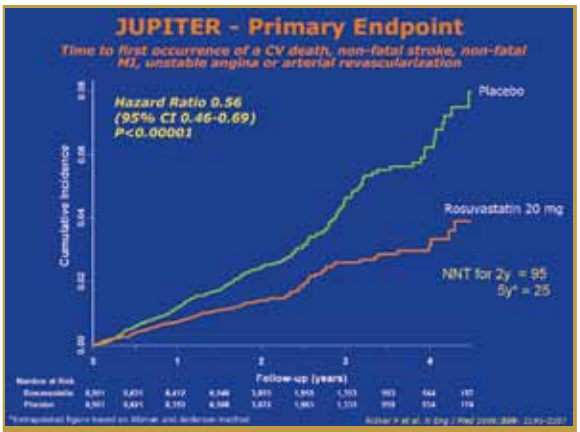


Figure 17

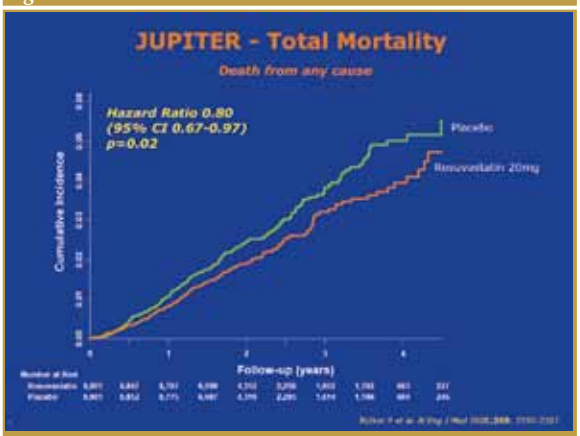


Figure 18

This is the first time in our 300, 000 years of Homo Sapiens existence that we have been able to treat 'normal' subjects with baseline characteristics:-

- Median age 66
- Median hsCRP 4.2mg/L
- Median LDL 2.8mmol/L
- Median BP 134/80mmHg and
- Median HBA1C 5.7%

with a statin and achieved a significant reduction in cardiovascular morbidity and mortality and total mortality.

Is a more powerful weapon available?

Ezetimibe (Ezetrol)
Ezetimibe (Ezetrol) is the newest lipid lowering agent and is the first of a new class of cholesterol absorption inhibitors. It has been marketed in Hong Kong since 2004.

Mechanism:
After absorption, ezetimibe localizes at the brush border of the small intestine to prevent and decrease the delivery of intestinal cholesterol to the liver. The

reduced hepatic cholesterol store leads to increased clearance of cholesterol from the blood.

Recommended dosing:
10mg QD co-administered with a statin.
Example:
Ezetimibe (Ezetrol) 10mg + simvastatin (Zocor) 20mg → Vytorin 10/20mg
Ezetimibe (Ezetrol) 10mg + simvastatin (Zocor) 40mg → Vytorin 10/40mg

Drug interactions:

- Cholestyramine: lessens the potency of ezetimibe on LDL lowering.
- Fibrate: safety data on co-administration not established
- No interaction with statins, digoxin, oral contraceptives, glipizide (Minidiab, Glucotrol XL), tolbutamine, midazolam (Dormicum), warfarin, or cimetidine (Zantac).

The efficacy:

- Additive effects of ezetimibe with atorvastatin (Lipitor), simvastatin (Zocor), pravastatin (Pravachol), or lovastatin (Mevacor) on LDL reduction
- LDL lowering efficacy of ezetimibe + lowest-dose statin is comparable with maximum dose of every statin (up to 60% lowering). (Figure 12)

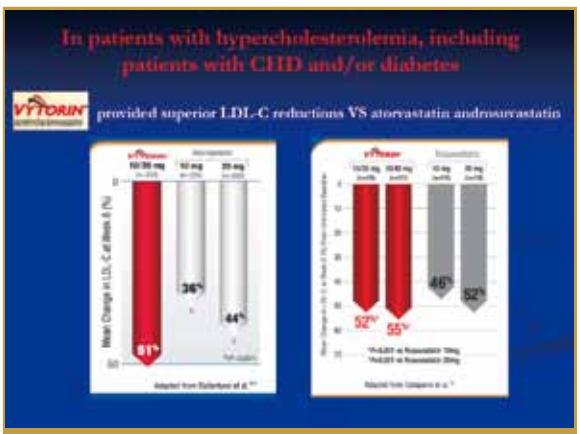


Figure 12
Combined with simvastatin (Vytorin), at a usual starting dose of 10/20mg (10mg ezetimibe/ 20mg simvastatin) LDL can be reduced by an average 50%.

- Beneficial additive effects on HDL (↓1-5%%), TG (↓7-13%) and C-reactive protein (↓35%) (a very good independent predictor of future cardiovascular events)
- More patients can achieve their target LDL compared with statin monotherapy (75% versus ~ 25%).

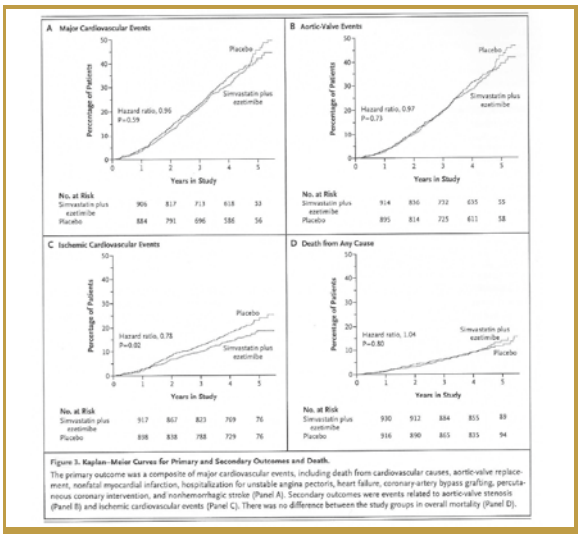
The safety and tolerability profile is good

- co-administration with a statin is well tolerated
- incidence of treatment-related adverse events is low (19.5% versus 18.1% of placebo)
- low rate of discontinuation due to adverse events (3.7% only)
- no rhabdomyolysis or myopathy
- no significant increase in creatine kinase (only 0.1% of patients CK 10 times upper limit of normal compared with 0.4% of those prescribed statin monotherapy)
- a slightly higher percentage of patients had elevated ALT/AST compared with statin monotherapy (~1%). All were asymptomatic, transient and reverted to baseline with discontinuation of therapy.

Vytorin (ezetimibe + simvastatin) ~ an update on the recent trials

SEAS Trial 2008'[24]
(Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis)

- 1, 873 patients
- Vytorin 10/40mg (10mg ezetimibe / 40mg simvastatin) vs placebo
- Patients with mild to moderate asymptomatic aortic stenosis
- Follow-up 52.2 months
- Primary end-point not reached (a composite of major cardiovascular events, including death from angina pectoris, heart failure, coronary artery bypass grafting, need for percutaneous coronary intervention and non-hemorrhagic stroke)
- Ischemic cardiovascular events were reduced by 22% in the vytorin group (P = 0.02)



SHARP (Study of Heart and Renal Protection)36 2011'

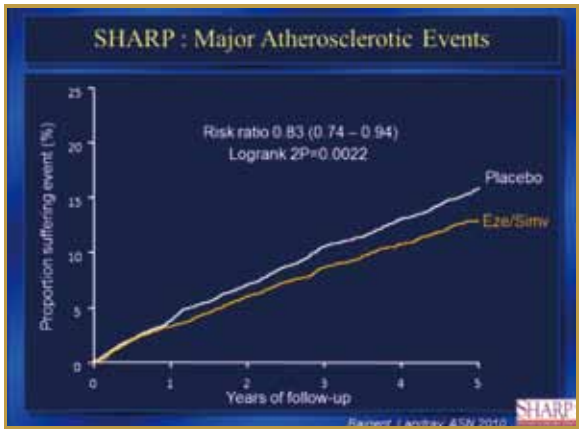
Patient No. 9,270
Patients:

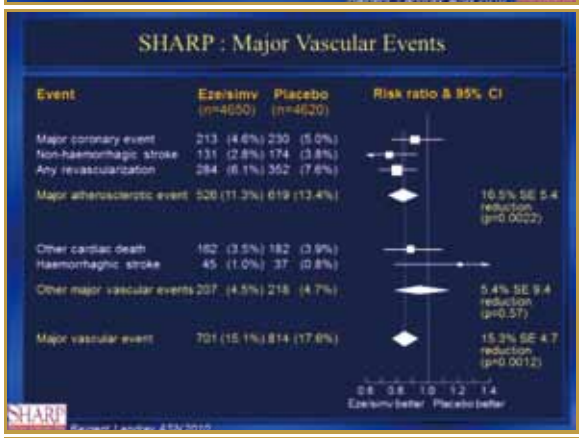
- Chronic kidney disease
  - Not on dialysis: elevated creatinine on two occasions
    - Men: ≥ 150umol/L
    - Women ≥ 130umol/L
  - On Hemodialysis or peritoneal dialysis

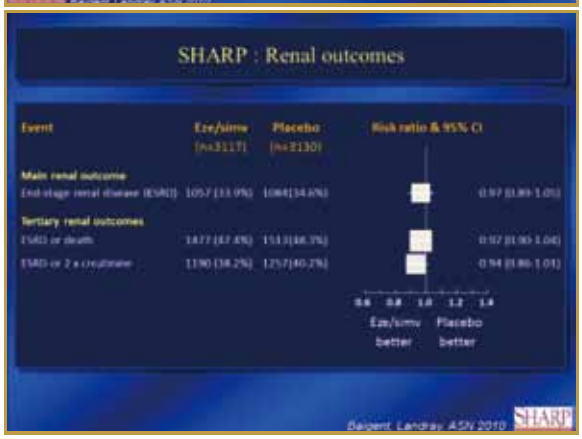
- Age > 40 years
- No Hx of MI or coronary revascularization
- Ezetimibe (Ezetrol) 10mg + simvastatin (Zocor) 20mg (Vytorin 10/20mg) vs simvastatin (Zocor) 20mg vs Placebo

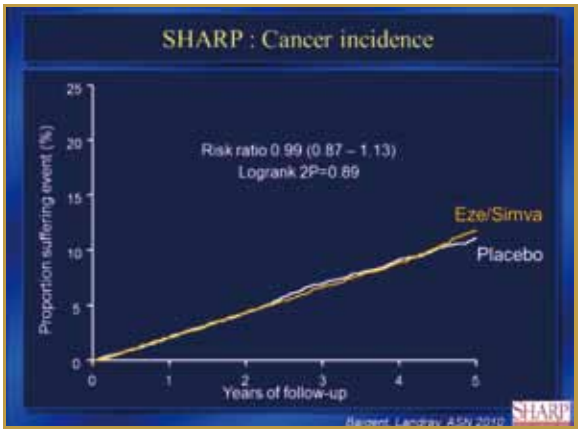
Median Follow-up 1.9 years
LDL difference: 0.85mmol/L (Baseline LDL 2.77-2.78mmol/L)
Result:

- 17% ↓ in major cardiovascular events (coronary death, MI, non-haemorrhagic stroke, or any surgery for revascularization).
- No significant difference in renal outcomes
- No significant difference in cancer incidence









The following is the largest, longest and most recent lipid lowering trial:

IMPROVE- IT[37] 2015'

- The Improved reduction of Outcomes: Vytorin Efficacy International trial
- Patient No: 18, 144
- Published: June 3, 2015
- Patients: ACS within 10 days
- Baseline: LDL
- On statin: 1.3-2.6mmol/L
- Not-on-statin: 1.3 – 3.2mmol/L
- Therapy: Simvastatin 40mg + Placebo vs Simvastatin 40mg + Ezetimibe 10mg (Vytorin 40/10)
- Results:
- mean LDL 1.8mmol/L → 1.4mmol/L (P< 0.001)
- Primary end point (CV death + non-fatal MI + UA hospitalization + PCI) 34.7% → 32.7%, 2%↓ (P=0.016)
- No significant difference in incidence of cancer, liver function derangement, myopathy or rhabdomyolysis

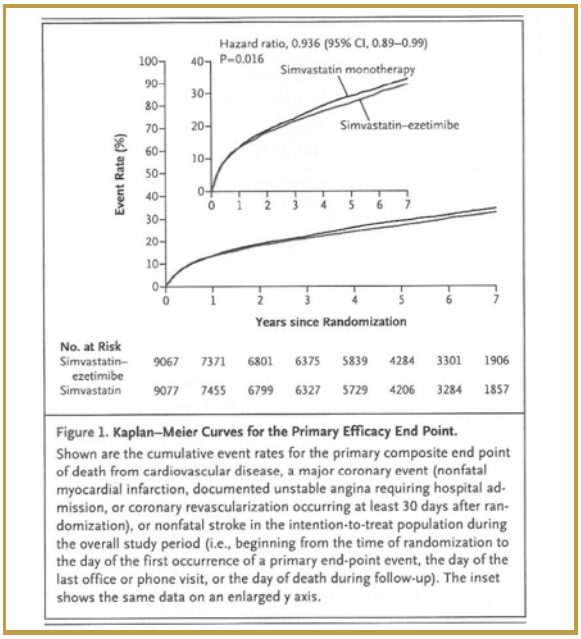
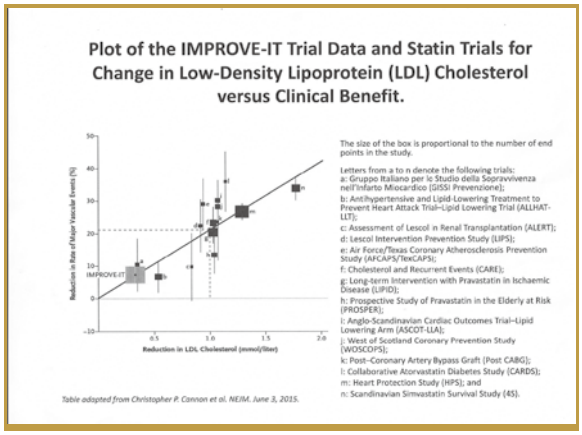


Figure 1. **Kaplan–Meier Curves for the Primary Efficacy End Point.**
Shown are the cumulative event rates for the primary composite end point of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke in the intention-to-treat population during the overall study period (i.e., beginning from the time of randomization to the day of the first occurrence of a primary end-point event, the day of the last office or phone visit, or the day of death during follow-up). The inset shows the same data on an enlarged y axis.



A very substantial portion of the population is not yet receiving the preventive or therapeutic measures that have been proved to be effective against cardiovascular disease.

~ Eugene Braunwald, Shattuck Lecture, 1997

In view of the SEAS, SHARP and IMPROVE-IT trials, Ezetimibe (Ezetrol) + Simvastatin (Zocor) → Vytorin is

- A very potent agent for lowering LDL
- Effective in reducing cardiovascular morbidity and mortality in high risk patients, namely those with:
  - Chronic renal impairment/failure (SEAS)
  - Aortic stenosis (SHARP)
  - Post ACS and from 10 days up to over 9 years (IMPROVE-IT)
- Very safe, and does not increase major side effects of cancer, liver function derangement, myopathy or rhabdomyolysis

Ezetimibe (Ezetrol) + Simvastatin (Zocor): Vytorin, after the results of IMPROVE-IT were published, has become one of the author's favourite prescriptions in daily practice!

Is there still a place for the older generation lipid lowering agents?

Bile acid-binding resins:
- Most commonly used is Cholestyramine resin
- interrupt enterohepatic bile acid circulation
- LDL ↓ 20-30%, HDL ↑ 5-15%, TG →
- cause gastrointestinal discomfort

Omega-3 fish oil

- GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivivenza nell'Infarto Miocardico) (ESC-Scientific Congress 2008)
  - 1 g daily dosage of Ω-3 PUFA (polyunsaturated fatty acid)
  - Post myocardial infarction, symptomatic congestive heart failure (New York Heart Association class II-IV) patients
  - 6, 975 patients
  - 3.9 years follow-up
  - 9% reduction in all cause mortality (very modest)
- GISSI (Gruppo Italiano per lo Studio della Sopravvivivenza nell'Infarto Miocardico) 1999'
  - 11, 324 patients
  - Recent acute myocardial infarction
  - 1 g daily dosage of Ω-3 PUFA (polyunsaturated fatty acid)
  - Compared with vitamin E and placebo
  - 3.5 years follow-up
  - 10% reduction in death, non-fatal myocardial infarction and stroke20
- Mild increase in bleeding risk, patients on warfarin must be closely monitored
- Halitosis, belching, dyspepsia, heart burn and nosebleed are not uncommon
- Long term use may increase the risk of vitamin E deficiency

Although they are not expensive, their use is limited by their relatively weak effect on LDL lowering (the most important key to reduce cardiovascular events), common side-effects and very limited benefit in reducing cardiovascular morbidity and mortality.

We must not cease from exploration. And the end of all our exploring will be to arrive where we began and to know the place for the first time.

~ Thomas Stearns Eliot (1888-1965)

Niaspan (Nicotinic Acid)

Niaspan is a once daily, prolonged-release formulation of nicotinic acid. It has been marketed in Hong Kong since 2005'. The use of the previous older generation nicotinic acid preparations was limited by their side-effect of flushing. Niaspan retains the traditional efficacy of immediate-release nicotinic acid, with improved tolerability (less flushing) and avoidance of the hepatotoxicity (<1% with elevated liver enzymes) associated with previous slow-release formulations. As monotherapy, Niaspan reduces LDL by 18-20%. Combined with a statin, Niaspan can reduce LDL by up to 50% and increase HDL by 30%.

From an old study carried out before the era of statins, the Coronary Drug project 1975', we know that nicotinic acid alone can reduce non-fatal MI by 26%, CVA by 24% and new-onset angina by 25%.[22]

Since 1990, there have been many well conducted trials of niacin and Niaspan. (Table 4)
Niaspan was shown to slow down the progression of atherosclerosis, regress the atherosclerotic plaque volume and decrease cardiovascular morbidity and mortality (surrogate and hard endpoints.)

The following are the most recent disappointing studies:
AIM-HIGH Study 2011'

- 3, 414 patients
- with atherosclerotic cardiovascular disease + LDL < 1.81mmol/L
- on top of simvastatin (Zocor) 40-80mg/day + Ezetimibe (Ezetrol) 10mg /day

- extended nicotinic acid (Niaspan) 1500-> 2000mg / day vs Placebo
- pre-mature termination after a mean follow-up of 3 years
- no significant clinical difference with placebo despite a significantly improved level of HDL and TG[38]
- **HPS2-THRIVE Study 2014'**
  - 25,673 adults with cardiovascular disease
  - A tablet that contained extended-release niacin + laropiprant
  - 2g extended-release niacin and 40mg laropiprant* vs placebo
  - Mean follow-up 3.9 years
  - No significant difference in major CV events (non-fatal MI, CV death, stroke or need for revascularization)
  - Statistically significant increase in adverse events of
    - Disturbances in DM control
    - Newly diagnosed DM
    - GI system discomfort
    - Musculoskeletal system
    - Skin
    - Infection
    - bleeding
  - the drug was withdrawn from the market in 2014'[39]

*- *a prostaglandin D2 receptor DP1 antagonist*
- improves compliance with niacin by reducing flushing by 70%

The side effect of Extended-Release Nicotinic Acid (Niaspan) that gives most cause for concern remains flushing. In the author's clinical experience, about 30% of patients experience some degree of flushing. Most episodes are very mild and decrease in intensity and frequency with prolonged use. Only around 5% of patients discontinue Niaspan because of flushing.

Some tips to reduce flushing:

- Take the tablet before sleep
- Avoid taking the tablet with alcohol
- Take the tablet with aspirin
- Avoid tablet surface scratching (there is a very thin invisible coating)
- Start at a low dosage and increase slowly

Based on review of the major studies for Nicotinic Acid (Niacin) since 1975, it is effective only in the absence of statins. Niacin is unlikely to be very beneficial in morbidity and mortality reduction in CV patients with good control of LDL (< 1.8mmo/L) by a statin.

- The author will occasionally prescribe Niaspan in the hope of further reducing cardiovascular morbidity and mortality in patients with
- Coronary artery disease,
- Low HDL with high TG and LDL (> 1.8mmol/L) by a high dose of statin, or statin intolerance.

Table 4. Major trials for Niacin and Niaspan since 1990'

Trial	Year	Pt population	Trial Design	Intervention	Results
FATS[29]	1990	126 men with CAD	Angio-graphic	Niacin +colestipol vs Lovastatin + colestipol vs usual care	decreased % of patients with progression, increased % of patients with regression ($p<0.005$)
FATS 10 yr F/U[30]	1998	75 pts who completed FATS	Open label contin-uation outcomes	Niacin +colestipol + Lovastatin vs usual care	93% reduction in total mortality ($p< 0.001$) 68% reduction cardio-vascular death/ nonfatal MI events ($p< 0.05$)
HATS[31]		167 pts w/ CAD	Coronary Angiogram	Niacin/ simvastatin +/- antioxidants	Regression in coronary stenosis 90% reduction in CVD events ($p=0.03$)
ARBITER 2[32]	2004	167 Pts w/ stable CAD	Carotid IMT	Niaspan/ statin vs statin alone for 1 year	slowed CIMT progression
ARBITER 3[33]	2006	Pts w/ stable CAD	Carotid IMT 1 year extension	Open label niacin plus statin X 24 mo.	CIMT regression at 24 months

Table 4. Major trials for Niacin and Niaspan since 1990'

Fibric acid derivatives

- Induce lipoprotein lipolysis, ↑LDL removal, ↑HDL production and reverse cholesterol transport
- LDL ↓ 5-20%, HDL ↑ 10-20%, TG ↓ 20-50%

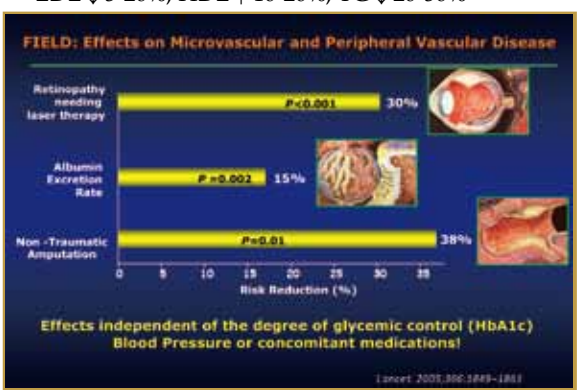


Figure 19 FIELD Study

FIELD study 2005': (Figure 19)[34]

- 9798 patients
- DM patients with total cholesterol 3.0-6.5mmol/l and either total cholesterol to HDL cholesterol ratio ≥4.0 or TG 1.0-5.0mmol/L
- 5 years follow-up
- Fenofibrate (Lipanthyl) 200mg QD vs Placebo
- Combined primary endpoint of reduced non-fatal MI or death from coronary heart disease did not reach statistical significance (hazard ratio 0.89, p=0.16)
- Microvascular and peripheral vascular disease was significantly benefited by fenofibrate
  - Retinopathy and need for laser therapy ↓ 30%
  - Albumin excretion rate ↓ 15%
  - Non-traumatic amputation ↓ 38%

ACCORD Study 2010':
- 5,518 NIDDM patients
- Mean follow-up 4.7 years
- On top of simvastatin (Zocor)
- Fenofibrate vs placebo
- No significant difference in fatal CV events, non-fatal MI, non-fatal stroke compared with simvastatin (Zocor) alone[40]

In the author's clinic, a statin is essential for over 95% of patients. In view of the possible rhabdomyolysis risk when using gemfibrocil with a statin, fenofibrate (Lipanthyl) is the only fibrate available in the author's pharmacy. (Figure 20) It's prescription is reserved largely for patients with DM and high TG and low HDL despite statin therapy, in the hope that the incidence of small vessel disease will be reduced, as demonstrated by the FIELD study.

Figure 20 The rhabdomyolysis risk of fenofibrate is much lower than that of gemfibrocil

After so many years of R&D, and apart from statins and ezetimibe, can we expect more new lipid lowering drugs?

PCSK9 inhibitory monoclonal antibodies
Mechanism:

- Proprotein convertase subtilisinkexin type 9 (PCSK9) inhibitory monoclonal antibody → increase in the numbers of LDL – receptors → further reduce LDL liver uptake in statin-receiving patients →↓↓LDL levels

Three drugs are being developed by three companies

- Alirocumab Praluent (Sanofi/Regeneron) – Phase III trial just finished,
- Evolocumab (Amgen) – Phase III trial ongoing
- Bococizumab (Pfizer/Rinat Neuroscience) – Phase III trial ongoing

Alirocumab (Praluent) – ODYSSEY Study 2015' [41]

- 2, 341 patients at high risk of CV events
- Baseline LDL level > 1.8mmol/L
- Prescribed in addition to maximum tolerated dose of statin
- Alirocumab 150mg (1ml) SC injection Q 2 weeks vs placebo
- Follow-up duration: 78 weeks
- LDL: ↓62% (P, 0.001)
- CV events (Post-Hoc analysis of pre-specified primary endpoint: CV death + non-fatal MI, fatal + non-fatal ischemic stroke + UA requiring admission): ↓48% (1.7 vs 3.3%), P= 0.02
- Adverse events :
  - o Overall similar (81% Alirocumab vs 82.5% Placebo)
  - o Significant adverse events:
    - ↑Myalgia (5.4 vs 2.9%, P = 0.006)

The PCSK9 inhibitory monoclonal antibody is our long-awaited breakthrough. It will be the most potent lipid lowering medication since the beginning of the statin era in the 1980's. As demonstrated by the Alirocumab – ODYSSEY Study, when combined with a statin, it can further reduce LDL by 60% and composite CV events by 50% with a very acceptable side effect profile. More data will be available from the Evolocumab and Bococizumab phase III trials very soon. We hope that Alirocumab will be available on the market very soon.

That which we persist in doing becomes easier ….. not that nature of the task has changes, but our ability to do has increased.

~ Ralph Waldo Emerson (1803-1882)

In a Nutshell – Practical Points

1. Hypercholesterolemia is a very important cause of CHD and CVA, the top killers in Hong Kong
2. Hypercholesterolemia is a disease that has no respect for age, affecting the very young and the very old.
3. Treatment that lowers cholesterol by 10% reduces the risk of CHD death by 15 %. Treatment for more than 5 years yields a 25% reduction in CHD events.
4. The 2013 ACC/AHA Guideline is up-dated, easy to use and good for patient education.
5. For patients with clinical ASCVD, LDL ≥4.9mmol/L and NIDDM, therapy with a moderate to high intensity statin can be started right away
6. For other patients, the friendly and free ASCVD risk estimation software can be used to estimate risk and the statin indication/intensity required accordingly.
7. Statins are a near perfect drug for hypercholesterolemia. They are simple to use (once-a day), efficient, effective, life-saving, and have few side-effects. They have been meticulously studied by numerous mega-trials, virtually without fatal adverse events and have a very reasonable price.
8. No matter which trial you are referring to, for primary or secondary prevention, or on morbidity or mortality, a statin can improve a patient's lipid profile by 20-30%.
9. The long–debated safety concerns about statins, suicidal and homicidal inclination, psychosis, carcinogenesis, rhabdomyolysis and liver damage, have been clarified.
10. The high potency Crestor, Ezetrol + Statin combination therapy and PCSK9 inhibitory monoclonal antibody + Statin therapy may help the patient achieve target LDL and HDL with minimal side-effects.
11. Most patients are asymptomatic when lipid lowering therapy is commenced with negligible side effects. Good communication is the cornerstone of successful lipid management.

References

1. LaRosa JC, Hunninghake D, Bush D, et al: The cholesterol facts. A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. A joint statement by the American Heart Association and the National Heart, Lung and Blood Institute. The Task Force on Cholesterol Issues, American Heart Association. Circulation 81:1721-1733, 1990
2. Link N, Tanner M. Coronary artery disease: Part 1. Epidemiology and diagnosis, West J Med. 2001; 174:257-61
3. Gould Al, Rossouw JE, Santanello NL et al; Cholesterol reduction yields clinical benefit: Imapct of statin trials. Circulation 97: 946-952, 1998
4. La Rosa JC, He J, Vupputuri S: Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. JAMA 282: 2340-2346, 1999
5. Verschuren WM, Jacobs DR, Bloemberg BP, et al: Serum total cholesterol and long-term coronary heart disease mortality in different cultures: Twenty-five-year follow-up of the seven countries study. JAMA 274:131-136, 1995
6. Wilson PW, Kannel WB, Silbershatz H, D'Agostino RB: clustering of metabolic factors and coronary heart disease. Arch Intern Med 159: 1104-1109, 1999
7. National Institutes of Health, National Heart, Lung, and Blood Institute: National Cholesterol Education Program, ATP III guidelines at-a-glance, quick desk reference, May 2001.
8. Lipid Research Clinics Coronary Primary Prevention Trial. JAMA 1994;272:1455-6
9. Helsinki Heart Study N Eng J Med, 1987; 317: 1237-45.
10. 4-S: Scandinavian Simvastatin Survival Study. Lancet 1994;344:1383-1389
11. WOSCOPS: West of Scotland Coronary Prevention Study. N Engl J Med 1995;333;1301-1307
12. CARE: Cholesterol and Recurrent Events. N Engl J Med 1996;335: 1001-1009
13. AFCAPS/TEXCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279:1615-1622
14. LIPIDS: Long-Term Intervention with Pravastatin in Ischemic Disease N Engl J Med 1998;339:1349-1357
15. Expert Panel on Detection, Evaluation, and Treatment of high Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of high Blood Cholesterol in Adults. (ATP III). JAMA. 2001;285:2486-2497.
16. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of Cholesterol Lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet. 2002;360(9326):7-22.
17. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Melinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized control trial. PROspective Study of Pravastatin in the Elderly ar Risk. Lancet. 2002;360:1623-1630.
18. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, et al; ASCOTinvestigators. Prevention of coronary and stroke events with atorvastation n hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lower Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361:1149-1158
19. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pferrer MA, Skene AM; Pravastatin or Atorvastatin Evaulation and Unfection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Eng J Med. 2004;350:1495-1504.
20. Gruppo Italiano per lo Studio della Sopravvivivenza nell'Infarto Miocardico: Dietary supplementation with n-3 polyunsaturation fatty acid and vitamin E after myocardial infarction: results of the GISSI-Prevention trial. Lancet 354:447, 1999.
21. ScottM. Grundy, James I. Cleeman; C. Noel Bairey Merz; H Bryan Brewer, Jr; Luther T. Clark; Donald B. Hunninghake; Richard D Pasternak; Sidney C. Smith, Jr; Neil J. Stone; for the Coordinating Committee of the National Cholesterol Education Program. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment III Guidelines. Circulation Vol. 110 No 2, July 2004: 227-239
22. Coronary Drug Project research Group. Clofibrate and niacin in coronary heart diease. JAMA 1975;231;360-81
23. John J.P. Kastelein et al., Simvastatin with or without Exetimibe in Famila Hypercholesterolemia. N Eng J Med 2008; Vol 358, 1431-1443
24. Anne B. Rossebo et al., Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. N Eng J Med 2008; Vol 359, 1343-1356
25. Jerome L. Fleg etal., Effect of Statin Alone Versus Statins Plus Ezetimibe on Carotid Atherosclerosis in Type 2 Diabetes., Journal of the American College of Cardiology, Vol.52, No.25, 2008
26. McKenney JM. Et al., Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin and pravastatin in achieving lipid goals; results from the STELLAR trial. Curr Med Res Opin 2003; 19:689-98.
27. Nissen SE., et al., Effect of very high-intensity statin therapy on regression of coronary atherosclerosis, JAMA 2006; 1556-65
28. Paul M Ridker et al., Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Eng J Med 2008, Vol 359; 2195 -2207
29. N Eng J Med 1990;323:1289-1298
30. Circulation 1998;98 (Suppl I):1-635
31. Brown BG et al., Simvastatin and niacin, antioxidantvitamins, or the ombination for the prevention of coronary disease. N Eng J Med. 2001;345:1583-1592
32. Taylor AJ et al., Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER)2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulatiojn. 2004;110:3512-3517.
33. Taylor AJ et al., The effects of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. Curr Med Res Opin. 2006;22:2243-2250
34. FIELD Study Investigators Lancet 2005; 366:1849-61
35. Dick de Zeeuw, Deborah A Anzalone et al., Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I) a randomised clinical trial. Lancet Diabetes Endocrinol 2015;3:181-90
36. Colin Baigent, Martin J Landay, Christina Reith et al., The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease 9Study of Heart and renal protection): a randomized placebo-controlled trial. Lancet Vol 377 June 25, 2011
37. Christopher P Canon, Michael A Blazing, Robert P Giugliano et al., Ezetimibe Added to Statin Therapy after Acute coronary Syndromes. NEJM June 3 2015, DOI: 10.1056/NEJMoa1410489
38. The AIM-HIGH Investigators. Niacin in Patients with Low LDL Cholesterol levels Receiving Intensive Statin Therapy. N Engl J Med 2011, 365:2255-2267
39. The HPS-THRIVE Collaborative Group Effect of Extended-release Niacin with Larodiprant in High-Risk Patients. N Eng J Med 2014:371:203-212
40. The Accord Study Group. Effect of Combination Lipid Therapy in Type 2 Diabetes Mellius N Eng L Med 2010; 362:1563-74
41. Jennifer G. Robinson, Michel Farnier, Michel Krempf, et al. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular events, N Engl J Med 372;1489-1499, 16 April 16, 2015

MCHK CME Programme Self-assessment Questions

Please read the article entitled "HYPERCHOLESTEROLEMIA - A GUIDE TO CLINICAL PRACTICE 2015 ~ An Update with Implications of Recent Clinical Trials & Medical Management with a Special Focus on New and Advanced Medications" by Dr Bernard BL WONG 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 2015. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

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

1. Hypercholeterolemia is a disease of the very old people only.
2. Treatment lower cholesterol by 10% for 5 years lower the CHD events by 5%.
3. 2013 ACC/AHA Guideline is not a user friendly lipid management guideline.
4. For NIDDM patient, we need to use ASCVD risk estimator to calculate their 10 year risk to consider whether we need to give the patient statin.
5. Statin is a weak class of drug, with no hard evidence on absolute CV disease morbidity and mortality reduction and full of dreadful side effects.
6. No matter, on what trial you are referring to, primary or secondary prevention, on morbidity or mortality, statin can give your patient a 20-30% improvement.
7. Up to this point of time, the long – debated safety issues on statin, suicidal and homicidal inclination, psychosis, carcinogenesis, rhabdomyolysis and liver damage was clarified.
8. The high potency Crestor, Ezetrol + Statin combination therapy and PCSK9 inhibitory monoclonal antibody + Statin therapy may help us to achieve the LDL and HDL goal with minimal side-effects.
9. PCSK9, when using with statin, can further reduce up to 60% of LDL level and 50% of CV morbidity and mortality, as shown in the latest ODSSEY 2015' study.
10. Since most of the patients do not have a single symptom when you are going to start your medication with non-negligible side effects, good communication is the core of successful lipid management.

ANSWER SHEET FOR DECEMBER 2015

Please return the completed answer sheet to the Federation Secretariat on or before 31 December 2015 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

HYPERCHOLESTEROLEMIA - A GUIDE TO CLINICAL PRACTICE 2015

~ An Update with Implications of Recent Clinical Trials & Medical Management with a Special Focus on New and Advanced Medications

Dr Bernard BL WONG

MBBS (HK); MRCP (UK); FRCP (Edin); FRCP, RCPS. (Glasg),
FHKCP (HK); FHKAM (MEDICINE); DGM (IRELAND); DCH (LONDON)
Specialist in Cardiology

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

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

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

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

Answers to November 2015 Issue

Palliative Care for the Aged

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

Most Taken and Recommended Statin by HK Physicians[1]

According to 2013 ACC/AHA Guideline, statin therapy should focus on ASCVD risk reduction.[2]

MIRACL[3]	SPARCL[4]	TNT[5]	ASCOT-LLA[6]	CARDS[7]	ARMYDA[8]	PROVE-IT[9]	IDEAL[10]	GREACE[11]
✓	✓	✓	✓	✓	✓	✓	✓	✓

Proven to reduce CV events by up to 50% in multiple major CV outcomes trials.[3-11]

- Efficacious LDL-C lowering[12,13]
- Proven CV outcomes evidence from landmark trials[3-11]
- NO dosage adjustment in patients* with renal impairment[12,14]

*excluding kidney transplant patients

LIPITOR
atorvastatin calcium
(crystalline form) tablets
Power. Evidence. Confidence.™

References 1. Ahead Research Consultants, "HCP's Statin Preference Research Report", 2013 n=120 physicians. 2. 2013 ACC/AHA Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. American Heart Association. Circulation. 2013;00:000–000. 3. Schwartz GG, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes - the MIRACL Study: A randomized controlled trial. JAMA 2001;285(13):1711-1718. 4. Amarenco P, et al. High-Dose Atorvastatin after Stroke of Transient Ischemic Attack. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL). N Engl J Med 2006;355(6):549-59. 5. LaRosa JC, et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Engl J Med. 2005;352:1425-35. 6. Sever PS, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58. 7. Colhoun HM, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96. 8. Di Sciascio G, et al. Efficacy of Atorvastatin Reload in Patients on Chronic Statin Therapy Undergoing Percutaneous Coronary Intervention: Results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. JACC 2009;54(6):558-565. 9. Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495-504. 10. Pedersen TR et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005;294(19):2437-45. 11. Athyros V et al. Treatment with Atorvastatin to the National Cholesterol Education Program Goal Versus 'Usual' Care in Secondary Coronary Heart Disease Prevention. The GREek Atorvastatin and Coronary-heart-disease evaluation (GREACE) Study. Curr Med Res Opin 2002;18:220–8. 12. Lipitor® (atorvastatin) Prescribing Information. Pfizer Corporation Hong Kong Limited. Version September 2011. 13. Law MR et al. BMJ 2003;326:1423-1427 14. KDOQI Clinical Practice Guideline For Diabetes and CKD: 2012 Update. Am J Kidney Dis 2012;60(5):850-886.

LIPITOR ABBREVIATED PACKAGE INSERT 1. TRADE NAME: Lipitor® **2. PRESENTATION:** The tablets for oral administration contain atorvastatin calcium equivalent to 10, 20, 40 or 80 mg atorvastatin. **3. INDICATIONS:** Adjunct to diet for the treatment of patients with elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in patients with primary hypercholesterolemia (heterozygous familial and non-familial hypercholesterolemia), combined (mixed) hyperlipidemia (Fredrickson Types IIa and IIb), elevated serum triglyceride levels (Fredrickson Type IV), and for patients with dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet. For the reduction of total cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolemia when response to diet and other non-pharmacological measures are inadequate. Reduce the risk of myocardial infarction, stroke, revascularization procedures and angina in adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease. Reduce the risk of myocardial infarction and stroke in patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension. Reduce the risk of non-fatal myocardial infarction, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF and angina in patients with clinically evident coronary heart disease. Atorvastatin is also indicated as an adjunct to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: a. LDL-C remains ≥ 190 mg/dL or b. LDL-C remains ≥ 160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the pediatric patient. **4. DOSAGE:** The recommended starting dose of Lipitor is 10 or 20mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40mg once daily. The dosage range is 10 to 80 mg once daily. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks, and dosage adjusted accordingly. **5. CONTRAINDICATIONS:** Hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal. Pregnant, breast-feeding, or of childbearing potential who are not using adequate contraceptive measures. Atorvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards to the fetus. **6. WARNINGS & PRECAUTIONS:** As with other lipid-lowering agents of the same class, moderate (>3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin. Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggesting liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality (ies) resolve(s). Should an increase in ALT or AST of greater than three times the upper limit of normal persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin can cause an elevation in transaminases. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Myalgia has been reported in atorvastatin-treated patients. **7. INTERACTIONS:** Cyclosporine, fibric acid derivatives, lipid-modifying doses of niacin or cytochrome P450 3A4 inhibitors (e.g., erythromycin, and azole antifungals), clarithromycin, protease inhibitors, diltiazem hydrochloride, itraconazole, grapefruit juice, inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin), antacids, colestipol, digoxin, oral contraceptives, fusidic acid **8. PREGNANCY AND LACTATION:** Atorvastatin is contraindicated in pregnancy and while breast-feeding. **9. SIDE EFFECTS:** Nasopharyngitis, hyperglycemia, pharyngolaryngeal pain, epistaxis, nausea, diarrhea, dyspepsia, flatulence, arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling, liver function test abnormal, blood creatine phosphokinase increased.
Reference: HK PI (SEP2011) Date of preparation: FEB2013 Identifier number: LIPI0213 **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

Pfizer **Pfizer Corporation Hong Kong Ltd**
18/F, Kerry Centre, 683 King's Road, Quarry Bay, Hong Kong Tel: (852) 28119711 Fax: (852) 25790599 Website: www.pfizer.com.hk

Collecting Antique String Instruments – Part 2

Dr Alex SB YIP

Dr Alex SB YIP

MBBS (London), MRCP (UK), FRCP (Edinburgh), FHKAM (Medicine)
Specialist in Cardiology and Internal Medicine

Last episode I gave an introduction to string instruments, and here I would like to elaborate and highlight certain aspects regarding choosing and collecting string instruments, with special mention of the violas and cellos.

A word on the condition of instruments is called for. Most of those over 100 years old are not in mint condition and different degree of repairs have been done. Some defects have more impact than others. Major defects very significantly affect the desirability of instruments include soundpost crack and basebar crack. The former especially at the back, even well repair can reduce the price of the instrument by half, especially for violins. Minor cracks if repaired well for example of the ribs generally not considered matter too much and acceptable to many. The scroll and head, if by a different maker, would reduce the price of the instrument somewhat but minimal effect on the sound which it can produce. Potential buyers must check carefully and ask for professional report of the condition of old string instruments before making the decision to purchase.

It is perhaps surprising that the same instrument when played by different players can sound very different, so different instruments will suit different players, with their different style of playing. Professional and even serious amateur players will not neglect the very significant effect on high quality bows on instruments. The top level bows, such as those made by Tourte and Peccatte from France in the 19th century, when matched with high level old Italian instruments, produce such a wide spectrum of tone colours that contemporary bows simply cannot match. However, such great bows will generally not have significant effect on more contemporary instruments, when high quality bows of the 20th century French makers, e.g. Sartory, Lamy, Fetique, Ouchard, may be more suitable. Bows that have been worn significantly through playing command lesser price than those in near mint condition.

Old instruments when not played for years, can be dormant and need time to be woken up by playing. Sometimes it can take a few years of regular playing to revitalize them. So it is logical that these quality instruments be played regularly to be kept alive, and when played by expert musicians their quality can further improve. It often takes months or even years to fully explore great instruments so that the individual artist can be thoroughly familiar with the instruments' fully potential and capabilities.

Violas, closely related to violins, although slightly bigger in size only, sound very different. Because of its lower frequency, its volume tends to be less penetrating than violins. Asian musicians, including Chinese violists, have a generally less massive build than Western counterparts and hence the size of viola is important. Chinese players are generally more comfortable when the length of back is no more than 16 inches, and even 15 inches instruments can produce good volume and very comfortable to play with.

In view of the escalating costs of quality old instruments, especially old Italian famed makers, modern Italian instruments which are approximately 100 years old are starting to catch up in price. Modern is not to be confused with contemporary makers which include those in last 30 to 40 years. As a rough rule of thumb, pre second World War (before 1940) considered by many more desirable than post second World War and at their best also produce very high quality instruments which are obviously more affordable than old vintage violins. Some contemporary famous makers have a waiting list for commission of new instruments and a time period of 2 years is not uncommon.

Cellos are more expensive than violins and violas, as vintage instruments in good condition much harder to find. Of note also, some famed makers in the past made better cellos than violins, such as 18th century Italian makers Testore, Grancino, David Tecchler, Godfrillar, Montagnana, their cellos by general concensus often better than their violins.

Many aspiring young string players are being loaned valuable string instruments from various organizations and music conservatories. Whereas there is no doubt that having such instruments are very important to further develop their instrumental achievement, when the moment comes that they have to return their loaned instrument is often a painful and depressing one, causing considerable stress to the players, for having to downgrade very substantially from an quality instrument for a few years can be very traumatic and takes a long time to readjust!

As I mentioned in my last article, it can be very misleading just to test the instrument with your own ear in a room of limited size, for some instruments which appear to have a big tone next to the ear turn out to have inadequate projection in a larger venue. Hence for any middle grade instruments, I would suggest to always ask your friends to listen from a distance in a reasonable size venue.

Finally, in deciding between whether to go for an instrument in mint condition made by a famed maker or an instrument with a tone much liked by the player but in less than immaculate condition, my advice is to go for the tone for the player, but for the mint condition one if you are an investor, provided that both instruments are asking for reasonable prices.

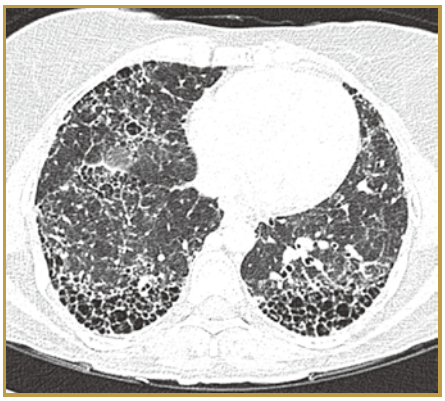
I was in the audience in Itzhak Perlman recital on 8 November and have the opportunity to sit in the choir seats in the first half and then in the balcony, both near central location in the hall. The sound from each location is different, being more silvery in the choir seats and stronger in the balcony. Although I cannot confirm that the instrument is his 'Soil" Stradivarius, but its superb projection and bell like top notes and its tonal variety had me completely bowled over!
Below left Italian violin made by Eugenio Degani , Venice 1897
Below right French violin made by Justin Derazay, Mirecourt 1875

Radiology Quiz

Dr Chun LEE

MBBS(HK)

Resident, Department of Radiology, Queen Mary Hospital



Questions:

1. What study is this?
2. What are the imaging findings?
3. What is your diagnosis and possible differential diagnosis?
4. What are the common underlying causes?

(See P.44 for answers)

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		★ HKMA Kowloon West Community Network - Advance in Rheumatic Diseases ★ HKMA Council Meeting ★ FMSHK Officers' Meeting **1**	★ HKMA Central, Western & Southern Community Network - Early Infant Feeding & Allergic Disorders **2**	★ HKMA Hong Kong East Community Network - A Pathophysiological Approach to the Treatment of Type 2 Diabetes **3**	★ HKPGA Capacity Conference cum Annual General Meeting 2015 Pre-conference Workshop on Mental Capacities ★ HKMA Yau Tsim Mong Community Network - Complementary and Alternative Medicine (CAM) for Childhood Asthma: An Overview of Evidence ★ The 9th Pong Ding Yuen International Symposium on TCM- Pre-conference Workshop: Biological Basis of Clinical Management in Mental Disease **4**	**5**
6	**7**	★ Inter-hospital Rheumatology Meeting 2015- 1. Cancer Risk and Mortality in Rheumatic Diseases (excluding inflammatory myopathies) 2. Case Presentation **8**	★ Hong Kong Neurosurgical Society Monthly Academic Meeting –Molecular Genetics in Glioma **9**	★ HKMA Kowloon East Community Network - Shingles Prevention from Infectious Disease Specialist's Perspective ★ HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2015 – Targeted Therapy for General Practitioners **10**	**11**	★ CME Lecture - Refresher Course for Health Care Providers 2015/2016 **12**
13	**14**	★ HKMA Kowloon West Community Network - Rosacea and Related Dermatoses ★ PET/ MR (MOLECULAR MR) SYMPOSIUM 2015 **15**	★ HKMA Shatin Doctors Network - Update on the Management of Hypertension **16**	★ HKMA New Territories West Community Network - New Insight for Atopic Eczema Treatment ★ KECN-HKCFP-UCH – Certificate Course for GPs 2015 (Session 6) – Update on DM Management ★ FMSHK Executive Committee Meeting **17**	**18**	**19**
20	**21**	**22**	**23**	**24**	**25**	**26**
27	**28**	**29**	**30**	★ FMSHK Annual Dinner 2015 ★ HKMA Annual Ball 2015 **31**		

Date / Time	Function	Enquiry / Remarks
1 TUE 1:00 PM	**HKMA Kowloon West Community Network - Advance in Rheumatic Diseases** Organiser: HKMA Kowloon West Community Network and Hong Kong Society of Rheumatology; Chairman: Dr. WONG Wai Hong, Bruce; Speaker: Dr. TSUI Hing Sum, Kenneth; Venue: Crystal Room IV-V, 3/F., Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
8:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. SHIH Tai Cho, Louis; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
2 WED 1:00 PM	**HKMA Central, Western & Southern Community Network - Early Infant Feeding & Allergic Disorders** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. YIK Ping Yin; Speaker: Dr. Barbara CC LAM, JP; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F., Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
3 THU 1:00 PM	**HKMA Hong Kong East Community Network - A Pathophysiological Approach to the Treatment of Type 2 Diabetes** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. AU YEUNG Shiu Hing; Speaker: Dr. MA Pui Shan; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
4 FRI 9:00 AM	**HKPGA Capacity Conference cum Annual General Meeting 2015** **Pre-conference Workshop on Mental Capacities** Organiser: Hong Kong Psychogeriatric Association; Speakers: Prof Sanford I. FINKEL, Prof Camelle PEISAH, Ms Olivia SM LEUNG; Venue: Thornton Room & Huthart Room I, 3/F, South Tower of the YMCA-The Salisbury Hotel	Ms Jossy TIN Tel: 2516 6128 Website: www.hkpga.org/main.php?id=141
9:00 AM	**HKMA Yau Tsim Mong Community Network - Complementary and Alternative Medicine (CAM) for Childhood Asthma: An Overview of Evidence** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHENG Kai Chi, Thomas; Speaker: Prof. HON Kam Lun, Ellis; Venue: Pearl Ballroom, Level 2, Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
5:30 PM	**The 9th Pong Ding Yuen International Symposium on TCM- Pre-conference Workshop: Biological Basis of Clinical Management in Mental Disease** Organiser: Hong Kong Association for Integration of Chinese-Western Medicine; Chairman: Dr YU Edwin Chau Leung; Prof ZHANG Zhang Jin; Speakers: Prof YUNG Ken Kin Lam; Dr YU Edwin Chau Leung; Dr LAW Andrew Chi Kin; Venue: MDLI (Multidisciplinary Laboratory 1, G/F, Lab Block, Faculty of Medicine Building, 21 Sasson Road, Pokfulam, HK	Miss Y.C. YEUNG Tel: 3119 1858 2 CME Point
8 TUE 6:00 PM	**Inter-hospital Rheumatology Meeting 2015- 1. Cancer Risk and Mortality in Rheumatic Diseases (excluding inflammatory myopathies) 2. Case Presentation** Organiser: The Hong Kong Society of Rheumatology; Chairman: Dr ML YIP; Speaker: Dr KWONG Ying Yui; Venue: Room 205S, Hospital Authority Headquarters	Dr LEE Ka Lai Tel: 2595 6111 1 CME Point
9 WED 7:30 AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting –Molecular Genetics in Glioma** Organiser: Hong Kong Neurosurgical Society; Chairman: Dr Jenny PU Speaker: Dr CHOW Shuk Wan, Joyce; Venue: M Block Ground Floor Lecture Theatre, Queen Elizabeth Hospital	Dr. LEE Wing Yan, Michael Tel: 2595 6456 1.5 CME Point
10 THU 1:00 PM	**HKMA Kowloon East Community Network - Shingles Prevention from Infectious Disease Specialist's Perspective** Organiser: HKMA Kowloon East Community Network; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. SO Man Kit, Thomas; Venue: Lei Garden Restaurant (利苑酒家) Shop no. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kowloon	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
2:00 PM	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2015 – Targeted Therapy for General Practitioners** Organiser: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. KWAN Wing Hong; Venue: Function Room A, HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
12 SAT 2:15 PM	**CME Lecture - Refresher Course for Health Care Providers 2015/2016** Organiser: The Hong Kong Medical Association; Speaker: Dr. Tam Kui Fu, Stanley; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara Tsang Tel: 2354 2440 2 CME Point
15 TUE 1:00 PM	**HKMA Kowloon West Community Network - Rosacea and Related Dermatoses** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LAM Ngam, Raymond; Speaker: Dr. LEE Tze Yuen; Venue: Crystal Room IV-V, 3/F., Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T.	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
6:00 PM	**PET/ MR (MOLECULAR MR) SYMPOSIUM 2015** Organiser:Hong Kong Sanatorium & Hospital; Chairpersons: Dr Gladys LO; Dr Garrett HO; Speakers: Prof Lale UMUTLU; Prof Robert C MCKINSTRY; Venue: Ballroom, JW Marriott Hotel Hong Kong.	Tel: 2835 3460/ 2835 3461
16 WED 1:00 PM	**HKMA Shatin Doctors Network - Update on the Management of Hypertension** Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. WONG Tai Hung, John; Venue: Jasmine Room, Level 2, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Karen WONG Tel: 3605 5843 1 CME Point
17 THU 1:00 PM	**HKMA New Territories West Community Network - New Insight for Atopic Eczema Treatment** Organiser: HKMA New Territories West Community Network; Chairman: Dr. CHUNG Siu Kwan, Ivan; Speaker: Dr. CHAN Yung;Venue: Pearl Ocean (金霞殿), 1/F., Gold Coast Yacht and Country Club (黃金海岸鄉村俱樂部-遊艇會), 1 Castle Peak Road, Castle Peak Bay, Hong Kong	Miss Hana YEUNG Tel: 2527 8285 1 CME Point

Date / Time	Function	Enquiry / Remarks
17 THU 1:00 PM	**KECN-HKCFP-UCH – Certificate Course for GPs 2015 (Session 6) – Update on DM Management** Organiser: HKMA Kowloon East Community Network & Hong Kong College of Family Physicians & United Christian Hospital; Chairman: Dr. SHA Kwok Yiu, Edmund; Speaker: Dr. KAM Yee Wai, Grace; Venue: V Cuisine, 6/F., Holiday Inn Express Hong Kong Kowloon East, 3 Tong Tak Street, Tseung Kwan O	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong, Veune: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
31 THU 7:00 PM	**FMSHK Annual Dinner 2015** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Run Run Shaw Hall, The Hong Kong Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen, Hong Kong	Ms Eva TSANG Tel: 2527 8898
8:00 PM	**HKMA Annual Ball 2015** Organiser: The Hong Kong Medical Association; Chairman: Dr. CHAN Yee Shing, Alvin; Venue: Conrad Hong Kong, One Pacific Place, 88 Queensway, Admiralty	Ms. Candy YUEN Miss Ellie FU Tel: 2527 8285

Answers to Radiology Quiz

Answer:

1. This is a HRCT study of the thorax. High-resolution computed tomography (HRCT) refers to computed tomography (CT) with high resolution. High resolution CT is a scanning protocol in which thin sections (usually 0.625 to 1.25 mm) are acquired at 10mm intervals and reconstructed using a sharp algorithm (e.g. bone algorithm). HRCT of the lung is commonly used for diagnosis and assessment of interstitial lung disease.

2. Imaging features include macrocystic honeycombing, reticular opacities, traction bronchiectasis, architectural distortion and some patchy ground-glass opacities. Distribution is apicobasal gradient (whole imaging series are not included here) and predominantly with peripheral subpleural location.

3. Diagnosis is usual interstitial pneumonitis/pneumonia (UIP), previously known as idiopathic pulmonary fibrosis. A key imaging differential on cross sectional imaging would be non specific interstitial pneumonia (NSIP) but there would be characteristic subpleural sparing and absence of honeycombing as distinguishing features. Predominant ground glass opacities would also be seen in NSIP.

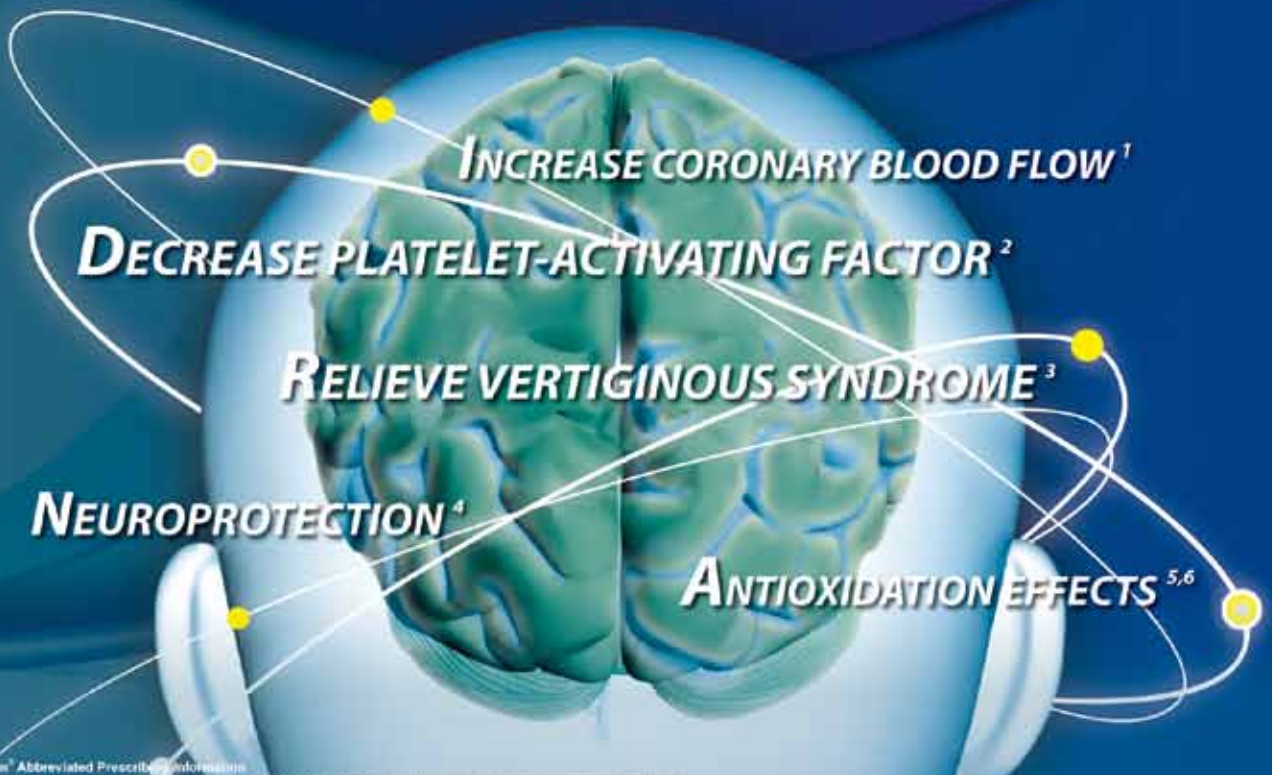
4. Common associations include:
   a. Connective tissue disorders
   - Rheumatoid arthritis: UIP is considered to be the dominant pattern in those with rheumatoid arthritis and concurrent interstitial lung disease
   - Systemic sclerosis: can have either a UIP or NSIP (commoner) pattern
   - Polymyositis/dermatomyositis: such patients can have a UIP or NSIP pattern.
   - Mixed connective tissue disease: can have either a UIP or NSIP pattern

   b. Asbestos related interstitial lung disease: asbestosis

   c. Idiopathic

Dr Chun LEE
MBBS(HK)
Resident, Department of Radiology, Queen Mary Hospital

NEUROPROTECTION POWERED BY VASCULAR CIRCULATION



TanaKan® Abbreviated Prescribing Information

Description: Each tablet contains standardized Ginkgo biloba extract (EGb 761) with 24% Ginkgo flavonoids and 6% of Ginkgolides-bilobalide. **Therapeutic indications:** Mild neurogenic disorders related to the age, symptomatic treatment of ulcers of the lower limbs due arteries disease involving painful claimax during walking), Ocular disorders and other disorders (hearing or vertigo) of circulatory origin, Raynaud's disease. **Dosage and administration:** One dose is equal to one tablet containing 40mg of extract. Usual dosage: 3 tablets per day in several doses at mealtimes. Tablets should be taken with a half-glass of water during meals. **Precautions:** Hypersensitivity to one of the ingredients of the tablet. Pregnancy. Breastfeeding. **Adverse effects:** Digestive disorders. Skin disorders. Headaches. **Contraindications:** The medicinal product contains lactose, it is contra-indicated in subjects presenting with congenital galactosemia, glucose or galactose malabsorption syndrome or with lactase deficiency. **Storage conditions and shelf life:** Store below 25°C. Do not exceed the expiry date plainly indicated on the packaging. Keep out reach of children. **Form and presentations:** tablets. Box of 20 tablets in blisters.

References:
1. Wu Y, Li S, Cui W, et al. Ginkgo biloba extract improves coronary blood flow in healthy elderly adults: role of endothelium-dependent vasodilation. Phytomedicine 2005;15:164-169. 2. Akisu M, Kultursay N, Goker I, et al. Platelet-activating factor is an important mediator in hypoxic ischemic brain injury in the newborn rat. Biol Neonate 1998;74:439-444. 3. Haguenauer JP, Cazenoit F, Koskas H and Perart H. (1986) Treatment of disturbed equilibrium with Ginkgo biloba extract. In: Fortgeld EW, Rokan (Ginkgo Biloba). Recent Results in Pharmacology and Clinic (pp. 260-268). Springer-Verlag Berlin Heidelberg New York. 4. Lee EJ, Chen HY, Wu TS, et al. Acute administration of ginkgo biloba extract (Egb 761) affords neuroprotection against permanent and transient focal cerebral ischemia in Sprague-dawley rats. J Neurosci Res 2002;68:636-645. 5. Le Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the ginkgo biloba extract EGb 761® in dementia. Dement Geriatr Cogn Disord 2000;11:230-237. 6. Pietri S, Seguin JR, d'Arbigny P, et al. Ginkgo biloba extract (EGb761) pre-treatment limits free radical-induced oxidative stress in patients undergoing coronary bypass surgery. Cardiovasc Drugs Ther 1997;11:121-131.

Place of origin: France

Full prescribing information is available upon request.

Manufactured by:

IPSEN
Innovation for patient care

Distributed by:

LF ASIA

LF Asia (Hong Kong) Limited - Healthcare Division
2/F, HK Spinners Industrial Building, Phases I & II,
800 Cheung Sha Wan Road, Kowloon, HK
Tel: 2635 5950 Fax: 2637 5818

tanakan®
Standardized Ginkgo Biloba Extract (EGb 761) 40mg

NOW APPROVED

FOR PATIENTS LIKE JANE

JARDIANCE PROVIDES A POSITIVE EXPERIENCE

CV: cardiovascular; SGLT-2: sodium glucose cotransporter 2

* JARDIANCE is not indicated for weight loss

† Weight change was a secondary endpoint in clinical trials

References:

1. Jardiance® Hong Kong prescribing information. **2.** Merker L, et al. Poster 1079-P. Presented at the 74th Scientific Session of American Diabetes Association, 13-17 June 2014, San Francisco, CA, USA. **3.** Roden M, et al. Lancet Diabetes Endocrinol. 2013;1:208-219. **4.** Häring HU, et al. Diabetes Care. 2014;37:1650-1659. **5.** Häring HU, et al. Diabetes Care. 2013;36:3396-3404. **6.** Rosenstock J, et al. Diabetes Obes Metab. 2015;17:936-948. **7.** Zinman B, et al. N Engl J Med. 2015 Sep 17. [Epub ahead of print].

JARDIANCE®

Presentation: Empagliflozin. Film-coated tablet 10 mg and 25 mg. **Indications:** Adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as monotherapy or as combination therapy with other glucose-lowing medicinal products including insulin. **Dosage and administration:** Recommended starting dose is 10 mg once daily. For patients who tolerate 10 mg and need additional glycaemic control, their dose can be increased to 25 mg once daily. Can be taken with or without food. **Contraindication:** Hypersensitivity to empagliflozin or to any of the excipients. **Special warnings and precautions:** Should not be used in patients with type 1 diabetes or diabetic ketoacidosis. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m^2 or CrCl <60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 or CrCl persistently below 45 ml/min. Should not be initiated in patients with eGFR below 60 ml/min/1.73 m^2 or CrCl <60 ml/min; ESRD or patients with dialysis; aged 85 years and older; severe hepatic impairment. Caution should be exercised in patients at risk for volume depletion. Temporary interruption of treatment until the fluid loss is corrected or in patients with complicated urinary tract infections. Caution in patients with NYHA III and IV cardiac failure. Avoid use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. A lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia when used in combination with empagliflozin. Test positive for glucose in urine. Should be avoided during pregnancy; breast-feeding. Caution when driving or operating machines. **Interactions:** Diuretics, insulin & insulin secretagogues. May decrease efficacy with inducers of UGT enzymes. **Adverse reactions: Very common:** hypoglycaemia when used with sulphonylurea or insulin. **Common:** vaginal moniliasis, vulvovaginitis, balantis and other genital infection, urinary tract infection, pruritus (generalised), increased urination. **Uncommon:** volume depletion, dysuria. **Note:** Before prescribing, please consult full prescribing information.

Boehringer Ingelheim

Boehringer Ingelheim (HK) Ltd.
1504-9, Great Eagle Centre, 23 Harbour Road, Wanchai, Hong Kong
Tel: (852) 2596 0033 Fax: (852) 2827 0162 www.boehringer-ingelheim.com

JAR-10-2015-02