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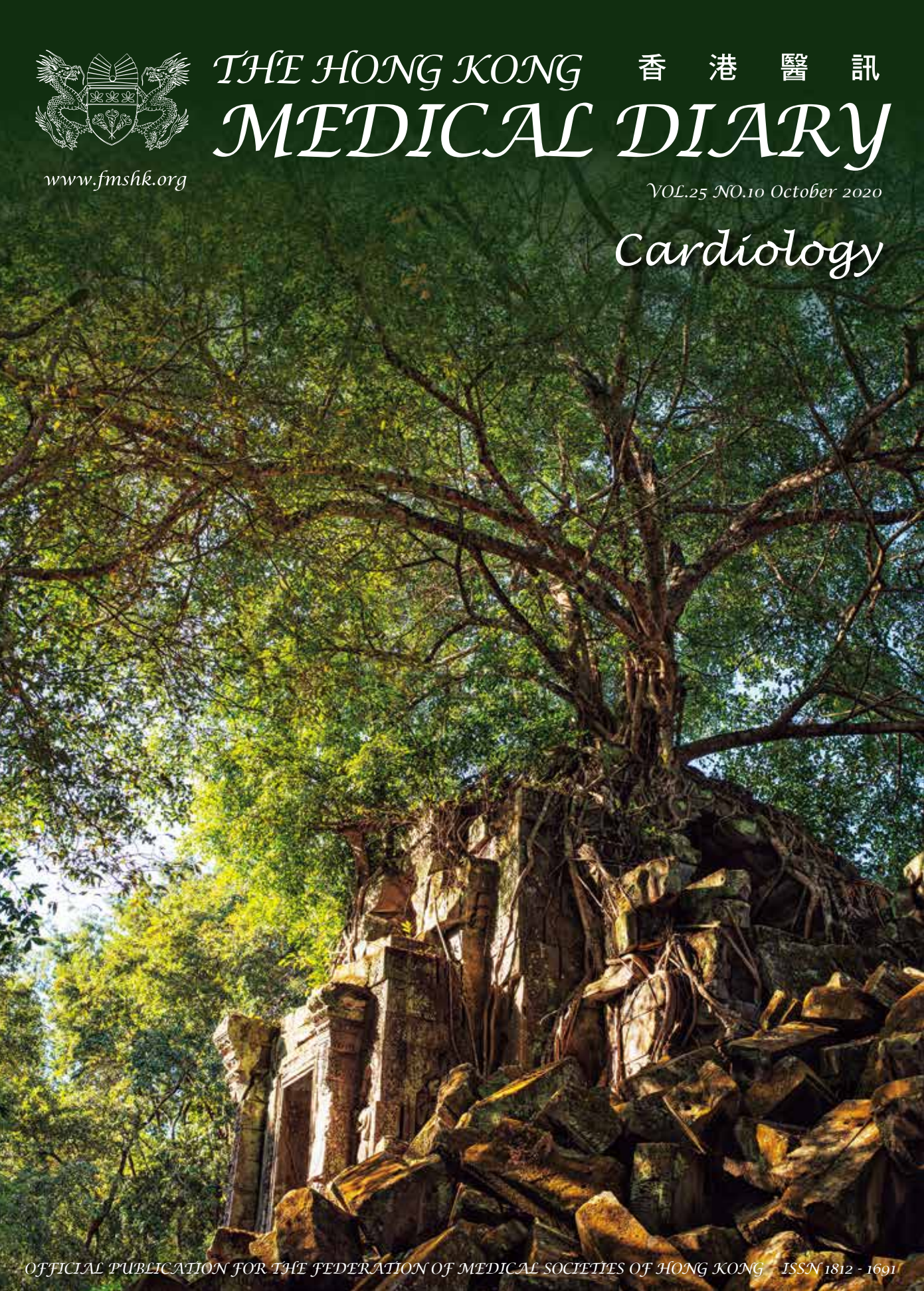
Cardiology



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Betmiga®
mirabegron

THE *1ST* β_3-AGONIST FOR **OAB* PATIENTS**
WITH PROMISING SAFETY PROFILE
PLACEBO-LIKE DRY MOUTH(1.7%) SIDE EFFECT[1]

Harnal OCAS®
tamsulosin

YOUR *1ST* STEP FOR **MALE LUTS+ PATIENTS**
WITH PROMISING SAFETY PROFILE#
PLACEBO-LIKE DIZZINESS(1.4%) SIDE EFFECT[2]

A *FRESH* STEP IN LUTS+ MANAGEMENT

*OAB: Overactive Bladder + LUTS: Lower Urinary Tract Symptoms
α_1-blockers are often considered the first line drug treatment of male LUTS[3]

Reference: **1.** Chapple C.R. et al. Neurourol Urodynam 2013 [doi 10.1002/nau22505] **2.** Chapple C.R. et al. Eur Urol Supp. 2005; 4:33-44
3. Gravas S, et al. EAU Guidelines on the Treatment of Non-neurogenic Male LUTS. European Association of Urology. 2017.

Abbreviated prescribing information of Harnal OCAS® 0.4 mg Tablets
Version: 002 PI version: Sep 2013. **Composition:** Tamsulosin HCl **Indication:** Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). **Dosage:** 1 tab daily, can be taken independently of food. **Administration:** Swallow whole, do not chew/crunch. **Contraindications:** Hypersensitivity to tamsulosin hydrochloride or to any of the excipients. **Special warnings and special precaution for use:** As with other α1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with Harnal OCAS® 0.4 mg Tablets, as a result of which, rarely, syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared. Before therapy with Harnal OCAS® 0.4 mg Tablets is initiated, the patient should be examined in order to exclude the presence of other conditions, which can cause the same symptoms as benign prostatic hyperplasia. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards. Treatment of patients with a history of orthostatic hypotension should be approached with caution. The treatment of patients with severe renal impairment (creatinine clearance of <10 ml/min) should be approached with caution, as these patients have not been studied. The treatment of patients with severe hepatic dysfunction should be approached with caution. The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin hydrochloride 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. IFIS has also been reported in patients who had discontinued tamsulosin for a longer period prior to the surgery. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery. Tamsulosin hydrochloride should not be given in combination with strong inhibitors of CYP3A4 in patients with poor metaboliser CYP2D6 phenotype. Tamsulosin hydrochloride should be used with caution in combination with strong and moderate inhibitors of CYP3A4. Cases of allergic reaction to tamsulosin in patients with a past history of sulfonamide allergy have been reported. If a patient reports a previously experienced sulfa allergy, caution is warranted when administrating tamsulosin hydrochloride. **Undesirable effects:** *Common (>1%, <10%), Uncommon (>0.1%, <1%), Rare (>0.01%, <0.1%), Very rare (<0.01%). Cardiac disorder: Uncommon:* Palpitations. *Gastrointestinal disorders: Uncommon:* Constipation, diarrhoea, nausea, vomiting. *General disorders and administration site conditions: Uncommon:* Asthenia. *Nervous systems disorders: Common:* Dizziness (1.3%). *Uncommon:* Headache. *Rare: Syncope. Reproductive system and breast disorders: Common:* Ejaculation disorders. *Very rare:* Priapism. *Respiratory, thoracic and mediastinal disorders: Uncommon:* Rhinitis. *Skin and subcutaneous tissue disorders: Uncommon:* Rash, pruritus, urticaria. *Rare:* Angioedema. *Vascular disorders: Uncommon:* Orthostatic hypotension. ***Post-marketing experience:*** The following events have also been reported during the post-marketing period. These events are reported voluntarily from a population of uncertain size, therefore it is not possible to reliably estimate their frequency: visual disorders (e.g. blurred vision, visual impairment), dermatitis exfoliative, erythema multiforme and epistaxis. During cataract and glaucoma surgery a small pupil situation, known as Intraoperative Floppy Iris Syndrome (IFIS), has been reported. **Full prescribing information is available upon request.**

Abbreviated prescribing information of Betmiga® prolonged-release tablets
Version: 003 PI version: Apr 2016. **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with - Hypersensitivity to the active substance or to any of the excipients. - Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m² or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,433 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Infections and infestations: Common: Urinary tract infection. Uncommon: Vaginal infection, Cystitis. Psychiatric disorders: Not known (cannot be estimated from the available data): Insomnia*. Eye disorders: Rare: Eyelid oedema. Cardiac disorders: Common: Tachycardia. Uncommon: Palpitation, Atrial fibrillation. Vascular disorders: Very rare: Hypertensive crisis*. Gastrointestinal disorders: Common: Nausea*, Constipation*, Diarrhoea*. Uncommon: Dyspepsia, Gastritis. Rare: Lip oedema. Skin and subcutaneous tissue disorders: Uncommon: Urticaria, Rash, Rash macular, Rash popular, Pruritus. Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. Musculoskeletal and connective tissue disorders: Uncommon: Joint swelling. Reproductive system and breast disorders: Uncommon: Vulvovaginal pruritus. Investigations: Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. Renal and urinary disorders: Rare: Urinary retention*. Nervous system disorders: Common: Headache*, Dizziness*. *observed during post-marketing experience. **Full prescribing information is available upon request.**

Astellas Pharma Hong Kong Co., Ltd. Unit 1103-08, 11/F, Tower 1, Grand Century Place, 193 Prince Edward Road West, Mongkok, Kowloon.
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Contents

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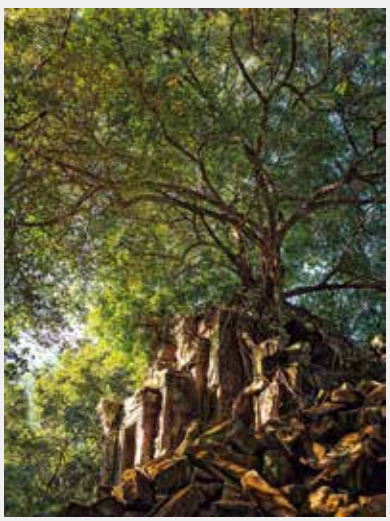

If you're looking for more inspiration in Cambodia rather than the traditional Angkor Wat, Beng Melea is an absolute standout. I went there with my wife and a local tour guide in the early morning. The whole archaeological site is embedded inside a jungle 80 km away from Angkor. The remoteness of the site and the late discovery in history due to its coverage by thick jungle renders the ruins untouched by modern civilisation. The whole place belongs to you with the enchanting sounds of the jungle surrounds. Beng Melea is a huge complex, and it takes quite a while to enjoy the vast photographic opportunities offered. This picture was obtained alongside the outer wall walk around the ancient city ruins. The trees grow through the ruins of the Hindu Temple, which has been standing there since the early 12th century. This photograph offers a unique sense of solitude and quietude, which is the main theme of this composition.

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Editorial

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Editor

Dr Godwin Tat-chi LEUNG

I would like to express my sincere gratitude to the Editorial Board of the FMSHK for inviting me to be the editor and to invite representatives of the Hong Kong College of Cardiology to contribute to this Cardiology issue of the Hong Kong Medical Diary. I wrote my first article for the Medical Diary in 2005. Since then, there have been numerous landmark studies, countless breakthroughs and tremendous advancements in the field of Cardiology. By flipping through the past issues, we can witness significant improvement in the prevention, detection and treatment of various heart diseases which have been proven to be of great benefit to our patients. I hope this issue can bring our readers the latest knowledge in some of these areas.

Cardiology is one of the most rapidly expanding specialities in Internal Medicine, and there are many different subspecialties. With a view to enhancing the practice and training in these various subspecialties, the Hong Kong College of Cardiology has established various chapters including Cardiovascular Intervention Chapter, Pacing and Clinical Electrophysiology Chapter, Preventive Cardiology and Cardiac Rehabilitation Chapter, Paediatric Cardiology Chapter, Cardiac Magnetic Resonance Imaging Chapter and Echocardiography Chapter. Each of these Chapters has been organising different scientific activities to achieve the goal of professional education and training for cardiology trainees, cardiologists and other professionals in Hong Kong.

I am honoured to have invited distinguished specialists from different chapters to enlighten us on various aspects of Cardiology in this issue. Despite established therapies for coronary artery disease, the residual risk of ischaemic events remains in many high-risk patients. Professor Bryan Yan shares his insight on dual pathway inhibition in high-risk chronic coronary syndrome patients. The presence of atrial fibrillation in patients with heart failure is associated with an increased risk of stroke, hospitalisations and all-cause mortality. Catheter ablation is playing an increasing role in the treatment of patients with atrial fibrillation. Drs Ngai-yin Chan and Ho-chuen Yuen discuss the benefits of rhythm control of atrial fibrillation in patients with heart failure. Interventional cardiology keeps expanding in scope since its inception. Refinement and development in equipment and technology will continue to extend the capabilities of interventional cardiologists and improve the safety and effectiveness of the procedures. Dr Andy Chan and Dr Raymond Fung give us an updated account of the latest developments in the ever-expanding field of coronary and structural heart intervention. Advancements in medical imaging have allowed us to better diagnose and treat our patients. Dr Carmen Chan explains to us the role of cardiac imaging in Cardio-oncology. Last but not least, our Paediatrician colleagues, Drs Tak-cheung Yung and Kwok-lap Chan write an updated review on Kawasaki disease, the most common cause of acquired heart disease in children in developed countries.

Apart from professional education and training, heart health promotion for the citizens of Hong Kong is another important mission of the Hong Kong College of Cardiology. The College has actively organised and involved in community projects to promote

cardiovascular health. In order to disseminate the heart health message to our young generation and encourage them to do regular exercise, a fun-filled dynamic programme, called "Jump Rope for Heart" programme, was launched in the late 90s. The Jump Rope for Heart programme continues its recruitment of school children for the promotion of heart health through rope skipping. The College has been supporting this programme, which is celebrating its 20th Anniversary this year. Dr Patrick Ko, one of the founders of this programme and Board Council Member of the Hong Kong Rope Skipping Association, will let us know more about this programme and the rope skipping development in Hong Kong.

Finally, I would like to thank all the contributing authors for their efforts and sincerely hope you will enjoy reading this issue.

Dual Pathway Inhibition Treatment Strategy in Coronary Artery Disease: Why, When & Who?

Prof Bryan Ping-yen YAN

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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 October 2020.

INTRODUCTION

Antiplatelet therapy has been the mainstay of cardiovascular (CV) prevention in patients with CV diseases (CVD). Single antiplatelet therapy (aspirin or clopidogrel) is the standard of care for patients with stable chronic coronary syndrome (CCS), whereas dual antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel) is the standard of care in patients with acute coronary syndrome (ACS)[1]. Despite current anti-thrombotic strategies, the residual risk of recurrent CV events remains high in patients with CCS ranging from 15% to 30% at three years[2]. Therefore, more effective anti-thrombotic treatment is needed beyond platelet inhibition. Recently published 2019 European Society of Cardiology (ESC) guidelines for the management of CCS recommend the addition of a second anti-thrombotic drug to aspirin for long-term secondary prevention in high ischemic risk patients without a high bleeding risk[1]. This article aims to describe the rationale and evidence of dual pathway inhibition (DPI) combining low-dose rivaroxaban (2.5 mg twice daily) plus aspirin in the treatment of coronary artery disease.

RATIONALE FOR COMBINING AN ANTIPLATELET AGENT WITH AN ANTICOAGULANT IN CARDIOVASCULAR DISEASE

Atherothrombotic events are caused by disruption or erosion of atherosclerotic plaques leading to simultaneous activation of platelets and coagulation pathway and the formation of thrombus. There is significant interplay between these two pathways. Thrombin is both a mediator in the coagulation cascade as well as a potent agonist that induces platelet activation and aggregation. On the other hand, activated platelets can amplify thrombin generation. Therefore, platelet inhibition alone may not fully prevent recurrent atherothrombotic events. Dual-pathway inhibition treatment strategies that combine an antiplatelet agent with a non-vitamin K antagonist oral anticoagulants (NOAC) which attenuate fibrin formation by selective inhibition of factor Xa or thrombin may be more effective than inhibiting via only one pathway.

EVIDENCE FOR DUAL PATHWAY INHIBITION IN CARDIOVASCULAR DISEASE

The first phase 3 trial to evaluate the efficacy and safety of DPI strategy was the ATLAS ACS2-TIMI 51 trial, which randomised rivaroxaban (2.5 mg or 5 mg twice daily) plus aspirin vs placebo in more than 15,000 patients with recent ACS[3]. In this study, rivaroxaban significantly reduced major adverse cardiovascular events (MACE, defined as composite of CV death, MI or stroke) compared with placebo (8.9% vs 10.7%, $p < 0.01$). More recently, the COMPASS trial demonstrated the benefits of DPI extended to patients with chronic coronary artery disease (CAD) and peripheral arterial disease (PAD)[4]. More than 27,000 participants with stable vascular disease were randomised to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The combination of rivaroxaban 2.5 mg twice daily plus aspirin but not rivaroxaban 5 mg twice daily alone was more effective than aspirin alone in reducing MACE (4.1% (rivaroxaban 2.5 mg plus aspirin) vs 5.4% (aspirin alone) vs 4.9% (rivaroxaban 5 mg alone)). As expected, the risk of major bleeding was increased with combined rivaroxaban and aspirin compared to aspirin alone in both the ATLAS ACS2-TIMI 51 and COMPASS trials. However, there was no significant increase in intracranial or fatal bleeding in both trials[3, 4].

In clinical practice, it may be difficult to weigh the benefits of CV protection against the increased risk of bleeding. The net clinical benefit is a measure of the patient overall outcome by combining the most severe efficacy and safety endpoints; and in this case CV death, stroke, MI, fatal or symptomatic bleeding into a critical organ. Based on the COMPASS trial, DPI with rivaroxaban 2.5 mg twice daily plus aspirin carries a favourable benefit-risk profile with a lower risk of composite net clinical benefit outcomes (Hazard ratio 0.80; 95% confidence interval 0.70 - 0.90, $p < 0.0005$) compared to aspirin alone[5]. These results led to the approval of rivaroxaban 2.5 mg twice daily plus aspirin for patients with chronic CAD[1].

WHY USE LOWER TWICE DAILY DOSE OF RIVAROXABAN THAN HIGHER ONCE DAILY DOSE USED IN ATRIAL FIBRILLATION AND VENOUS THROMBOEMBOLISM?

The recommended doses of rivaroxaban are higher for patients with atrial fibrillation and venous thromboembolism than for reducing residual CV risk in patients with CAD. Given the increased risk of bleeding when anticoagulant and antiplatelet therapies are combined, the lowest effective dose of the anticoagulant should be used to minimise the risk of bleeding. In the phase 2 ATLAS ACS-TIMI 46 trial, the total daily dose of rivaroxaban ranging from 5 to 20 mg once or twice daily was evaluated, and the study found an increasing risk of bleeding with higher doses of rivaroxaban[6]. Low dose rivaroxaban 2.5 mg twice daily had the best balance between safety and efficacy in patients with recent ACS in ATLAS ACS2-TIMI 51 trial and in patients with stable CVD in COMPASS trial[3, 4].

Rivaroxaban is absorbed rapidly with maximum plasma concentrations and peak factor Xa inhibition approximately 3 hours after oral administration[7]. The half-life of rivaroxaban is dose-dependent, and is approximately 5 hours in 2.5 mg and twice as long in 10 or 20 mg doses[6]. Rivaroxaban 5 mg once daily is not therapeutically equivalent to rivaroxaban 2.5 mg twice daily because plasma trough levels for once daily doses of rivaroxaban below 10 mg is insufficient and twice daily dosing is needed to maintain effective plasma levels and CV protection throughout the day. The longer half-life of rivaroxaban doses of 10 mg and above allows for once daily dosing used in atrial fibrillation and venous thromboembolism.

WHICH PATIENTS WILL BENEFIT THE MOST FROM DUAL PATHWAY INHIBITION?

The ATLAS ACS 2-TIMI 51 and COMPASS demonstrated benefits of DPI therapy in a broad range of patients with acute and chronic coronary syndromes as well as consistent efficacy and safety across major subgroups[3, 4]. Patients with the highest baseline risk including those with the poly-vascular disease, renal impairment (estimated glomerular filtration rate [eGFR] < 60 mL/min) and those with a history of heart failure or diabetes experienced the greatest benefit with DPI therapy in COMPASS trial. The 2019 ESC guidelines on CCS recommend adding a second anti-thrombotic agent to aspirin for long-term secondary prevention in patients with a low bleeding risk who are at high risk of ischemic events (i.e., those with diffuse multi-vessel CAD with at least one additional risk factor, such as diabetes that requires medication, recurrent MI, PAD, or chronic kidney disease with eGFR 15–59 mL/min)[1]. Dual pathway inhibition therapy with rivaroxaban plus aspirin is recommended in patients > 1 year post-MI or multi-vessel CAD; whereas DAPT is recommended for up to 1 year post-MI or longer in patients at low risk for bleeding and high risk for recurrent ischemic events based on the PEGASUS trial[8]. There is no head-to-head comparison between DAPT and DPI in patients with CVD. Intensification of anti-thrombotic therapy by either DPI or DAPT strategies is associated with increased risk of bleeding and should be avoided in patients at high risk of bleeding (including the history of ICH; ischemic stroke or other intracranial pathology; recent gastrointestinal (GI) bleeding; anaemia due to possible GI blood loss or other GI pathology associated with increased bleeding risk; liver failure; bleeding diathesis or coagulopathy; extreme old age or frailty; or renal failure requiring dialysis or eGFR < 15 mL/min/m^2). Selection of patients for DPI needs to be individualised balancing the risks of ischemic events and bleeding. Patients at high ischemic risk have a more favourable benefit-risk profile and are likely candidates for DPI. A recent review proposed a practical algorithm for selecting an anti-thrombotic strategy in patients with CCS[9].

It is important to stress that the management of patients with chronic CVD is not limited to anti-thrombotic therapy. Lifestyle modification including smoking cessation, regular physical activity, healthy diet and maintaining a healthy weight should be enforced; and pharmacological treatment should be used to control CV risk factors such as dyslipidemia, diabetes, and hypertension according to therapeutics guidelines[1].

CONCLUSION

Antiplatelet therapy has been the standard of care for secondary prevention in CAD management. However, residual risk of ischaemic events remains in many patients despite the availability of established therapies. Dual pathway inhibition is a novel strategy that combines an antiplatelet with an anticoagulant agent to prevent CV events. Current ESC guidelines recommend the use of DPI for long-term secondary prevention in patients with CAD who are at low risk of bleeding but high risk of ischemic events. To date, low dose rivaroxaban (2.5 mg twice daily) is the only anticoagulant shown to be effective in combination with aspirin as part of the DPI strategy. Further study is required to determine whether the use of other low-dose NOACs provides a similar benefit-risk profile in a DPI strategy.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Dual Pathway Inhibition Treatment Strategy in Coronary Artery Disease: Why, When & Who?" by Prof Bryan P YAN 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 October 2020 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. **Do the current European Society of Cardiology (ESC) guidelines for the management of chronic coronary syndrome recommend the addition of an anti-thrombotic drug to aspirin for long-term secondary prevention in high-ischemic-risk patients without a high bleeding risk?**
2. **Rivaroxaban 2.5 mg bid has been shown to be effective in combination with aspirin for cardiovascular protection in patients with stable cardiovascular diseases.**
3. **In the COMPASS study, combination of rivaroxaban and aspirin is only effective in patients with coronary artery disease.**
4. **Prolonged dual antiplatelet therapy with aspirin and P2Y12 inhibitor is the standard of care for patients with chronic stable coronary artery disease.**
5. **Patients with chronic coronary artery disease at high bleeding risk should not be a candidate for prolonged dual antiplatelet therapy or combined antiplatelet and anticoagulation therapy.**
6. **Rivaroxaban 2.5 mg can be given as a daily dose in combination with aspirin in dual pathway inhibition strategy for cardiovascular protection in stable patients with cardiovascular diseases.**
7. **Patients with mild to moderate renal impairment (eGFR 15-59 ml/min) are not candidates for dual pathway inhibition.**
8. **Dual pathway inhibition is recommended for patients >1 year post- myocardial infarction or with multi-vessel coronary artery disease.**
9. **In the COMPASS trial, dual pathway inhibition with rivaroxaban 2.5 mg bid and aspirin is associated with lower risk of composite net clinical benefits compared to aspirin alone.**
10. **Thrombin is a potent agonist that induces platelet activation and aggregation.**

ANSWER SHEET FOR OCTOBER 2020

Please return the completed answer sheet to the Federation Secretariat on or before 31 October 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Dual Pathway Inhibition Treatment Strategy in Coronary Artery Disease: Why, When & Who?

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Answers to September 2020 Issue

Advanced Hepatocellular Carcinoma in Chinese - What Do We Really Need?

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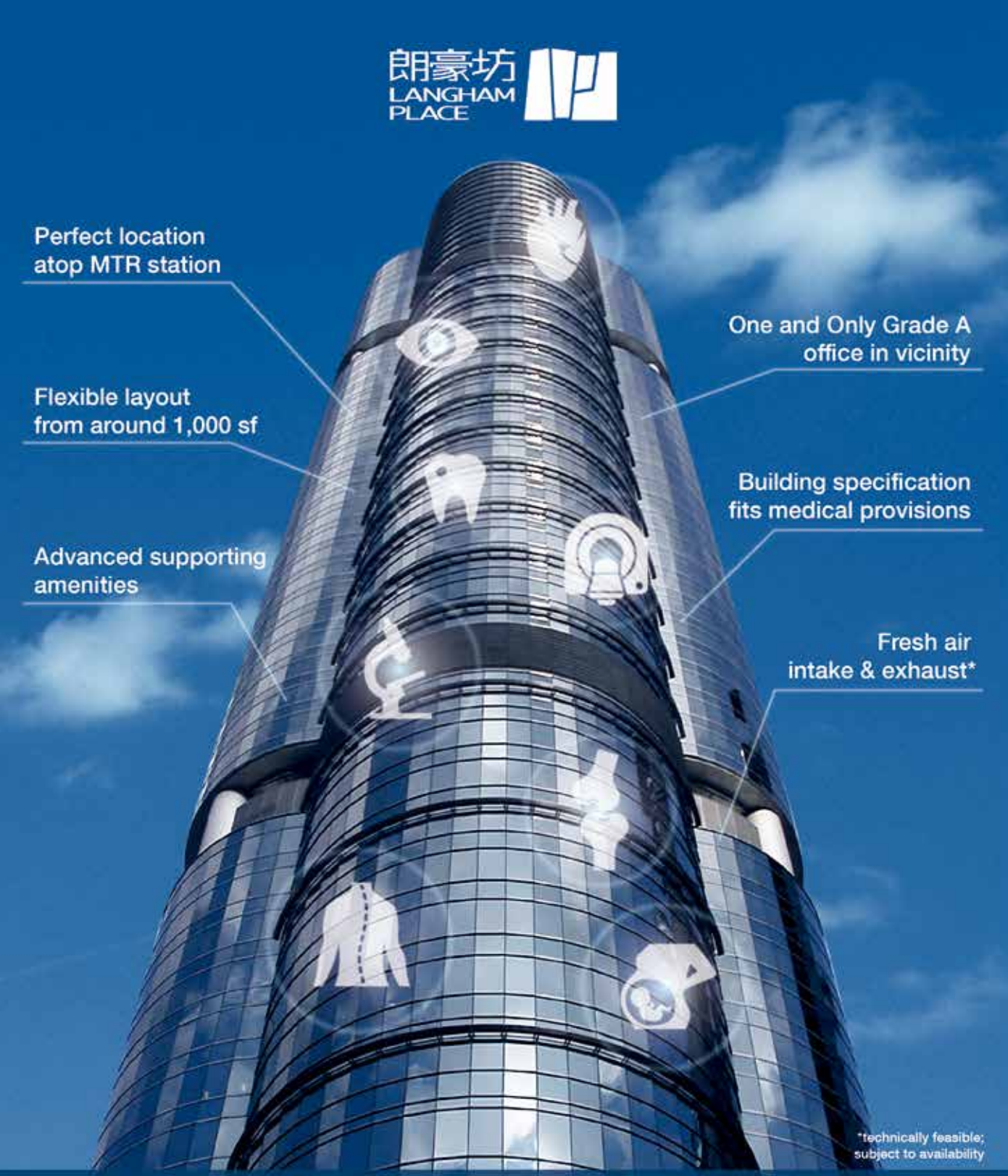

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Rhythm Versus Rate Control of Atrial Fibrillation in Patients with Heart Failure

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The presence of atrial fibrillation (AF) in patients with heart failure (HF) with reduced ejection fraction is associated with an increased risk of re-hospitalisation and all-cause death. It is reasonable to think that restoration and maintenance of sinus rhythm may be beneficial in patients with heart failure with reduced ejection fraction (HFrEF) because atrial systole may play an important role in left ventricular filling. Moreover, persistent AF, even in good rate control, may cause deterioration in left ventricular function because of atrioventricular dys-synchrony and irregular heart rate. However, cardiovascular outcomes were not different significantly between rate and rhythm control-based strategies in the HFrEF population in previous large-scale trials. Therefore, current clinical guidelines suggest a rate control strategy for patients with AF and HFrEF over rhythm control.

The reason for negative results from previous trials is thought to be related to poor efficacy and side effects of antiarrhythmic drugs for rhythm control of AF. Only two antiarrhythmic drugs, dofetilide and amiodarone, are available for rhythm control of AF in HFrEF. Dofetilide did not offer a mortality benefit compared with rate control in HFrEF. It is probably due to its proarrhythmic effects. Although amiodarone is effective in rhythm control, its use is limited by its side effects including thyroid dysfunction, liver derangement and lung fibrosis. Moreover, amiodarone also did not show a significant benefit compared with rate control in HFrEF.

Catheter ablation has emerged to be a more effective rhythm control strategy for AF in recent years. Thanks to the early work of Haissaguerre, pulmonary vein (PV) has been identified as a source of ectopic activity initiating atrial fibrillation. PVs have muscular sleeves which extend into the left atrium, and special cells (P cells, transitional cells, and Purkinje cells) are found in these muscular extensions in histopathological observations. This forms the basis for pulmonary vein isolation (PVI) as an ablation strategy for AF. Electrical isolation of PVs by catheter ablation significantly reduces the burden of AF as compared to antiarrhythmic drugs. The promising results of catheter ablation bring rhythm control back to the field in the battle of AF management.

Below are the five recent trials comparing catheter ablation with rate control (either atrioventricular node ablation or pharmacological) or pharmacological rhythm control in patients with HFrEF.

COMPARISON OF PULMONARY VEIN ISOLATION VERSUS AV NODAL ABLATION WITH BIVENTRICULAR PACING FOR PATIENTS WITH ATRIAL FIBRILLATION WITH CONGESTIVE HEART FAILURE (PABA CHF) [1]

PVI was shown to be superior to atrioventricular node ablation with biventricular pacing in patients with HFrEF and uncontrolled AF in terms of cardiac function, exercise capacity and quality of life.

Rate control strategy used in PABA CHF was atrioventricular node ablation and pacemaker (PM) implantation. This strategy ensures a more effective rate control when compared with pharmacological rate control. To our surprise, the result of PVI was even better than this stringent rate control strategy, indicating that rhythm control really has the edge over rate control.

CATHETER ABLATION VS MEDICAL TREATMENT OF AF IN HEART FAILURE (CAMTAF)[2]

Unlike PABA CHF, the rate control strategy used in CAMTAF was pharmacological. At six months, catheter ablation showed a significant improvement in ejection fraction when compared with pharmacological rate control. Quality of life was also improved in the catheter ablation arm.

ABLATION VS AMIODARONE FOR TREATMENT OF ATRIAL FIBRILLATION IN PATIENTS WITH CONGESTIVE HEART FAILURE AND AN IMPLANTED ICD/CRTD (AATAC)[3]

The study population in AATAC were those patients who did not previously fail medical treatment. All patients in AATAC were implanted with dual-chamber ICD or CRT device, ensuring accurate monitoring of AF recurrence during follow-up. Recurrence of AF was the primary endpoint. All-cause mortality and unplanned hospitalisation were the secondary endpoints. Amiodarone therapy was found to be significantly more likely to fail in maintaining sinus rhythm than catheter

ablation at two years. Concerning clinical endpoints, a significant reduction in unplanned hospitalisation for HF and overall mortality was demonstrated in catheter ablation arm compared with amiodarone treatment.

CATHETER ABLATION VS STANDARD CONVENTIONAL THERAPY IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AND ATRIAL FIBRILLATION (CASTLE-AF)[4]

Unlike AATAC, the study population in CASTLE-AF were those patients who did not respond to antiarrhythmic drugs or had significant side effects from the medications. It demonstrated a significant reduction in HF re-hospitalisation in the catheter ablation group. More importantly, a significant improvement in all-cause mortality in the catheter ablation group became evident after three years of follow-up.

CATHETER ABLATION VS ANTI-ARRHYTHMIC DRUG THERAPY FOR ATRIAL FIBRILLATION (CABANA)[5]

The study population in CABANA included a diversity of patients with paroxysmal, persistent or long-standing persistent AF. These patients were randomised to catheter-based treatment or rhythm and/or rate control drug therapy. In this study, catheter ablation failed to demonstrate superiority in term of the composite primary endpoint of death, stroke, serious bleeding or cardiac arrest when compared with medical treatment (rate or rhythm control). However, the secondary endpoint of mortality or cardiovascular hospitalisation showed a significant 17% relative lower event rate for the catheter ablation group.

Table 1 showed the main trials on catheter ablation of AF in patients with HFrEF[6]. Because of the potential benefit in both mortality rate and re-hospitalisation shown in recent trials, AHA/ACC/HRS guidelines in 2019 recommend that it is a Class IIb indication for catheter ablation in patients with symptomatic AF and HFrEF.

Although catheter ablation of AF is effective, its potential complications including pericardial effusion, stroke, phrenic nerve palsy, pulmonary vein stenosis and rarely atrioesophageal fistula should not be overlooked. Luckily, with increasing experience and advancement in ablation technology, recent study showed that modern cohort of patients receiving catheter ablation of AF (2014-2015) had fewer complications than the older cohort (2009-2011) (2.3% vs 5%, p = 0.007)[7].

CONCLUSION

Although current clinical guidelines favour a rate control strategy for patients with AF and HFrEF over rhythm control, the success of catheter ablation of AF may change the landscape of AF management in the future. Catheter ablation of AF is a more effective way to rhythm control when compared with antiarrhythmic therapy. Use of catheter ablation for rhythm control of AF also avoids the long-term side effects of antiarrhythmic drugs. Most importantly, there are increasing evidence showing that catheter ablation is associated with a significant reduction in HF re-hospitalisation and mortality.

Table 1: Trials on Catheter Ablation of AF in Patients with Heart Failure With Reduced Ejection Fraction (Excerpted from Michela Faggioni, Domenico G Della Rocca, Sanghamitra Mohanty, et al. 6)

Trial	Inclusion Criteria	Sample	Endpoint	Results
PABA CHF 2008	Symptomatic AF, NYHA class II-III, LVEF <40%	Total no = 81; CA (n=41), AV nodal ablation with biventricular pacing (n=40)	Primary: composite of EF, 6-minute walk distance and MLWHF score	CA group was superior to AV nodal ablation with biventricular pacing
CAMTAF 2014	Persistent AF, NYHA class II–IV, LVEF <50%	Total no = 50; CA (n=26), medical therapy (rate; n=24)	Primary: change in LVEF at 6 months, peak oxygen consumption, QOL	81% AF-free survival in the CA group at 6 months; significant increase in LVEF, functional capacity and QOL in CA group
AATAC 2016	Persistent AF, ICD/CRT-D, NYHA Class II or III, LVEF <40%	Total no = 203; CA (n=101), amiodarone (n=102)	Primary: freedom from AF; secondary: all-cause death and unplanned hospitalisation	CA group was associated with significant improvement of freedom from AF, all-cause death and unplanned hospitalisation
CASTLE-AF 2018	Symptomatic paroxysmal or persistent AF, ICD, NYHA Class II-IV, EF <35%	Total no = 363; CA (n=179), medical therapy (rate/rhythm; n=184)	Primary: composite of death or HF hospitalisation	Significant improvement in primary composite endpoint of death or HF hospitalisation in CA group
CABANA 2019	Paroxysmal, persistent or long-standing persistent AF, >=65 or <65 with >=1 CVA or CV risk factor	Total no = 2,204; CA (n=1,108), medical therapy (rate/rhythm; n=1,096)	Primary: death, CVA, serious bleeding or cardiac arrest; secondary: all-cause death or CV hospitalisation	CA group was associated with non-significant reduction in the primary composite endpoint but significant reduction in secondary endpoint

CA = catheter ablation; MLWHF = Minnesota Living with Heart Failure; QOL = quality of life; ICD = implantable cardioverter defibrillator; CRT-D = cardiac resynchronisation therapy-defibrillator; CV = cardiovascular; CVA = cerebrovascular accident; EF = ejection fraction; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

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References: 1. Granger CB, et al. *N Engl J Med* 2011;365:981-992. **2.** Ruff CT, et al. *Lancet* 2014;383:955-962. **3.** IQVIA MIDAS, Days of Treatment volume a calculation of IQVIA Standard Units, Q2 2019, divided by recommended administration of each NOAC within 24hrs. [apixaban BID, dabigatran BID, edoxaban QD, rivaroxaban QD] **4.** Agnelli G, et al. *N Engl J Med* 2013;369:799-808.

ELIQUIS ABBREVIATED PACKAGE INSERT 1. TRADE NAME: ELIQUIS 2. PRESENTATION: 2.5 mg and 5 mg film-coated tablets **3. INDICATIONS:** Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. For 2.5 mg only – Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. **4. DOSAGE:** Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF): 5 mg twice daily. 2.5 mg twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl (133 micromole/L). Treatment of DVT, PE and prevention of recurrent DVT and PE (VTE): 10 mg twice daily for the first 7 days followed by 5 mg twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with Eliquis 5 mg twice daily or with another anticoagulant. Prevention of VTE in elective hip or knee replacement surgery: 2.5 mg twice daily initiated 12 to 24 hours after surgery. **5. METHOD OF ADMINISTRATION:** Eliquis should be swallowed with water, with or without food. For patients who are unable to swallow whole tablets, Eliquis tablets may be crushed and suspended in water or 5% dextrose in water (D5W) and immediately administered orally. Alternatively, Eliquis tablets may be crushed and suspended in 60mL of water or D5W and immediately delivered through a nasogastric tube. Crushed Eliquis tablets are stable in water and D5W for up to 4 hours. **6. CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Active clinically significant bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Lesion or condition if considered a significant risk factor for major bleeding. Concomitant treatment with any other anticoagulant agent. **7. WARNINGS & PRECAUTIONS:** Haemorrhage risk: carefully observed for signs of bleeding. Eliquis should be discontinued if severe haemorrhage occurs. Use of thrombolytic agents for the treatment of acute ischemic stroke: There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered Eliquis. Patients with prosthetic heart valves: Eliquis is not recommended. Surgery and invasive procedures: Eliquis should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. Renal impairment: In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended. Hepatic impairment: Not recommended in patients with severe hepatic impairment. Laboratory parameters: Clotting tests (e.g., prothrombin time (PT), international normalised ratio (INR), and activated partial thromboplastin time (aPTT)) are affected as expected by the mechanism of action of apixaban. For 2.5mg - Spinal/epidural anaesthesia or puncture. **8. INTERACTIONS:** Eliquis is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp. Concomitant use of Eliquis with strong CYP3A4 and P-gp inducers may lead to a ~50% reduction in apixaban exposure. **9. PREGNANCY AND LACTATION:** There are no data from the use of apixaban in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Apixaban is not recommended during pregnancy. It is unknown whether apixaban or its metabolites are excreted in human milk. A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy. **10. SIDE EFFECTS:** Common: anaemia, haemorrhage, nausea, contusion and haematoma. (Please refer to the full Prescribing Information for details) Reference: Eliquis 2.5 mg and 5 mg HK Prescribing Information (July 2019) Date of preparation: Sept 2019 Identifier number: ELIQ0919 FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST

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Update on Interventional Cardiology

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CORONARY INTERVENTION

Percutaneous coronary intervention (PCI) is a minimally invasive procedure for the treatment of ischaemic heart disease (IHD). Although many IHD patients can benefit from this approach, some patients are better revascularised with coronary artery bypass grafting (CABG)[1]. Coronary lesions such as bifurcation lesions, left main stenosis, chronic total occlusion and calcified lesions are technically challenging when treated percutaneously. In the past, patients with such lesions may be referred for surgical bypass. With the advancement of PCI, more and more patients with complex IHD can be treated with PCI.

Traditionally coronary angiograms (Fig. 1) are considered gold standard for diagnosing coronary artery disease. However, angiograms only allow visualisation of the lumen of the coronary arteries. Intracoronary imaging tools such as intravascular ultrasound (IVUS) (Fig. 2) or optical coherence tomography (OCT) (Fig. 3) can give better pictures of the coronary vessels and lesions[2,3]. IVUS uses ultrasound, whereas OCT uses near-infrared light to generate circumferential tomographic images of the coronary vessels. The resulting pictures provide better temporal and special resolutions which give more details about the underlying structures. Different tissues of atherosclerotic plaque such as fibrous, lipid, thrombus and calcium can be detected. The amount and distribution of calcium can be assessed (Fig. 4). This information can affect the subsequent treatment strategies. In the old days, balloon angioplasty and rotational atherectomy (Fig. 5) were the only available options. But now we have orbital atherectomy and lithotripsy balloons (Fig. 6) which can reduce calcified plaque volume and create dissections to allow better device crossing and stents deployment. In the treatment of intracoronary thrombus (Fig. 7), several different types of thrombectomy devices are available for thrombus removal (Fig. 8A, 8B). Intracoronary imaging devices can also make accurate measurements for the vessel size and segment length. They can also be used to assess the adequacy of stent deployment after PCI. The latest version of OCT gives automatic measurements of coronary images, and high-definition IVUS gives images with higher spatial resolution.

Physiological measuring devices such as Fractional Flow Reserve (FFR) (Fig. 9) allow objective detection of functional ischaemia. A clinical trial showed that functional guided coronary intervention with FFR has a better clinical outcome compared with optimal medical treatment alone[4]. Despite its efficacy in guiding coronary intervention, the use of FFR is still not very popular. One of the reasons is that using FFR required maximal hyperaemia with agents such as adenosine. Some patients may have an adverse reaction to the hyperemic agents. Recently several resting physiological indexes such as instantaneous wave-free ratio (iFR), resting full-cycle ratio (RFR) or diastolic pressure ratio (dPR) have been developed. These resting pressure indexes can be measured without hyperaemic agents. Studies showed that they could be used to guide treatment strategy[5].

Regarding coronary stents, newer generation drug-eluting stents (DES) have ultrathin strut (60 micrometres). They may be associated with a lower risk of restenosis and thrombosis[6]. Some new DES is biopolymer free which allow shorter duration of dual antiplatelet agents if necessary[7].

Chronic total occlusion intervention is a challenge for many interventionists. CTO dedicated devices such as specially designed coronary guidewires and single/double microcatheters have been developed to treat these lesions. Stingray LP reentry system (Fig. 10) is a designated device to facilitate the redirection of the guidewire from subintima back to true lumen when treating CTO. All these devices make this complex PCI easier to accomplish.

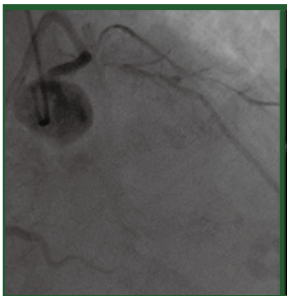

Fig.1 Coronary angiogram (Personal Collection)

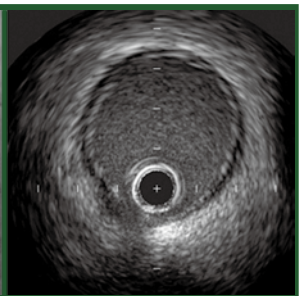

Fig. 2 Circumferential tomographic image of coronary artery generated by intravascular ultrasound (With permission from Boston Scientific)

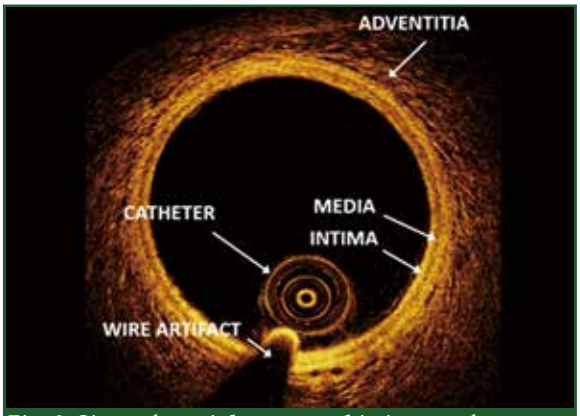

Fig. 3 Circumferential tomographic image of coronary artery generated by optical coherence tomography (With permission from Abbott Vascular)

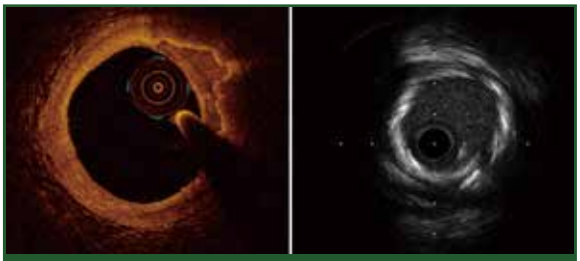

Fig. 4 Calcium detected by OCT and IVUS (With permission from Abbott Vascular)

Fig.5 Rotational atherectomy (With permission from Boston Scientific)

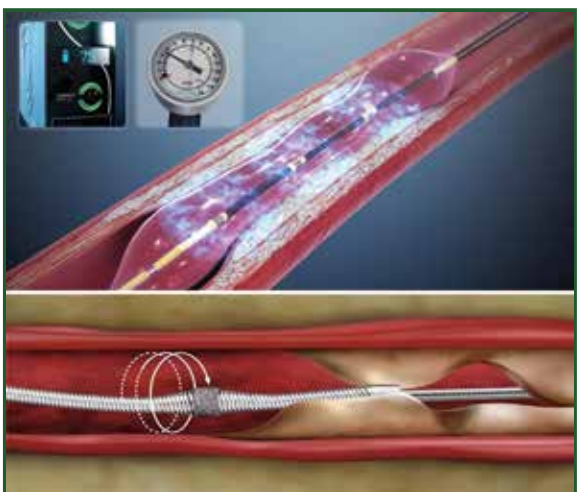

Fig. 6 Lithotripsy balloon and Orbital atherectomy (With permission from Kerry Medical and OrbusNeich)

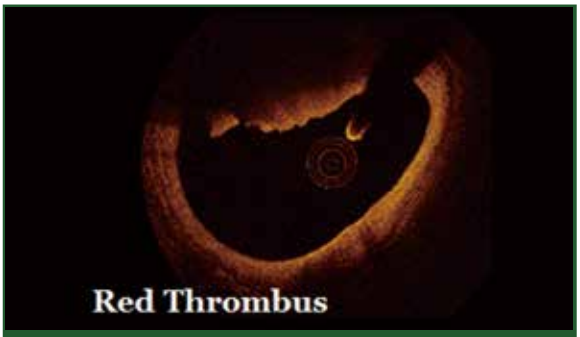

Fig. 7 Intracoronary thrombus (With permission from Abbott Vascular)

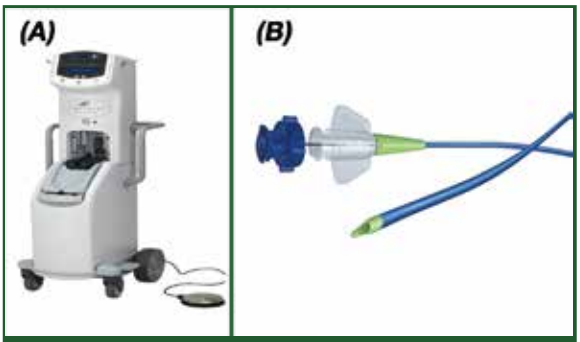

Fig. 8A Angiojet thrombectomy system (With permission from Boston Scientific)

Fig. 8B Aspiration catheter (With permission from Medtronic)

Fig. 9 Fractional flow reserve (With permission from Abbott Vascular)

Fig. 10. Stingray LP reentry device (With permission from Boston Scientific)

HAEMODYNAMIC SUPPORTIVE DEVICES

Both CABG and PCI risks are high in patients with an impaired cardiac function who are haemodynamically unstable. Intra-aortic balloon pump (IABP) counterpulsation can provide mechanical haemodynamic supports for PCI in these patients. It reduces afterload and increases coronary blood flow. Despite these benefits, routine use of IABP in supporting PCI for AMI patients with cardiogenic shock was not supported by clinical trials[8]. Newer percutaneous haemodynamic supportive devices such as extracorporeal membrane oxygenation (ECMO) or Impella (Fig. 11) allow high risk PCI to be performed in a relatively safe environment. Unlike IABP which can only augment up to 0.5-1 L/min cardiac output, ECMO and Impella can support up to 5 L/min cardiac output. To achieve optimal augmentation, balloon inflation and deflation of the IABP must be correctly timed with the cardiac cycle. The haemodynamic effectiveness may be limited by tachycardia. Both ECMO and Impella use pumps to circulate blood. They are less affected by tachycardia. ECMO has the additional benefit of being capable of providing complete cardiopulmonary support. For the patient who has cardiac arrest not responsive to cardiopulmonary resuscitation (CPR), ECMO can be used to provide circulatory support until the insult is reverted (ECPR). Although ECMO can provide full cardiac support, it fails to unload left ventricle (LV). The increased LV load may aggravate pulmonary oedema. Impella can unload LV by pulling blood from LV and expelling it in the aorta. Besides the above supportive devices, Lund University Cardiopulmonary Assist System (LUCAS) is another device that can be used in cardiac catheterisation laboratory during PCI to provide high quality mechanical CPR support when the patient developed cardiac arrest.

Fig. 11 Impella (With permission from Abiomed)

STRUCTURAL INTERVENTION

Many non-coronary cardiac disorders that are traditionally surgically treated are now managed percutaneously.

Transcatheter aortic valve implantation (TAVI) (Fig. 12) is one of the most promising percutaneous devices for the treatment of valvular heart disease. TAVI can be considered for patients with high surgical risk or inoperable aortic stenosis (AS). For some intermediate-risk AS patients, TAVI is non-inferior or even superior to surgical replacement[9]. The newer generation TAVI has a lower profile for better delivery. It is retrievable if deployment position is suboptimal. Mitraclip is another percutaneous valvular device that can be used to treat mitral valve prolapse and functional mitral regurgitation[9]. Many other percutaneous devices are in the experimental phase but can potentially be used in other structural heart diseases.

Coronary fistulas are traditionally treated by surgical ligation. For those patients who are unfit for surgery, percutaneously intervention is the treatment of choice. Depends on the site and size of coronary fistulas, different devices can be considered[10,11]. Isolated fistula not adjacent to any significant side branch can be closed with covered stent implanted over the main coronary vessel across the fistula. Small fistulas can be closed by using coils (Fig. 13). Large fistulas can be closed by ductal occluders or vascular plugs.

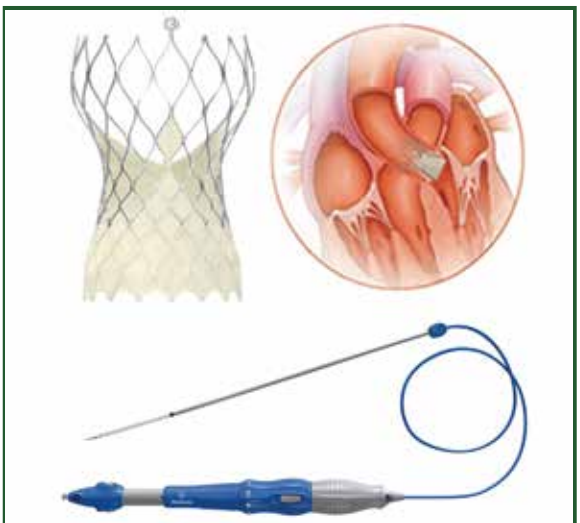

Fig. 12 TAVI (With permission from Medtronic)

Fig. 13 Coil (With permission from Boston Scientific)

For patients with symptomatic hypertrophic obstructive cardiomyopathy not responsive to medical treatment, surgical myectomy is traditionally the first-line treatment. A similar effect can be achieved by alcohol septal ablation in a less invasive way[12]. Alcohol septal ablation reduces left ventricular outflow tract

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CV: cardiovascular; RRR: relative risk reduction; ADA: American Diabetes Association; EASD: European Association for the Study of Diabetes; CVD: cardiovascular disease; OAD: oral antidiabetic drug; T2DM: type 2 diabetes mellitus

Reference: 1. Zinman B, et al. N Engl J Med. 2015;373(22):2117-2118. **2.** Jardiance Hong Kong Prescribing Information. **3.** Davies MJ, D'Alessio DA, Fradkin J,et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018.

† JARDIANCE demonstrated RRR in CV death in adult patients with insufficiently controlled type 2 diabetes (baseline HbA1c 7-10%) and established CV disease (coronary artery disease, peripheral artery disease, or a history of myocardial infarction or stroke).[1]

‡ Standard of care included CV medications and glucose-lowering agents given at the discretion of physicians.[1]

§ Empagliflozin versus placebo on top of standard of care.[1]

Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the ADA and EASD stated that among patients with established CVD, there is likely cardiovascular benefit, with the evidence of benefit modestly stronger for empagliflozin than canagliflozin[3]

JARDIANCE® Abbreviated Prescribing Information (aPI-JAR-12-13-V1 R1)

Presentation: Empagliflozin. Film-coated tablets 10 mg; 25 mg. **Indications:** Indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as: monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance; and as add-on combination therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. Indicated in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death. **Dosage and administration:** 10 mg once daily. In patients tolerating 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. Can be taken with or without food. No dose adjustment is required for patients with eGFR ≥45mL/min/1.73m^2 or with hepatic impairment, or for elderly patients. **Contraindication:** Hypersensitivity to empagliflozin or any of the excipients. Patients on dialysis, eGFR <30mL/min/1.73m^2 or CrCl <30mL/min, or eGFR persistently <45mL/min/1.73m^2 or CrCl persistently <45mL/min. Rare hereditary conditions that may be incompatible with an excipient. **Special warnings and precautions:** Should not be used in patients with type 1 diabetes or for treatment of DKA. Discontinue immediately when DKA is suspected or diagnosed. Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses, and may be restarted once the patient's condition has stabilised. Discontinue when the eGFR is persistently <45mL/min/1.73m^2 or CrCl <45mL/min. Discontinue in cases of recurrent UTI. Due to a risk of modest decrease in blood pressure, caution should be exercised in patients with known cardiovascular disease, patients on diuretics, patients with history of hypotension or patients aged 75 years and older. Monitoring of volume status and electrolytes is recommended. Regularly examine the feet and counsel patients on routine preventative footcare. Caution is advised in patients at increased risk of genital infections. Avoid use during pregnancy and breast-feeding. Safety and effectiveness in children under 18 years of age have not been established. Initiation is not recommended in patients aged 85 years and older.Urine will test positive for glucose while patients are taking JARDIANCE. **Interactions:** Risk of dehydration and hypotension may increase when used in combination with thiazide and loop diuretics. Lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE. **Adverse reactions:** Hypoglycaemia (depends on type of background therapy of patients); Urinary tract infection, vaginal moniliasis, vulvovaginitis, balanitis and other genital infection; Increased urination, dysuria; Pruritus; Volume depletion; Thirst; Glomerular filtration rate decreased, blood creatinine increased, haematocrit increased, serum lipids increased. Post-marketing experience: Ketoacidosis, urosepsis, pyelonephritis, necrotising fasciitis of the perineum (Fournier's gangrene), allergic skin reaction, angioedema. **Storage condition:** Please refer to outer packaging for special precautions for storage. **Note:** Before prescribing, please consult full prescribing information.

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THE ONLY OAD WITH CV INDICATION

Jardiance is indicated in T2DM patients and established cardiovascular disease to reduce the risk of cardiovascular death[2]

PC-HK-100376 (Aug 2020)

obstruction by creating a localised septal scar through selective injection of alcohol into the septal perforator artery. The use of contrast echo in locating target myocardium allows selection of sub-branch of septal branches for the ablation. It can reduce the chance of heart block, extensive myocardial ischaemia and unintentional ablation of other normal myocardium.

Patients with atrial fibrillation (AF) have an increased risk of stroke due to cardiac emboli. More than 90% of thrombus are found in left atrial appendage (LAA) of patients with AF[13]. Anticoagulants such as warfarin[14] and direct oral anticoagulant[15] can reduce the risk of stroke. However, anticoagulants can also increase patients' risk of bleeding. Left atrial appendage occluder is a device that can be implanted in the LAA (Fig. 14). After the device is endothelialised, patients can simply take aspirin instead of anticoagulants for stroke prevention[16]. The new generation devices are easier to deliver. They are also retrievable and safer to implant.

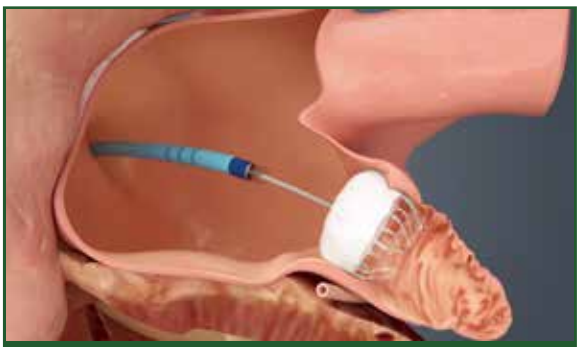

Fig. 14 Left atrial appendage occlude (With permission from Boston Scientific)

FUTURE

Robotic PCI allows operators to control intravascular devices remotely while sitting in a shielded interventional cockpit. It has an advantage of reducing radiation exposure to the primary operator. It also allows more precise measurements of lesion length and more stable deployment of angioplasty balloons and stents. At this moment, it is mainly suitable for patients with relatively simple coronary lesions. In the future, its potential use may include other complex coronary intervention and remote-control PCI.

Adjunctive devices such as intracoronary imaging, invasive or noninvasive physiologic studies, 3D or 4D echocardiography, computed tomography will all be integrated with fluoroscopy. Such integration allows simultaneous multi-modalities approach for coronary or structural intervention.

CONCLUSION

More and more cardiovascular disease can be treated by percutaneous intervention. In the future, improvement in technical skills together with advancement in technology may bring forth even better clinical outcomes in interventional cardiology.

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Role of Cardiac Imaging in Cardio-oncology

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INTRODUCTION

Cardio-oncology is a rapidly developing subspecialty in cardiology that focuses on the detection, monitoring and management of cardiac complications related to cancer treatment.

Just in the year 2018 alone, there are already more than 18 million cases of newly diagnosed cancer.[1] With the prosperity of available novel chemotherapies, more than half of survivors are expected to live ten years or even longer. As such, we are facing the unprecedented interlinking relationship between oncology and cardiac complications, not to mention many of those patients are vulnerable elderly that have already multiple medical comorbidities at baseline.

Historically used Multiple-Gated Acquisition (MUGA) scan and two-dimensional echocardiogram for ventricular function monitoring are no longer adequate to acknowledge the growing range of cardiovascular sequelae, including myocarditis, coronary artery disease, valvular dysfunction, pulmonary hypertension or pericardial disease (Fig. 1). Newer techniques including three-dimensional echocardiogram, tissue Doppler technique, Computed tomography (CT), Cardiovascular Magnetic Resonance (CMR) Imaging and Positron Emission Tomography (PET) have been proven helpful to address clinical conditions happening at different stages of the disease, in many cases alongside with other parameters like biomarkers (Table 1).

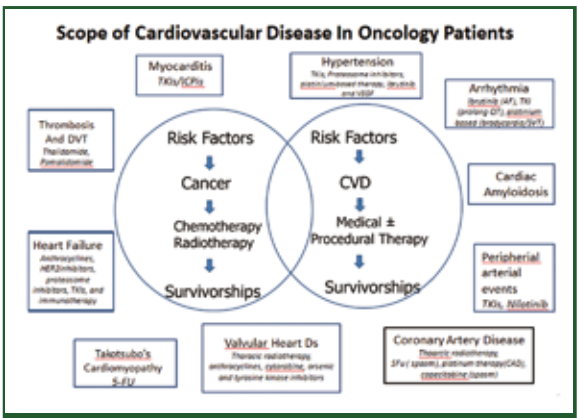


Fig. 1 The scope of cardiovascular disease in oncology patients.
There is an interlinking relationship between cancer and cardiovascular disease patients.
The cardiovascular complicated caused by the respective chemotherapeutic agents or radiotherapy are included under difficult disease entity.
Abbreviations: 5Fu, 5 –fluorouracil; HER2, human epidermal growth factor receptor 2, ICPis, immune checkpoint inhibitors;TKIs, tyrosine kinase inhibitors VEGF, vascular endothelial growth factor.
(Developed by author)

Table 1. A summary of the diagnostic accuracy of non-invasive cardiac imaging modalities in different cardiovascular complications of the oncology patients.
Abbreviation: 2D echo, 2-dimensional echocardiography, 3D echo, 3-dimensional echocardiography, Stress echo. Stress echocardiography, CMR, Cardiac Magnetic Resonance Imaging, PET, Position emission tomography, CTA, Computed Tomography coronary angiogram. (Developed by author)

Imaging Modality For assessment (Diagnostic accuracy)	Volume and function	Coronary artery disease	Tissue Characterisation (myocarditis, infiltration & fibrosis)	Valvular structure	Pericardial disease	Radiation hazard	Availability
Echocardiogram	3D is better than 2D	Stress echo is high	3D echo	Gold standard	Reasonable	Free	High
CMR	Gold standard	High (functional)	High	Intermediate	High	Free	Centre Dependent
CTA	Reasonable	High (anatomical)	Low for myocarditis/ inflammation Reasonable for fibrosis	Reasonable	High is calcification detection	Presence	Intermediate
PET	Reasonable	High	Intermediate	No	Intermediate	Presence	Centre Dependent

CANCER THERAPY-RELATED CARDIAC DYSFUNCTION (CTRCD)

As cancer treatment paradigms have moved toward prolonged targeted therapy, cardiologists are facing the challenge to a huge population of patients with potential cardiotoxicity risk and manage symptomatic and asymptomatic LV systolic dysfunction that may develop years after the initial therapy.

Though there are several postulated definitions among different professional organisations, it is generally defined as a decrease in left ventricular ejection fraction (LVEF) of more than 10% to below the lower limit of normal, which is considered an LVEF of 53%, despite symptoms.[2]

Two types of CTRCD have been described. Type 1 is irreversible, dose-dependent toxicity that results from ultra-structural changes in the myocardium. Typical example is dose-related cardiotoxicity of anthracyclines, and the risk rises dramatically after cumulative doses above 400 mg/m^2.[3] Type 2 CTRCD is largely reversible, not dose-dependent, and without ultra-structural changes in the myocardium. Trastuzumab and other targeted therapies,including tyrosine kinase inhibitors and immunotherapy, have been associated with Type 2 cardiac dysfunction.[4] A baseline echocardiogram for structure and LV ejection fraction is recommended in all patients before receiving any potential cardiotoxic therapy.[5] Serial LVEF is also suggested for monitoring during and after the treatment course.

Echocardiography is the recommended first-line screening tool for cardiotoxicity. This is readily available, at low cost, free from radiation and with wide patient acceptance. However, echocardiography carries significant inter-observer, and intra-observer variability, the test-retest variability in LVEF measurement by 2D echocardiography having been reported up to 10%, making identifying subtle changes in LVEF difficult.[6] Three-dimensional echocardiography has been shown to carry higher accuracy. In contrast, CMR provides a highly reproducible volumetric measurement given the high tissue contrast between the endocardial border and the blood pool. CMR acquires three-dimensional data and is independent of geometry assumption. There is no limitation in imaging windows. Therefore, CMR allows accurate and precise assessment and monitoring of ventricular function and volume.[7] CMR also allows a better assessment of regional wall contraction and provides a better way of assessing the functional recovery after revascularisation among patients with significant coronary artery disease.

LV mass index is an independent predictor of major adverse cardiac events in patients with anthracycline-induced cardiomyopathy. The modest accuracy of LVEF measurement by MUGA scan compared with CMR, the underestimation of LVEF by SPECT compared with echocardiogram and the radiation exposure have limited the role of these imaging tools in monitoring for cardiotoxicity.[8]

EARLY DETECTION OF SUBCLINICAL CARDIOTOXICITY

The detection of subclinical cardiotoxicity before the drop in LVEF is important to prevent the progression into irreversible cardiomyopathy.

Left ventricular global longitudinal strain (GLS) measures the maximal shortening of myocardial longitudinal length during systole compared to the resting length in diastole. Reduced GLS may reflect abnormal systolic function beforethe loss of ejection fraction becomes apparent.[9]

Both European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) recommend including GLS in the routine protocol of the clinical echocardiograms in patients at risk for type 1 or type 2 cardiotoxicity.[2] Subclinical LV dysfunction is considered absent if the relative decrease in GLS is < 8%; subclinical LV dysfunction is considered present if the relative decrease in GLS is > 15%. For the gray zone, defined as a relative decrease in GLS between 8% and 15%, closer follow-up should be considered to observe for the trend at the next echo assessment.

The ongoing SUCCOUR trial (Strain sUrveillance of Chemotherapy for improving Cardiovascular Outcomes) will be the first prospective randomised controlled trial of GLS and will provide evidence on the placement of GLS for surveillance in the CTRCD guidelines.[10]

Alternatively, CMR can also provide GLS assessment given its ability to detect early LV dysfunction before the drop in LVEF in post-chemotherapy patients and be an independent predictor of all-cause mortality across different cardiomyopathies. The myocardial tissue characterisation by means of late gadolinium enhancement (LGE) allows the identification of focal myocardial fibrosis, infiltration and infarction. Based on the presence, size, pattern and extension of myocardial late gadolinium enhancement, the etiologies of an underlying ultra-structural lesion can be differentiated, and the prognosis can be predicted.

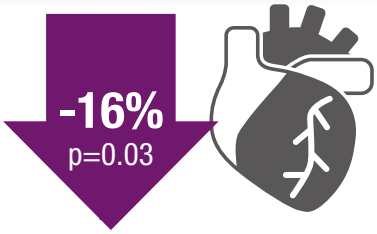
However, it has been observed that diffuse myocardial fibrosis that may not be shown up as focal LGE in post-anthracycline patients can be quantified by the pre- and post-contrast T1 mapping technique.(Fig. 2) In fact, the increased value of T1 mapping and extracellular volume fraction (ECV) was elevated in those patients treated with anthracyclines compared with age- and sex-matched controls, suggesting that diffuse fibrosis can be the culprit for future cardiomyopathy development.[11,12,13] Besides, by quantifying T2 relaxation time, which is increased with the presence of myocardial oedema and inflammation, myocarditis caused by chemotherapeutics like tyrosine kinase inhibitors and immune checkpoint inhibitors can be identified early. In fact, evidence shows elevated T2 values can be the earliest marker of myocardial damage after administration of anthracyclines, despite normal T1, ECV values and undetectable LVEF abnormalities. By stopping anthracyclines at this stage, T2 value normalised and no progression of LV dysfunction was

Improved outcomes matter

BRILINTA™ ticagrelor tablets

Reduction in CV events[1†]

Reduction in MI[1]



Reduction in stroke[1]

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes[2]

Recommendations	Class	Level
Adding a **second antithrombotic drug[§] to aspirin for long-term secondary prevention should be considered** in patients with a high risk of ischaemic events and without high bleeding risk, e.g. **ticagrelor 60 mg b.i.d.** for post-MI in patients who have tolerated DAPT for 1 year.	**IIa** NEW update	A

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD[3]

Recommendations	Class	Level
Prolongation of DAPT beyond 12 months (e.g. ticagrelor 60 mg b.i.d.)[¶] should be considered, for up to 3 years, in **patients with DM** who have tolerated DAPT without major bleeding complications.	**IIa** NEW update	A

* The PEGASUS-TIMI 54 study was a randomised, double-blind, placebo-controlled trial. 21,162 patients aged ≥50 years with a history of spontaneous MI 1-3 years prior to enrollment and at least one additional atherothrombotic risk factor (age ≥65 years, DM requiring medication, a second prior spontaneous MI, multivessel CAD, or CKD) were randomised 1:1:1 to receive either BRILINTA™ 90 mg twice daily, BRILINTA™ 60 mg twice daily or placebo for a median follow-up of 33 months. All the patients took aspirin at a dose of 75 to 150 mg daily[1].

† CV events = CV death, MI, or stroke.

‡ Prespecified exploratory endpoints.

§ Drug options also include clopidogrel 75 mg o.d., prasugrel 10 mg o.d. or 5 mg o.d., and rivaroxaban 2.5 mg b.i.d., with different indications.

¶ Full-dose clopidogrel is another option.

Abbreviations: b.i.d. = twice daily; CAD = coronary artery disease; CKD = chronic kidney disease; CV = cardiovascular; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; EASD = European Association for the Study of Diabetes; ESC = European Society of Cardiology; MI = myocardial infarction.

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Presentation: Ticagrelor 60mg film-coated tablet. **Indication:** Co-administered with aspirin, for prevention of atherothrombotic events in adult patients with ACS; or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event. **Dosage:** Ticagrelor 60mg twice daily when extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event. Co-administered with 75-150mg aspirin daily. **Contraindications:** Hypersensitivity to any ingredients of this product; Active pathological bleeding; History of intracranial haemorrhage; Severe hepatic impairment; Co-administration with strong CYP3A4 inhibitors e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir. **Precautions and Interactions:** Children <18 years; Pregnancy and lactation. Patients with a propensity to bleed; Concomitant use of medicinal products that may increase the risk of bleeding within 24 hours of dosing or known to alter haemostasis e.g. antifibrinolytic therapy and/or recombinant factor VIIa; Stop for 7-day before surgery; Moderate hepatic impairment; Patients at risk for bradycardic events; Concomitant use of medicinal products known to induce bradycardia; History of asthma and/or COPD; Patients ≥75 years; Moderate/severe renal impairment; Concomitant treatment with an ARB; History of hyperuricaemia or gouty arthritis; Uric acid nephropathy; High aspirin maintenance dose (>300mg); Premature treatment discontinuation; Co-administration with potent CYP3A inducers e.g. rifampicin, phenytoin, carbamazepine and phenobarbital; Co-administration with CYP3A4 substrates with narrow therapeutic indices i.e. cisapride and ergot alkaloids; Patients on renal dialysis; Concomitant use of simvastatin or lovastatin ≥40mg; Medicinal products metabolised by CYP3A4; CYP3A4 substrates with narrow therapeutic indices; Cyclosporine; SSRIs e.g. paroxetine, sertraline and citalopram. **Undesirable effects:** Blood disorder bleedings (bruise, spontaneous haematoma, haemorrhagic diathesis), hyperuricaemia, dyspnoea, gout/gouty arthritis, dizziness, syncope, headache, vertigo, hypotension, respiratory system bleedings (epistaxis, haemoptysis), gastrointestinal haemorrhage (gingival bleeding, rectal bleeding, gastric ulcer haemorrhage), diarrhea, nausea, dyspepsia, constipation, subcutaneous or dermal bleeding (ecchymosis, skin haemorrhage, petechiae), rash, pruritus, urinary tract bleeding (haematuria, cystitis haemorrhage), blood creatinine increased, post procedural haemorrhage, traumatic bleedings (contusion, traumatic haematoma, traumatic haemorrhage). **Full local prescribing information is available upon request. API.HK.BRIL60.0516**

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- ↓24% Cardiorenal composite endpoint†
- ↓47% Renal-specific composite endpoint†

Reassured safety profile of Forxiga®[1]

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* hHF alone was a separate, nominally significant exploratory endpoint in the DECLARE trial – the primary endpoint composite of CV death/hHF was driven by hHF.
† Nominally significant, prespecified exploratory outcome.

ASCVD=atherosclerotic cardiovascular disease. CV=cardiovascular. CVOT=cardiovascular outcome trial. hHF=hospitalisation for heart failure. HF=heart failure. SGLT2i=sodium-glucose cotransporter 2 inhibitors. T2DM=type 2 diabetes mellitus.

Reference: 1. Wiviott SD, et al. N Engl J Med 2019;380:347-57.

Abridged Prescribing Information (API)
FORXIGA® (dapagliflozin)
Composition: Dapagliflozin propanediol monohydrate film coated tablet, 5 mg or 10 mg. **Therapeutic Indications:** For the treatment of insufficiently controlled type 2 diabetes mellitus in adults as an adjunct to diet and exercise, either as monotherapy when metformin is considered inappropriate due to intolerance, or in addition to other medicinal products for the treatment of type 2 diabetes. **Dosage and Administration:** Recommended dose is 10 mg to be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. **Contraindications:** Hypersensitivity to the active substance or to any of its excipients. **Warnings and Precautions:** Renal function, risk of volume depletion and/or hypotension should be taken into account in patients. Dosage of insulin and sulphonylurea (SU) may need to be readjusted to reduce the risk of hypoclycaemia. May add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Use with caution in patients with increased risk of diabetic ketoacidosis; on anti-hypertensive therapy with a history of hypotension; elderly (≥ 65 years). Treatment should be temporarily interrupted when volume depleted; when treating pyelonephritis or urosepsis; in patients who are hospitalized for major surgical procedures or acute serious medical illnesses, until ketone values are normal. Should not be initiated in patients with a GFR < 60 ml/min; with type 1 diabetes; with hereditary problems of galactose intolerance, the total lactase deficiency, or glucose-galactose malabsorption. Discontinue if GFR is persistently below 45 ml/min; if suspected or diagnosed diabetic ketoacidosis; if Fournier's gangrene is suspected; when pregnancy is detected; while breast-feeding. Limited or no data in cardiac failure; pregnancy; and paediatric population. **Adverse Reactions:** Very common: hypoglycaemia when used with SU or insulin. Common: vulvovaginitis, balanitis and related genital infections, urinary tract infection, dizziness, rash, back pain, dysuria, polyuria, dyslipidaemia, decreased creatinine renal clearance (during initial treatment), and increased haematocrit. Uncommon: Fungal infection, volume depletion, thirst, constipation, dry mouth, nocturia, vulvovaginal and genital pruritus, increased blood creatinine (during initial treatment), increased blood urea, and decreased weight. Rare: diabetic ketoacidosis. Very rare: necrotising fasciitis of the perineum (Fournier's gangrene), angioedema. Not known: acute kidney injury. **Drug interaction:** Coadministration with rifampicin may reduce dapagliflozin systemic exposure; coadministration with mefenamic acid may increase dapagliflozin systemic exposure. Monitoring glycaemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. **Storage:** Store below 30 °C. **Local prescribing information is available upon request. API.HK.FOR.0720**

Please contact HKPatientSafety@astrazeneca.com for reporting of Individual Case Safety Report (ICSR) to AstraZeneca Hong Kong Limited.
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HK-4119 14/08/2020 4IC_1441A

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forxiga® dapagliflozin

identified, suggesting that the myocardial damage is largely reversible and provide support in clinical decision making on the chemotherapy protocol.

Another option for detecting myocardial injury and metabolism is the PET imaging. Its renowned ability to detect myocardial glucose metabolism[14] and inflammation has been shown to have a high sensitivity in diagnosing cardiotoxicities after anthracycline treatment though it is a costly examination.

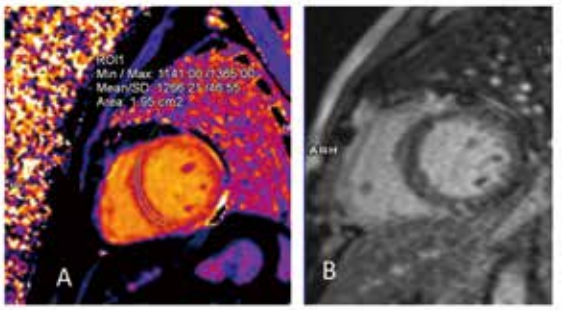

Fig. 2. (A) The T1 mapping at mid-ventricular level Increased T1 value (1266.2 ms, normal 950-1000ms at 1.5 T, Siemens Healthineers) suggestive possibility of myocardial fibrosis though it cannot be identified any focal Late gadolinium enhancement (B) at the same corresponding level. (Personal collection)

EVALUATION OF ISCHEMIC HEART DISEASE

Several mechanisms are accounting for the increased prevalence of ischemic heart disease and coronary events in cancer patients who have received chemotherapeutics (as shown in Fig. 1) and/or thoracic radiotherapy treatment. These include accelerated atherosclerosis, endothelial damage, coronary spasm and acute thrombotic events.

Computed tomography coronary angiography (CTA) is an effective, accurate, and non-invasive tool for diagnosing coronary artery disease in both symptomatic patients and asymptomatic patients. Instead of just a lumenogram in a conventional coronary angiogram, CTA also allows visualisationof vessel wall thickness, calcificationand plaque characteristics that can be a sign of early atherosclerosis. Even more, the excellent negative predictive value of CTA provides a reliable test for the exclusion of significant coronary artery disease. Patients with normal coronary CTA resultshaveshown to be benefitted from an event-free survival period of 10 years against cardiac death and nonfatal myocardial infarction.[15] As a result, risk stratification according to coronary CTA results allowed for the delineation of clearly diverging prognostic groups and reclassified approximately two-thirds of all patients from clinical risk groups in suspected coronary artery patients.

Both CMR and nuclear myocardial perfusion imaging can be considered for assessment of myocardial ischemia and flow reserve. Stressors including adenosine, regadenoson and dobutamineor exercise are included in the study protocol to uncloak the ischemic area. (Fig. 3) CMR and PET both have high accuracy, and SPECT has moderate accuracy in detecting hemodynamically significant CAD with FFR as the reference standard.[16]

As validated from previous studies, contrast-enhanced MRI can identify a wide range of infarct sizes that vary from small subendocardial or subepicardial infarcts to transmural myocardial damage owing to a high-resolution imaging technique that can be unrecognised by SPECT. The degree of transmurality of infarction (TEI) can predict the functional recovery after revascularisation. It has been recently reported that segments with ≤ 75% TEI on the acute CMR scan after AMI had a sensitivity of 98% but a specificity of 66% in predicting viability at followup.[17]

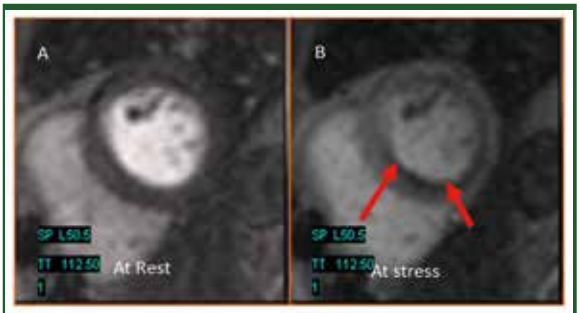

Fig. 3. CMR adenosine first passes perfusion imaging for myocardial ischemia assessment.
There is no perfusion defect at the septal area at rest (A) while a dark rim of perfusion defect (B) indicated by arrow due to the late arrival of contrast agent at area supplied by significant stenotic Left anterior descending artery. (Personal collection)

DETECTION OF CARDIAC AMYLOIDOSIS

Cardiac amyloidosis may present as unexplained symptomatic heart failure, with concentric thickening of the ventricular wall or prominent diastolic dysfunction. Further description includes a sparkling or speckled appearance on echocardiogram and profound apical sparing on strain maps.[18] In fact, it has been reported that diastolic dysfunction, increased wall thickness, atrial enlargement, and pericardial effusion are all independent prognosticators in patients with cardiac amyloidosis.

Other than endomyocardial biopsy, the early washout of the gadolinium contrast at the myocardium, subendocardial or transmural LGE; the grossly elevated myocardial T1 value (usually greater than 1,300 ms at 1.5T) and ECV levels all help to identify cardiac infiltration by abnormal protein.[19]

CMR cannot distinguish between the ATTR and AL amyloid; however, such distinction becomes possible with single-photon emission computed tomography using bone tracers (99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid [DPD], 99mTc-Hydroxymethylene diphosphonate [HMDP], 99mTc-pyrophosphate [PYP]) that preferentially bind to ATTR versus AL deposits. Of note is that the binding of 99mTc-DPD to amyloid deposits in the heart seems to

be more specific to the ATTR type rather than the AL type. Even though novel PET tracers(11C-PiB;18F-florbetapir) have also been shown to have the potential to monitor the degree of amyloid deposition during or after appropriate chemotherapy, more evidence is warranted.[20]

MONITORING ON PERICARDIAL AND VALVULAR HEART DISEASE

Patients who have received thoracic radiotherapy and/or chemotherapeutic agents like anthracyclines, cytarabine, arsenic and tyrosine kinase inhibitors are more likely to develop pericardial disease and valvular heart disease over a latent interval of 10 years or so.

For the valvular heart disease, echocardiogram remains the gold standard for qualitative and quantitative evaluation of both stenotic and regurgitant valves; in the post valvular operation followup. On the other hand, CT and MR can also be used for valve planimetry in patients with limited acoustic window. CMR can also measure the flow across values by using phase-contrast imaging although its temporal resolution is inferior to an echocardiogram.

For pericardial disease, an echocardiogram is the first-line tool to diagnosis and evaluates the real-time constrictive and tamponade physiology. While CMR can provide supplementary information on the pericardial thickness and the ventricular interdependence imaging during respiration, which is concordant with the abnormal septal motion and the appearance of pericardial tethering, CT allows the identification of pericardial calcification.

CONCLUSION

Cardiovascular disease is a common cause of morbidity and mortality among cancer patients. However, with the rapidly evolving treatment options, prevention, and early detection of potential cardiac complications is essential to warrant the health and good quality of life in survivors. Different cardiac imaging techniques have complementary roles in providing a more accurate and comprehensive way of early detection of subclinical cardiomyopathy, diagnosis and monitoring of cardiovascular complication and risk prognostication.

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Radiology Quiz

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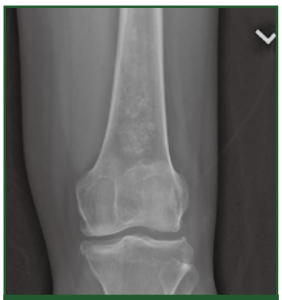

Fig. 1. Frontal radiograph of the L distal femur. There is a sclerotic intramedullary bone lesion with a narrow zone of transition and characteristic "ring and arc" calcifications.

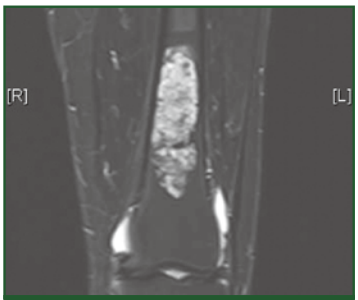

Fig. 2. T2W coronal MR image with fat suppression of the same lesion. The lesion demonstrates background hyperintense signals with focal signal drop out, signifying calcifications.

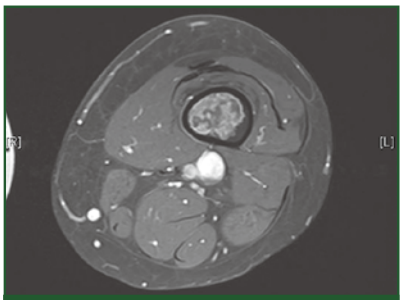

Fig. 3. Gadolinium-enhanced T1W axial MR image with fat saturation on the same lesion. The lesion shows contrast enhancement, with no associated endosteal scalloping, periosteal reaction or extra-osseous extension.

A 50 year-old lady presented to the general clinic with left distal thigh pain for months. The left lower limb power and left knee range of movement were full on physical examination. Radiographs were taken for evaluation.

Questions

1. What is the abnormality depicted on the radiographs?
2. What is the differential diagnosis?
3. What further radiological examination(s) should be considered?
4. What are the clinical or radiological features that may suggest malignancy?
5. What should be the next step of management?

(See P.36 for answers)

Kawasaki Disease: an Update Review

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In memory of Dr Tomisaku Kawasaki (1925 – 2020)

INTRODUCTION

Kawasaki disease (KD) is a systemic inflammatory vasculitis that affects medium-sized vessels and may result in irreversible coronary artery aneurysms (CAA). It is the most common cause of acquired heart disease in children in developed countries[1], and typically afflicts children less than five years of age. In the past 53 years since the first report by Dr Tomisaku Kawasaki, much has been learnt about this intriguing disease with possible serious acute and long-term consequences. Yet we are still on the path to fully understand the aetiology and pathogenesis of KD, to formulate diagnostic pathway, and to develop optimal treatment and surveillance to prevent long-term complications. This review summarises the latest advances in these aspects.

PATHOGENESIS

Available evidence from genetic, immunological and experimental data suggests that KD is the end result of a complex interplay between innate and adaptive immune responses to one or more traditional antigens in genetically susceptible individuals (Fig. 1)[2-3].

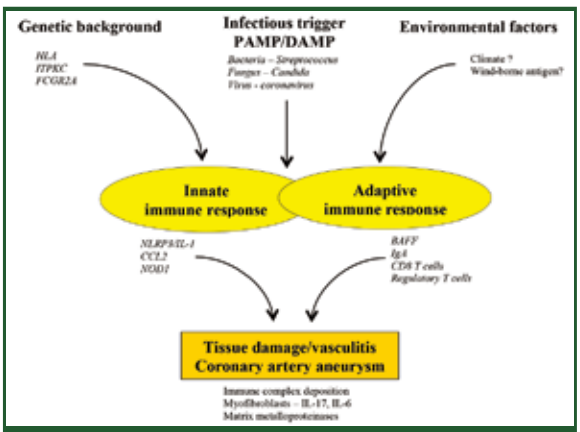


Fig. 1. Conceptual model of KD pathogenesis. A few examples of factors proposed to influence each aspect are shown in italics. (Excepted from Lo M.S.[3])

Multiple features of KD appear to suggest an infectious aetiology. These include community clusters and outbreaks within families, a seasonal pattern corresponding to the peaking of respiratory viral infections, as well as low recurrence rate suggestive of protective immunity[4-5]. Although many infectious agents have been proposed as the aetiology of KD, none has been consistently associated with the illness. The finding of oligoclonal IgA plasma cell infiltrates in the inflamed tissues, and in the vascular wall of coronary artery of KD patients implicated that the immune response in KD is antigen-driven[6]. Further identification of an antigen-driven IgA response directed at intracytoplasmic inclusion bodies within the ciliated bronchial epithelium of KD patients suggested that viral pathogen is involved in KD[7].

In the recent COVID-19 pandemic, some infected children developed a multisystem hyperinflammatory syndrome with features overlapping with KD[8-9]. Mucocutaneous features are common, and many cases fulfill the complete or partial criteria for KD[9]. The affected patients typically present with persistent fever, shock, single or multi-organ dysfunction, lymphopenia, high C-reactive protein (CRP), hyperferritinemia, elevated NT-proBNP level and cytokine overexpression including interleukin-6 (IL-6) and IL-10. Echocardiographic findings include myocardial dysfunction, pericardial effusion and coronary aneurysms[8-9]. These patients typically have either positive PCR or serological evidence of COVID-19 infection. These findings may provide further evidence of viral pathogen as a trigger for KD.

Environmental factors have been explored as etiological agents of KD, including wind current effects on fungal toxin concentration and hence the spatial and temporal pattern of KD[10]. Currently, there is no clear evidence to show these factors are involved in disease pathogenesis[11].

The evidence of the genetic basis for the pathogenesis of KD is very compelling. An epidemiological study reported an incidence of KD in Japan of 309/100,000 in children aged 0-4 years[12] while in United States it was about 20/100,000 in children of same ages[13]. Japanese children who live a Western lifestyle continue to experience the same increased risk of KD[14]. This striking ethnic difference is postulated to be caused by genetic variations. Genome-wide association studies have greatly expanded the number of gene variants linked to KD. A recent systematic review of genetic association studies reported 16 gene polymorphisms *(ACE, BLK, CASP3, CD40, FCGR2A, FGb, HLA-E, IL1A, IL6, ITPKC, LTA, MPO, PD1, SMAD3, CL17 and TNF gene)* correlated with susceptibility to KD[15]. Most of the genes are involved in immune system regulation[15]. For instance, FCGR2A encodes a low-affinity type IIa

Fc fragment receptor[16]. This surface receptor plays a role in phagocytosis and clearing of immune complexes by macrophages and neutrophils. The FCGR2A-131H haplotype is significantly correlated with KD susceptibility in both Asians and Caucasians, and also significantly associated with coronary artery lesions in Asians[15].

DIAGNOSIS

The diagnosis of KD remains clinical, and there is no pathognomonic diagnostic test. Diagnostic criteria for KD in the American Heart Association (AHA) 2017 guidelines are based on clinical variables (Table 1)[17].

Table 1. AHA 2017 clinical diagnostic guidelines of Kawasaki disease. (Excepted from McCrindle[17])

Fever for at least 5 days And at least 4 out of 5 of the following:
Bilateral bulbar conjunctival injection without exudates
Erythema and cracking of the lips, strawberry tongue, or erythema of the oral and pharyngeal mucosa
Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
Rash: maculopapular, diffuse erythroderma or erythema multiform like
Changes in extremities with erythema of palms and/or soles; edema of hands and/or feet in the acute phase and periungual peeling of fingers and toes in weeks 2 and 3

Applying the clinical criteria to diagnose KD remains challenging in some patients because of 1) sequential appearance of clinical features which may have resolved by the time of presentation, 2) the presence of concomitant infection in up to 22% of patients with KD[18], and 3) atypical or incomplete KD features, especially in young infants, which accounts for 20-30% of patients[19].

The current guidelines have proposed pathways to tackle atypical presentation[17] (Fig. 2). Index of suspicion of KD is raised when 2 or 3 criteria are met with fever > 5 days, or in infants less than six months with unexplained fever for seven days. It is prudent to evaluate supporting clinical features that are not part of the formal criteria[20] (Table 2), particularly in patients with deranged biochemical markers including elevated acute phase reactants, leukocytosis, hyponatremia, hypoalbuminemia, raised transaminases or gamma-GT, hyperbilirubinemia, and sterile pyuria.

Table 2. Other recognised findings in Kawasaki disease. (Excepted from Kelly A.[20])

- Extreme irritability
- Aseptic meningitis
- Erythema and induration at the BCG site
- Hydrops of the gall bladder
- Perineal erythema and desquamation
- Arthralgia and arthritis
- Myocarditis
- Pericardial effusions
- Congestive cardiac failure
- Valvular dysfunction
- Diarrhea, vomiting and abdominal pain
- Testicular swelling
- Anterior uveitis

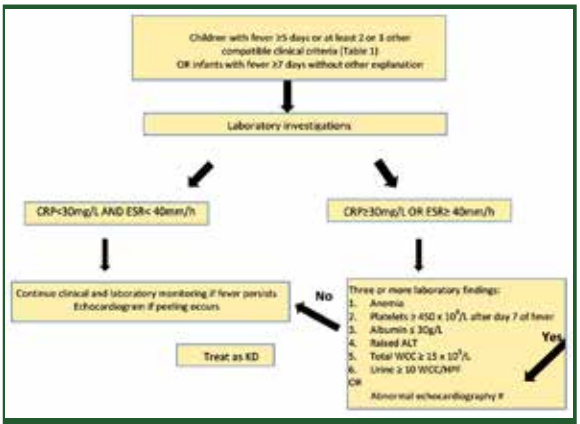


Fig. 2. Evaluation of suspected incomplete Kawasaki disease (Adapted from AHA 2017[17])
#Echocardiography is considered positive for purposes of this algorithm if any of 3 conditions are met: Z score of left anterior descending coronary artery or right coronary artery ≥2.5; coronary artery aneurysm is observed; or ≥3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z scores in left anterior descending coronary artery or right coronary artery of 2 to 2.5.
Abbreviations: AHA, American Heart Association; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; ALT, Alanine transaminase; HPF, High power field, KD, Kawasaki disease, WCC, White cell count.

Novel biomarkers including NT-proBNP, IL-6 and inflammatory cytokines have been explored as adjuvant diagnostic markers, although their role still requires further evaluation[21-22]. Beyond biochemical markers, the role of molecular modalities is gaining interest. Study of gene expression signature showed that patients with KD have a unique gene expression pattern. Wright and colleagues developed and validated a unique 13-transcript gene expression signature to differentiate KD from other febrile conditions[23]. Among the 13 genes identified, 5 showed a lower expression in patients with KD, while S100P and CD 163 were more expressed in bacterial and IFI27 in viral infections. If verified, this approach may assist in early diagnosis and early treatment of KD.

ECHOCARDIOGRAPHIC ASSESSMENT OF CORONARY ARTERIES

Echocardiography is the primary imaging modality for cardiac assessment in KD. Echocardiogram is usually normal in the first week of illness. Echocardiography should be performed at diagnosis as a baseline to evaluate the early coronary status and associated cardiac involvement such as mitral regurgitation, aortic root dilatation, aortic regurgitation, myocardial dysfunction, and pericardial effusion. Echocardiography helps in the diagnosis of incomplete KD by identifying coronary dilatation and aneursym.

The Japanese Ministry of Health (JMH) 2013 KD guidelines[24] define CAA by the absolute internal diameter of the coronary artery with respect to age. In 2017 AHA recommended using Z score of coronary artery dimension to define coronary aneurysm[17] (Table 3). The Z score approach allows comparison

across time and populations and makes it less likely to underestimate coronary abnormalities when compared to the JMH measurement criteria[25]. Different formulae for calculating Z scores have been derived. Currently, the more widely used models are the Z score calculators by Dallaire and colleagues in a Canadian population[26] and the calculator based on a Japanese population by Kobayashi and colleagues[27]. Both are based on large-scale studies and showed comparable coronary Z scores when applied in different KD populations[17].

Table 3. AHA vs JMH guidelines for coronary aneurysm. (Summarised from reference[17,24])

	JMH criteria < 5 years	JMH criteria ≥ 5 years	AHA 2017 criteria
No involvement			Z score < 2
Transient dilatation			Z score ≥ 2 to < 2.5
Small	≤ 4 mm	1.5x diameter of adjacent segment	Z score ≥ 2.5 to < 5
Medium	> 4 mm to ≤ 8 mm	1.5-4x diameter of adjacent segment	Z score ≥ 5 to < 10 and absolute < 8 mm
Giant	> 8 mm	> 4x diameter of adjacent segment	Z score > 10 or absolute > 8mm

Abbreviations: AHA, American Heart Association; JMH, Japanese Ministry for Health

ACUTE TREATMENT

Current standard first-line management of KD includes the use of intravenous immunoglobulins (IVIG) 2 g/kg as a single infusion plus oral aspirin (high dose, 80 to 100 mg/kg/day, or moderate dose, 30 to 50 mg/kg/day in 4 divided doses for anti-inflammatory effect) until the patient stays afebrile for 48 hours. This is followed by antiplatelet dosing of oral aspirin (3 to 5 mg/kg/day) for 6 to 8 weeks, which can then be discontinued if no further CAA is present on follow-up[17,24]. Single high-dose IVIG treatment can reduce the risk of CAA from 25% to less than 5%[28]. Timely administration of IVIG within ten days of illness is important as delayed treatment is associated with a higher incidence of CAA (16% vs 5%)[29].

The role and dosing of oral aspirin (ASA) in acute management remains controversial with regards to IVIG resistance rates and CAA incidence. Currently, there is insufficient evidence that oral aspirin reduces CAA[17]. The AHA 2017 guidelines recommend that both high and moderate doses of ASA are reasonable for acute treatment. A multicentre randomised controlled trial is underway to evaluate the efficacy of IVIG alone or IVIG with high-dose aspirin using CAA at 6-8 weeks as the primary endpoint[30].

Corticosteroids alone should not be used as primary treatment for uncomplicated KD[17] as randomised controlled trial has shown that it did not reduce CAA risk, hospital days nor adverse events compared to placebo[31]. However, there is increasing evidence that the addition of steroids to IVIG may be of benefit to patients at high risk of IVIG resistance (see next section). A randomised study on treatment of KD patients predicted as IVIG non-responder demonstrated that IVIG and prednisolone combination reduced fever duration and coronary artery Z scores better than IVIG alone[32]. Two recent meta-analyses also showed that early addition of corticosteroids as primary adjunctive treatment in patients at high risk is associated with reduced risk of CAA compared with IVIG therapy alone[33-34].

In the AHA 2017 guidelines, the use of primary adjunctive steroid therapy in addition to IVIG and aspirin is a class IIb recommendation, and may be considered for the treatment of high-risk patients with acute KD[17]. A 2018 European consensus recommends primary adjunctive pulse steroid therapy for patients with severe KD, which was defined as Kobayashi score ≥ 5, features of shock or haemophagocytic lymphohistiocytosis, young infants < 1 year of age, and coronary or peripheral aneurysms at diagnosis[35].

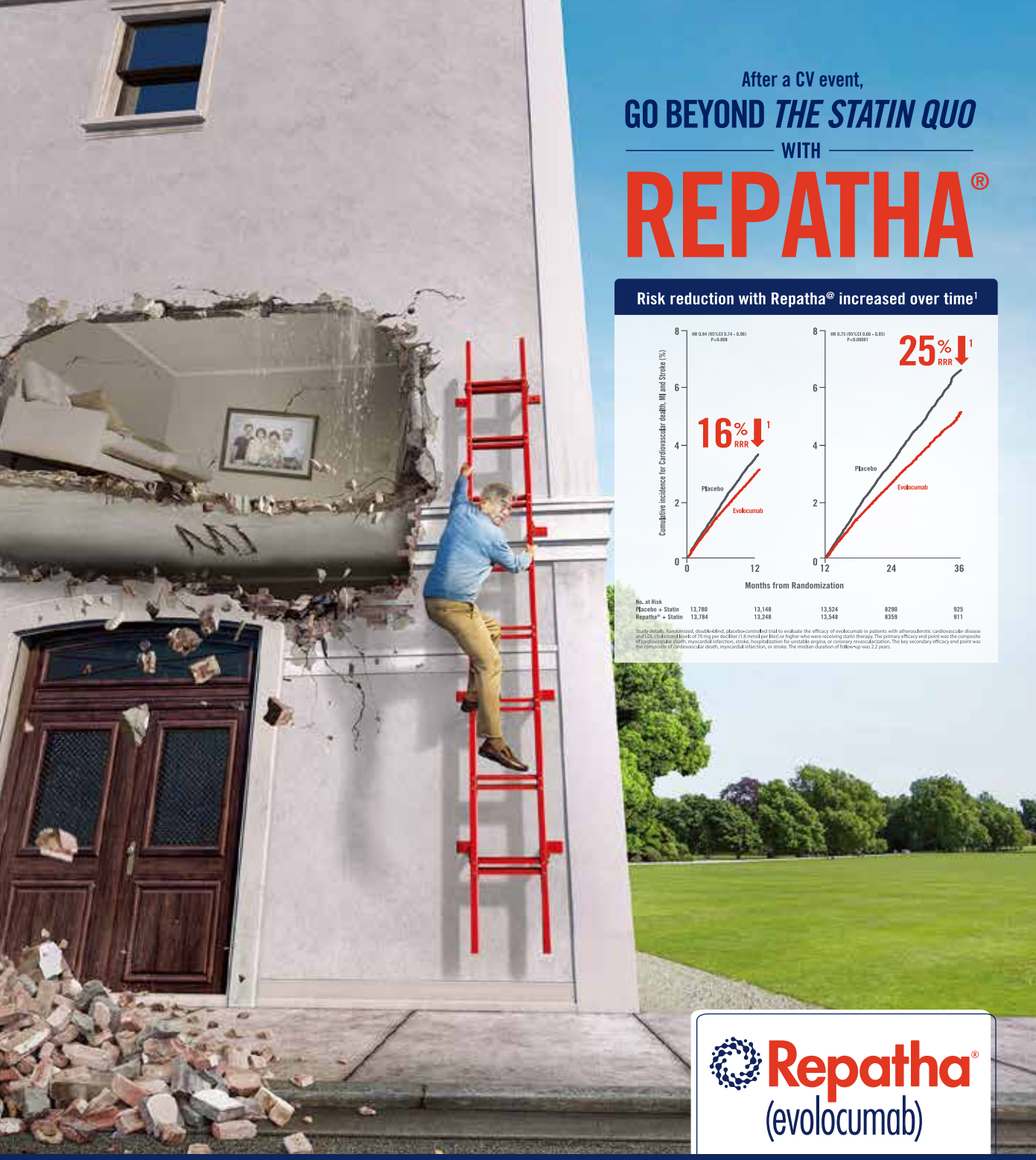
IVIG RESISTANCE

About 10-20% of KD patients develop recrudescent or persistent fever at least 36 hours after IVIG infusion and are termed IVIG resistant[17,36]. These patients may have up to nine-fold increased risk of CAA[37]. The exact immunological basis of IVIG resistance is unknown, but it is likely that host factors such as polymorphisms in the Fc gamma receptors play a role in both the response and resistance to IVIG[38]. Three risk scores based on the Japanese populations have been suggested as predictors of IVIG non-responder[39-41]. However, when tested on a North American population, the scores demonstrated a sensitivity of 33–42% only, although maintaining high specificity[42]. Better predictive models, perhaps incorporating biomarkers or genetic variants, should be developed for use outside Japan.

For the treatment of IVIG resistance, a second dose of IVIG is suggested by current guidelines[17,35]. Corticosteroids, as mentioned above, are used both as primary adjunctive therapy to IVIG in patients predicted to be at high risk of IVIG resistance and as a rescue treatment in patients who fail the first and/or the second administration of IVIG[17,35]. There is also growing evidence supporting the use of immunomodulatory agents for refractory KD. The AHA 2017 guidelines suggest that infliximab, an anti-TNF-alpha monoclonal antibody, may be used as an alternative to second-dose IVIG and corticosteroids for IVIG-resistant patients. A retrospective study of a single dose of infliximab showed shortened fever duration and hospital stay, but CAA and adverse event outcome were similar to the second-dose IVIG group[43]. A phase 3 randomised trial is ongoing to study second-dose IVIG versus infliximab[44]. Other large clinical trials are also ongoing for other immunomodulatory agents, including IL-1 blocker (anakinra) and cyclosporin[45-46].

LONG TERM SURVEILLANCE OF POST KD CHILDREN AND ADULTS

As more children with a history of KD reach adulthood, the adult cardiologist looking after these patients must be vigilant on the coronary sequelae of KD. Studies have shown that coronary aneurysms are present in 5.0% to 9.2% of young adults evaluated by angiography



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INDICATIONS: Hypercholesterolaemia and mixed dyslipidaemia: Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non familial) or mixed dyslipidaemia, as an adjunct to diet; in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL C goals with the maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. Homozygous familial hypercholesterolaemia: Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies. Established atherosclerotic cardiovascular disease: Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. **DOSAGE AND ADMINISTRATION:** Primary hypercholesterolaemia and mixed dyslipidaemia in adults: The recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly, both doses are clinically equivalent. Homozygous familial hypercholesterolaemia in adults and adolescents aged 12 years and over: The initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule. Established atherosclerotic cardiovascular disease in adults: The recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly, both doses are clinically equivalent. No dose adjustment is necessary in patients with mild to moderate renal impairment. No dose adjustment is necessary in patients with mild hepatic impairment. No dose adjustment is necessary in elderly patients. The safety and efficacy of Repatha in children aged less than 18 years has not been established in the indication for primary hypercholesterolaemia and mixed dyslipidaemia. The safety and efficacy of Repatha in children aged less than 12 years has not been established in the indication for homozygous familial hypercholesterolaemia. Repatha is for subcutaneous injection into the abdomen, thigh or upper arm region. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard. Repatha must not be administered intravenously or intramuscularly. The 420 mg dose should be delivered using three pre-filled syringes/ autoinjectors administered consecutively within 30 minutes. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** Renal impairment: There is limited experience with Repatha in patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m2). Repatha should be used with caution in patients with severe renal impairment. Hepatic impairment: In patients with moderate hepatic impairment, a reduction in total evolocumab exposure was observed that may lead to a reduced effect on LDL C reduction. Therefore, close monitoring may be warranted in these patients. Patients with severe hepatic impairment (Child-Pugh C) have not been studied. Repatha should be used with caution in patients with severe hepatic impairment. Dry natural rubber: The needle cover of the glass pre-filled syringe/ autoinjector is made from dry natural rubber (a derivative of latex), which may cause allergic reactions. Sodium content: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'. **INTERACTIONS:** An approximately 20% increase in the clearance of evolocumab was observed in patients co-administered statins. This increased clearance is in part mediated by statins increasing the concentration of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) which did not adversely impact the pharmacodynamic effect of evolocumab on lipids. No statin dose adjustments are necessary when used in combination with Repatha. **PREGNANCY AND LACTATION:** Pregnancy: There are no or limited amount of data from the use of Repatha in pregnant women. Repatha should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab. Breast-feeding: It is unknown whether evolocumab is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or discontinue/abstain from Repatha therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Fertility: No data on the effect of evolocumab on human fertility are available. **ADVERSE REACTIONS:** The most commonly reported adverse reactions during pivotal trials, at the recommended doses, were nasopharyngitis (7.4%), upper respiratory tract infection (4.6%), back pain (4.4%), arthralgia (3.9%), influenza (3.2%), and injection site reactions (2.2%). The safety profile in the homozygous familial hypercholesterolaemia population was consistent with that demonstrated in the primary hypercholesterolaemia and mixed dyslipidaemia population. Injection site reactions: The most frequent injection site reactions were injection site bruising, erythema, haemorrhage, injection site pain, and swelling. Paediatric population: There is limited experience with Repatha in paediatric patients. No difference in safety was observed between adolescent and adult patients with homozygous familial hypercholesterolaemia. The safety and effectiveness of Repatha in paediatric patients with primary hypercholesterolaemia and mixed dyslipidaemia has not been established. Elderly population: No overall differences in safety or efficacy were observed between these patients and younger patients. Immunogenicity: In clinical studies, 0.3% of patients (48 out of 17,992 patients) treated with at least one dose of Repatha tested positive for binding antibody development. The patients whose sera tested positive for binding antibodies were further evaluated for neutralising antibodies and none of the patients tested positive for neutralising antibodies. The presence of anti-evolocumab binding antibodies did not impact the pharmacokinetic profile, clinical response, or safety of Repatha. **SPECIAL PRECAUTIONS FOR STORAGE, DISPOSAL AND OTHER HANDLING:** Store in a refrigerator (2°C – 8°C). Do not freeze. Keep in the original carton in order to protect from light. If removed from the refrigerator, Repatha may be stored at room temperature (up to 25°C) in the original carton and must be used within 1 month. Before administration, the solution should be inspected. Do not inject the solution if it contains particles, or is cloudy or discoloured. To avoid discomfort at the site of injection, allow the medicine to reach room temperature (up to 25°C) before injecting. Inject the entire contents.

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Reference: 1. Sabatine MS, et al. Supplementary Appendix to: Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722.

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for myocardial ischemia or presenting with sudden cardiac death[47-48]. The risk of thrombotic and stenotic complications is related to aneurysm size[49]. Patients with a large or giant aneurysm are the least likely to undergo resolution and carry a higher rate of complications. One study on patients with giant CAA has demonstrated a cumulative coronary intervention rate of ~ 60% at 25 years after disease onset[50].

KD patients with no coronary involvement or with small CAA demonstrate a favourable long-term outcome. A large cohort in Canada involving 2,623 KD patients followed up for up to 40 years demonstrated good outcome for patients without CAA or with small aneurysms. Mortality was only shown in patients with giant aneurysms[51].

For KD patients with CAA, current guidelines recommend assessing for inducible myocardial ischemia via stress echocardiography, stress magnetic resonance (MRI) or stress nuclear myocardial scan every 2-3 years. Surveillance coronary angiography with computer tomographic (CT) and/or MRI angiography every 2-5 years is also recommended[17,52]. More frequent surveillance is suggested for patients with giant CAA. It should be noted that exercise treadmill ECG test alone should not be used for assessment of inducible myocardial ischemia owing to false-negative results[17].

LONG-TERM THROMBOPROPHYLAXIS

Current guidelines recommend KD patients with small aneurysms (persistent after 6 weeks) should be put on long-term aspirin, including those in whom there is regression of CAA[17,24,52]. For KD patients with giant aneurysm, anticoagulation with either warfarin or low molecular weight heparin (LMWH) plus antiplatelet treatment is recommended[17,24,52]. For medium-sized CAA, AHA 2017 guidelines suggest consideration of dual anti-platelet therapy while JMH 2013 guidelines suggest anticoagulation[17,24].

Currently, there is no randomised clinical trial on the level of antithrombotic prophylaxis for KD patients with giant CAA. Su and colleagues performed a meta-analysis of 6 case-controlled studies reviewing the safety and efficacy of the combination of warfarin plus aspirin for KD patients with giant CAA[53]. There was evidence that warfarin plus aspirin reduced the incidence of coronary artery occlusion, myocardial infarction and death. A recent review of data from the International Kawasaki Disease Registry showed that among 383 KD patients with giant aneurysms, the cumulative incidence of coronary artery thrombosis with LMWH was 5.7 ± 3.0%, warfarin 6.7 ± 3.7% and with no anticoagulation 20.6 ± 3.0% ($p < 0.001$) at 2.5 years after the start of thromboprophylaxis[54]. Severe bleeding complications were generally rare (1.6 events per 100 patient-years), and noted equally for patients on LMWH and warfarin. It was concluded that all patients with giant CAA should receive anticoagulation, but the choice of agent might be determined by secondary risk factors and patient preferences. Future study should evaluate the use of direct oral anticoagulants in children as an alternative to warfarin.

CONCLUSIONS

Latest research findings regarding Kawasaki disease pathogenesis, diagnostic tests and immunomodulatory treatment seem promising, but more evidence is required to allow early diagnosis and recognition of patients at high risk and to identify the best treatment options. With rapid advances in research and collaboration among specialists in this field, we will be more successful in diagnosis, risk-stratification and management of KD patients to achieve better long-term outcome.

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Footnotes: a) Defined as fatal bleeding, ICH and critical organ bleeding **b)** The recommended dose is 2.5 mg twice daily, with a daily dose of 75 - 100 mg ASA.
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Reference: 1. Anand S.S., Bosch J., Eikelboom J.W. et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; doi: 10.1016/S0140–6736(17)32409–1. **2.** Frank U., Nikol S. et al. European Society for Vascular Medicine (ESVM). Guideline on peripheral arterial disease. Vasa. 2019;48, Supplement 102; doi 10.1024/0301-1526/a000834. **3.** Xarelto® Hong Kong Prescribing Information 2.5mg (February 2019).

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Rope Skipping in Hong Kong

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Specialist in Cardiology

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Dr Patrick Tak-him KO

The Hong Kong College of Cardiology (HKCC) and the Hong Kong Rope Skipping Association, China (HKRSA) began to develop rope skipping 22 - 23 years ago.

The HKCC launched the Jump Rope for Heart (JRFH) in 1998 to encourage our young generation to adopt a heart-healthy lifestyle via exercise. School students aged 7 to 15 are encouraged to participate in the programme, and in 4 to 6 weeks they learn the basic skills of rope skipping. During this period, ways to adopt a healthy lifestyle in order to prevent cardiovascular diseases are introduced to these students. The JRFH has thus played a key role in our overall heart health program for the community of Hong Kong. The Skippers and their coaches are able to develop their own rope skipping styles and compete in an annual JRFH Inter-School Rope Skipping Competition.

The HKRSA was founded a year earlier by a group of Physical Education students at the Chinese University of Hong Kong, led by Prof Amy Ha. Over the next several years, HKRSA members focused on advanced techniques of rope skipping and became professional rope-skipping coaches and judges at competitions, while some started their own rope-skipping clubs, where they provide intensive training for elite rope-skippers.

The HKCC and HKRSA have worked closely together since the year 2000. The JRFH of the HKCC targets at a large number of students. Each year, more than 50,000 students from around 100 schools in Hong Kong join the JRFH. Over the past 20 years, over 1.2 million students from around 650 primary and secondary schools have participated in JRFH. Many of the top rope-skipping athletes or those who have done well at rope-skipping competitions are then "drafted" to receive further training in advanced rope-skipping techniques.

Hong Kong has been sending her own team to participate in the Asian Rope Skipping Championships as well as the World Rope Skipping Championships (WRSC) since 2004; the Hong Kong Team has done very well in both international championship events. The following is a list of how the Hong Kong Team has done in the World Rope Skipping Championships in the last ten years:

- 2004 Sydney, Australia (4 athletes + 2 officials): no medals
- 2006 Toronto, Canada (16 athletes + 4 officials): 5 gold, 7 silver and 1 bronze medals
- 2008 Cape Town, South Africa (9 athletes + 4 officials): 7 gold, 6 silver and 4 bronze medals
- 2010 Loughborough, UK (52 athletes + 12 officials): 20 gold, 13 silver and 15 bronze medals
- 2012 Tampa Florida, USA (53 athletes + 13 officials): 18 gold, 19 silver and 13 bronze medals – including 4 world records
- 2014 Hong Kong (160 athletes + 10 officials): 28 gold, 30 silver and 34 bronze medals – including 4 new world records
- 2016 Malmo, Sweden (127 athletes + 1- officials): 27 gold, 27 silver and 26 bronze
- 2018 Shanghai, China (139 athletes and coaches): 23 gold, 31 silver and 34 bronze
- 2020 WRSC scheduled to be held in Ottawa, Canada has been postponed to July 2021.

In particular, the 2014 World Rope Skipping Championships were held in Hong Kong at the Hong Kong Coliseum and was supported by the Leisure and Cultural Services Department (LCSD) of the Government of HKSAR, and the Hong Kong Jockey Club. This event received a grant of HK$0.8 million from the LCSD and HK$2.5 million from the Charity Trust of the Hong Kong Jockey Club. This was the first World Rope Skipping Championships ever held in Asia, and attracted 1,200 rope skipping athletes from 20 countries.

The 2016 World Rope Skipping Championships were held in Malmo, Sweden from July 23 to August 2, 2016. 127 athletes and 10 coaches constituted a very strong Hong Kong Team. They were able to capture a total of 80 medals: 27 gold, 27 silver and 26 bronze medals, including the World Cup of Rope Skipping on August 1, 2016. The Hong Kong male teams dominated the team competition by capturing gold, silver and bronze. They smashed their 4 x 45 seconds double dutch relay world record, which they have held since 2012, by a wide margin.

The 2018 World Rope Skipping Championships were held in Shanghai (for the first in China) from July 24 to August 2, 2018. Team Hong Kong again did a fantastic job, capturing 23 gold, 31 silver and 34 bronze medals. Rope skipping athletes from mainland China improved immensely, especially in the individual speed competitions, but Hong Kong skippers still dominated the team and freestyle categories. Our female skippers also vastly improved, winning many medals!

The Hong Kong Team of Rope Skippers has thus become a legend in the world of rope skipping. Their success is no doubt due to the hard work, dedication and passion of all the rope skippers, coaches and other parties involved, plus the support from their parents and the many people who have unconditionally given them monetary and other support over the years. The International Jump Rope Union (IJRU) has, since Oct 2019, become a unified international organisation for the sole management of the sport at the international level. The Hong Kong Rope Skipping Association, China represents Hong Kong in the IJRU and, as such, will likely be recognised by the Sports Federation and Olympic Committee, China and the Government of Hong Kong. We know there is a lot of innovative talent among our rope skippers and coaches who, time and again, have given us pleasant surprises! We are proud of our rope-skipping team, and we look forward to further development of rope skipping in Hong Kong.

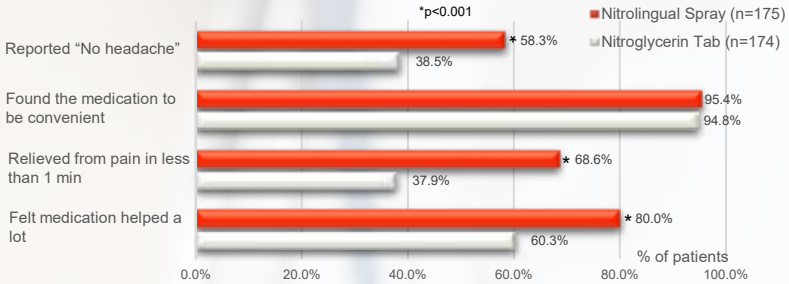
Ho Chu-ting and Chow Wing-lok participated in the Group Synchronise Competition in 2018 World Rope Skipping Championships, Shanghai (Personal Collection)

10th Asian Rope Skipping Championships were held in HK at Tsuen Wan Sports Centre (Collection of Hong Kong Rope Skipping Association, China)

Group photo of Hong Kong Team after winning the World Cup in the 2016 World Rope Skipping Championships in Malmo, Sweden (Personal Collection)

Why does Nitrolingual®-Spray outweigh NTG Tablet?

Sublingual Nitroglycerin or Spray in the treatment of Angina[1]



- Significantly fewer headache and hypotension episodes [2]
- Faster, greater and more prolonged vasodilation effect than conventional NTG tablet [3]
- Proven stability for up to 3 years after first use [4]

	Dosage	Administration
Acute Relief	One to two metered sprays	At the onset of an attack, administer one to two metered sprays sublingually Repeat again after 10 minutes if there is no response
Prophylactic Use		One to two metered sprays prior to exercise

RETHINK Angina Treatment

Reference:
1. M J Vandenburg et al. BJCP (1986) 40:12. 2. K L Chien et al. Cardiology (2000) 93, 137-141. 3. A Ducharme et al. Am J Cardiol (1999) 84, 952-954. 4. Nitrolingual® Spray local package insert.

Manufacturer:
G. Pohl-Boskamp GmbH & Co. KG, Germany

For further information:
HONGKONG MEDICAL SUPPLIES LTD.
Tel: 2806 3112 Fax: 2887 3425
Email: sales2@hkmedsup.com.hk
Website: www.hongkongmedical.com.hk

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Pleasant Iron for Better Health

Ferrum Hausmann®
Iron (III) hydroxide polymaltose complex

Ferrum Hausmann®: Optimal Daily Formulations to Treat ID or IDA

General Supplementation			Therapeutic Dosing		
Drops	Syrup	Chewable Tablet	Drops	Syrup	Chewable Tablet
2.5mg/drop	10mg/ml	100mg/ chewable tab	2.5mg/drop	10mg/ml	100mg/ chewable tab
20 - 40 drops	N/A	X 1	40 - 120 drops	10 - 30 ml	X 1 - 3


Drops


Syrup


Chewable tablets

Ferrum Hausmann® Chewable Tablet Abbreviated Prescribing Information
Composition: Each chewable tablet contains 100mg of iron as Iron(III)-Hydroxide Polymaltose Complex (IPC), cyclamate, flavouring, excip. procompresso. Indication: Treatment of latent iron deficiency and iron deficiency anaemia. Prophylactic therapy of iron deficiency during pregnancy. Dosage & administration: Dosage and duration of therapy are dependent upon the extent of iron deficiency. Iron deficiency anaemia children (>12years), adults and nursing mothers: 1 chewable tablet 1 to 3 times daily or can be taken at one time until a normalization of the haemoglobin value is achieved, the therapy should be continued for several weeks with 1 chewable tablet daily to replenish the iron stores. Pregnant women: 1 chewable tablet 2 to 3 times daily or can be taken at one time until a normalization of the haemoglobin value is achieved, the therapy should be continued for several weeks with 1 chewable tablet daily to replenish the iron stores. Latent iron deficiency – Children (>12years), adults, nursing mothers and pregnant women: 1 chewable tablet daily. Prophylactic therapy: pregnant women: 1 chewable tablet daily. Ferrum Hausmann® Chewable Tablet can be chewed or swallowed whole and should be taken during or immediately after a meal. Contraindications, Warnings, Precaution: Ferrum Hausmann® Chewable Tablet is contraindicated for iron overload (e.g. haemochromatosis, haemosiderosis) or disturbances in iron utilization (e.g. lead anaemia, sidero-achresticanaemia, thalassaemia) and anaemia not caused by iron deficiency (e.g. haemolytic anaemia), known in tolerance of any of the ingredients. During pregnancy and lactation Ferrum Hausmann® Chewable Tablet should be used only after consulting a medical doctor or pharmacist. In cases of anaemia due to infections or malignancy, the substituted iron is stored in the reticulo-endothelial system, from which it is mobilized and utilized only after curing the primary disease. Undesirable effects: Very rare: constipation, diarrhea, nausea, abdominal pain, gastric disorders, indigestion, vomiting, rash; a dark colouration of the stool due to elimination is of no clinical significance. Legal Classification: Not A Poison. Date of preparation: September 2018. Full prescribing information provided upon request. Adverse event should be reported. For further information please contact Hongkong Medical Supplies Ltd., 28063112, sales2@hkmedsup.com. Hk and the Pharmacovigilance Departmentat Vifor Pharma Asia Pacific Pte. Ltd., Safety. APAC@viforpharma.com

For further information:
Hongkong Medical Supplies Ltd.
Tel: 2806 3112 Fax: 2887 3425
Email: sales2@hkmedsup.com.hk
Website: www.hongkongmedical.com.hk

VIFOR PHARMA

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1	2	3
4	5	6	★ Facebook Live New Era in Lipid Management: from the Viewpoint of a Cardiologist and an Endocrinologist ★ Certificate Course on Respiratory Medicine 2020 (Video Lectures) 7	★ Certificate Course on Renal Medicine 2020 (Video Lectures) 8	9	10
11	12	13	★ The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed ★ Facebook Live Update in Management of Lung Cancer ★ Certificate Course on Respiratory Medicine 2020 (Video Lectures) 14	★ Certificate Course on Renal Medicine 2020 (Video Lectures) 15	16	17
18	19	★ Facebook Live Latest Epidemiology, Recommendation and Vaccination Schedule of the Deadly Meningococcal Disease 20	★ Facebook Live Advancing T2D Management with Evidence: What's the Insight from Latest Update? ★ Certificate Course on Respiratory Medicine 2020 (Video Lectures) 21	22	★ Facebook Live An Overview of Obesity Management 23	★ Facebook Live or Zoom 1) STIs Clinical Diagnosis & Management in Primary Care Setting ★ Facebook Live or Zoom 2) HIV Prevention & Management – 2000s vs 2020s 24
25	26	★ Facebook Live Update on Colorectal Cancer Program 2020 27	★ Certificate Course on Respiratory Medicine 2020 (Video Lectures) 28	★ Facebook Live Nutrition Management of Type 2 Diabetes 29	30	31

IMPROVE-IT
OUTCOMES RESULTS*

THINK BEYOND MONOTHERAPY

Atozet®
(ezetimibe and atorvastatin) tablets

ACHIEVE TARGET LDL-C LEVELS WITH POWERFUL DUAL ACTION OF

ATOZET®

Abbreviation: LDL-C: low-density lipoprotein cholesterol
Reference: 1. Hong Kong Product Circular (Atozet, MSD)

Selected Safety Information on ATOZET

Indications: Prevention of Cardiovascular Events ATOZET is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not. Hypercholesterolaemia ATOZET is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hypercholesterolaemia, where use of a combination product is appropriate: • patients not appropriately controlled with a statin alone • patients already treated with a statin and ezetimibe. Homozygous Familial Hypercholesterolaemia (HoFH) ATOZET is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis). Contraindications: • Hypersensitivity to the active substances or to any of the excipients. • Therapy with ATOZET is contraindicated during pregnancy and breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures. ATOZET is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN). Precautions: • Myopathy/Rhabdomyolysis ► In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. Rhabdomyolysis has been reported very rarely with ezetimibe monotherapy. ► Also, ATOZET contains atorvastatin, which is a HMG-CoA reductase inhibitor. Atorvastatin may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis. ► A CPK level should be measured before starting treatment. If CPK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started. ► Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ATOZET. • Liver Enzymes ► Liver function tests should be performed before the initiation of treatment and periodically thereafter. Should an increase in transaminases of greater than 3 times the ULN persist, reduction of dose or withdrawal of ATOZET is recommended. • Hepatic Insufficiency ► Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ATOZET is not recommended. • Interstitial lung disease ► If it is suspected that a patient has developed interstitial lung disease, statin therapy should be discontinued. • Diabetes mellitus. ► Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI >30kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. • Excipients. ► ATOZET contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine. Adverse events: • Common adverse reactions (≥1/100, <1/10) include diarrhoea and myalgia. • In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was 0.6% for patients treated with ATOZET. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy. Please consult the full prescribing information for detailed adverse events.

Before prescribing, please consult the full prescribing information.

MSD

Merck Sharp & Dohme (Asia) Ltd.
3106, Low Block, Two Pacific Place, 88 Queensway, Hong Kong
Tel: (852) 3521 2800 Fax: (852) 2804 0766 www.msd.com.hk

HK-ATO-400059 01/19

Date / Time	Function	Enquiry / Remarks
7 WED 2:00 PM	**Facebook Live** **New Era in Lipid Management: from the Viewpoint of a Cardiologist and an Endocrinologist** Organiser: HKMA Central, Western & Southern Community Networks; Speaker: 1.) Dr Norman Nor CHAN 2.) Dr Adrian Yan-yu CHEONG	Miss Antonia LEE 3108 2514 1 CME Point
7:00 PM	**Certificate Course on Respiratory Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Chung-kong NG	Ms. Vienna LAM Tel: 2527 8898
8 THU 7:30 PM	**Certificate Course on Renal Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Wing-fai PANG, Dr Ka-fai YIM	Ms. Vienna LAM Tel: 2527 8898
14 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organiser: Hong Kong Neurosurgical Society; Speaker(s): Dr Ben Chat-fong NG Chairman: Dr CHEUNG Fung-ching; Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061 1.5 points College of Surgeons of Hong Kong
2:00 PM	**Facebook Live** **Update in Management of Lung Cancer** Organiser: HKMA Central, Western & Southern Community Networks; Speaker: Dr AU Siu-kie;	Miss Antonia LEE 3108 2514 1 CME Point
7:00 PM	**Certificate Course on Respiratory Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Pik-shan CHEUNG	Ms. Vienna LAM Tel: 2527 8898
15 THU 7:00 PM	**Certificate Course on Renal Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Wai-yan LAU, Dr Anthony Kai-ching HAU	Ms. Vienna LAM Tel: 2527 8898
20 TUE 2:00 PM	**Facebook Live** **Latest Epidemiology, Recommendation and Vaccination Schedule of the Deadly Meningococcal Disease** Organiser: HKMA Kowloon West Community Network; Speaker: Dr Helene WAN	Miss Antonia LEE 3108 2514 1 CME Point
21 WED 2:00 PM	**Facebook Live** **Advancing T2D Management with Evidence: What's the Insight from Latest Update?** Organiser: HKMA Central, Western & Southern Community Networks; Speaker: Dr Enoch WU	Miss Antonia LEE 3108 2514 1 CME Point
7:00 PM	**Certificate Course on Respiratory Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr HC FAN	Ms. Vienna LAM Tel: 2527 8898
23 FRI 2:00 PM	**Facebook Live** **An Overview of Obesity Management** Organiser: HKMA-Shatin Community Network; Speaker: Dr TSUI Tsun-miu	Ms. Candice TONG 3108 2513 1 CME Point
24 SAT 2:00 PM	**Facebook Live or Zoom** **1) STIs Clinical Diagnosis & Management in Primary Care Setting** Organiser: Hong Kong Medical Association; Speaker: Dr KWAN Chi-keung	HKMA CME Dept. 3108 2516 1 CME Point
3:00 PM	**Facebook Live or Zoom** **2) HIV Prevention & Management – 2000s vs 2020s** Organiser: Hong Kong Medical Association; Speaker: Dr Wilson LAM	HKMA CME Dept. 3108 2516 1 CME Point
27 TUE 2:00 PM	**Facebook Live** **Update on Colorectal Cancer Program 2020** Organiser: HKMA New Territories West Community Network; Speaker: Dr Henry Wai-tak TANG	Miss Antonia LEE 3108 2514 1 CME Point
28 WED 7:00 PM	**Certificate Course on Respiratory Medicine 2020 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong; Speaker: Dr Jerry HO	Ms. Vienna LAM Tel: 2527 8898
29 THU 2:00 PM	**Facebook Live** **Nutrition Management of Type 2 Diabetes** Organiser: HKMA Kowloon East Community Network; Speaker: Dr AU YEUNG Yick-cheung;	Miss Antonia LEE 3108 2514 1 CME Point

Answers to Radiology Quiz

Answers:

1. An intramedullary sclerotic bone lesion is noted at the left distal femur metadiaphyseal region. It is with a narrow zone of transition and with "ring and arc" matrix calcifications. No definite periosteal reaction or endosteal scalloping is seen.

2. Features favour a non-aggressive bone lesion. "Ring and arc" matrix calcification is pathognomonic for a chondroid lesion. Differentials include enchondroma or low grade chondrosarcoma.

3. MRI with contrast should be considered. It would provide additional information on the tumour composition, suspicious features for malignancy, the local extent of the tumour and presence of skip lesions.

4. Large tumour size > 5-6 cm, cortical breach, deep endosteal scalloping involving > 2/3 of cortical thickness, extra-osseous soft tissue component and presentation with pain are important features that should raise the suspicion of malignancy.

5. Although there were no suspicious radiological features, a biopsy was offered in view of the associated pain.

Dr Jeremy Man-leung YU
MBChB, FRCR

KEYTRUDA®
(pembrolizumab)

Regardless of PD-L1 Expression Level[2]

THE ONLY ANTI-PD-1 FIRST-LINE COMBINATION TREATMENT FOR NONSQUAMOUS mNSCLC*

KEYTRUDA: **HELPING TO REDEFINE SURVIVAL EXPECTATIONS** FOR MORE PATIENTS WITH NONSQUAMOUS mNSCLC[1]

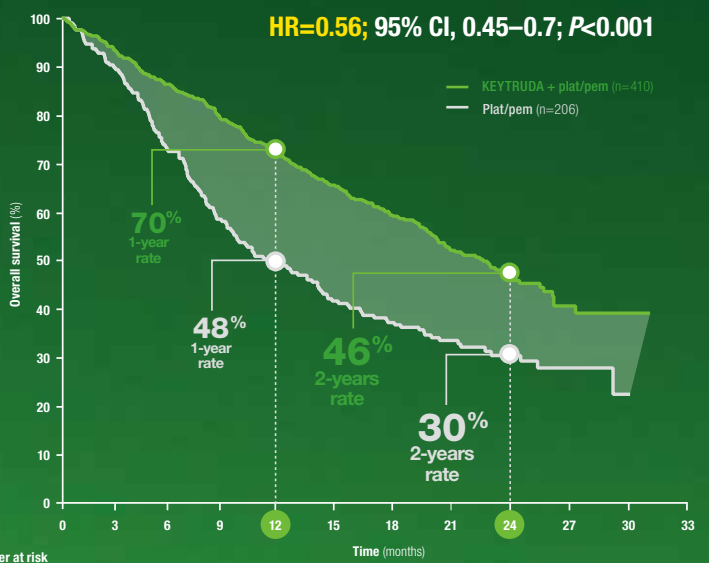
* **KEYTRUDA,** in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.[2]

22 MONTHS MEDIAN OS WITH KEYTRUDA + plat/pem[a] (95% CI, 19.5 - 25.2)
vs 10.7 months with plat/pem alone (95% CI, 8.7 - 13.6)

9 MONTHS MEDIAN PFS WITH KEYTRUDA + plat/pem[a] (95% CI, 8.1 - 9.9)
vs 4.9 months with plat/pem alone (95% CI, 4.7 - 5.5)

46% 2-YEAR OS RATE WITH KEYTRUDA + plat/pem[a]
vs 30% with plat/pem alone

Kaplan-Meier Estimates of OS in KEYNOTE-189 (ITT)[1,a,b]



Number at risk												
KEYTRUDA + plat/pem	410	377	346	316	283	256	234	144	79	28	2	0
Plat/pem	206	183	149	115	99	82	72	45	26	10	0	0

Adverse reaction profile for KEYTRUDA in combination with pemetrexed and platinum chemotherapy was consistent with that for each of the individual products.

[a] At data cutoff, median follow-up time was 23.1 months.[2] [b] HR based on the stratified Cox proportional hazard model; P value based on stratified log-rank test.[1]
mNSCLC = metastatic NSCLC; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase. Plat/pem = cisplatin or carboplatin + pemetrexed; OS = overall survival; HR = hazard ratio; CI = confidence interval.

Study Design: A Phase 3, randomized, multicenter, double-blind, placebo-controlled trial in treatment-naive patients with nonsquamous mNSCLC, including patients with no PD-L1 expression. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or patients who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by smoking history, cisplatin vs carboplatin, objective response rate (ORR) and PD-L1 tumor expression (TPS <1% vs TPS ≥1%). Patients were randomized (2:1) to receive: KEYTRUDA 200 mg (n=410), cisplatin or carboplatin, and pemetrexed intravenously Q3W for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed Q3W for up to 24 months, or placebo (n=206), cisplatin or carboplatin, and pemetrexed intravenously Q3W for 4 cycles followed by placebo and pemetrexed Q3W. Treatment continued until progression of disease or unacceptable toxicity. Primary efficacy outcome measures were OS and PFS as assessed by BICR per RECIST 1.1. Additional efficacy outcome measures were ORR and duration of response (DOR) as assessed by BICR per RECIST 1.1. Patients receiving placebo, platinum chemotherapy, and pemetrexed who experienced disease progression could cross over to receive KEYTRUDA as monotherapy.

Selected Safety Information for KEYTRUDA (pembrolizumab)
Indications: • Melanoma – KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma. • Non-Small Cell Lung Cancer – KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. – KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%] as determined by a validated test, with no EGFR or ALK genomic tumor aberrations. – KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) as determined by a validated test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA. • Urothelial Carcinoma – KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. – KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. • Classical Hodgkin Lymphoma – KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. **Dosage and administration:** • Patient Selection: Select patients for treatment of metastatic NSCLC with KEYTRUDA as a single agent based on the presence of positive PD-L1 expression. • **Melanoma:** 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. • **NSCLC:** - In combination with pemetrexed and platinum chemotherapy or as a single agent for metastatic NSCLC patients that has not been previously treated with chemotherapy: 200mg. When administering KEYTRUDA in combination with chemotherapy, it should be administered prior to chemotherapy when given on the same day. - As a single agent for metastatic NSCLC patients that has been previously treated with chemotherapy: 2mg/kg. – KEYTRUDA should be administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. • **Urothelial Carcinoma:** 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. • **Classical Hodgkin Lymphoma:** 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression. **Contraindications:** • None **Precautions:** • Immune-Mediated Pneumonitis • Immune-Mediated Colitis • Immune-Mediated Hepatitis • Immune-Mediated Endocrinopathies (hypophysitis; thyroid disorders - hyperthyroidism, hypothyroidism and thyroiditis; Type 1 diabetes) • Immune-Mediated Nephritis and Renal Dysfunction • Immune-Mediated Skin Adverse Reactions (SJS, TEN, exfoliative dermatitis or bullous pemphigoid) • Other Immune-Mediated Adverse Reactions • Infusion-Related Reactions (including hypersensitivity and anaphylaxis) • Complications of Allogeneic HSCT in Patients with Allogeneic HSCT prior to KEYTRUDA treatment • Increased Mortality in Patients with Multiple Myeloma • Embryofetal Toxicity • **For detailed precautions, please consult the full prescribing information. Adverse Events:** Most common adverse reactions (reported in ≥20% of patients) when Keytruda was used as a single agent were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain; when Keytruda was used in combination with pemetrexed and platinum chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, and pyrexia. • Immune-mediated pneumonitis • Immune-mediated colitis • Immune-mediated hepatitis • Immune-mediated endocrinopathies • Immune-mediated nephritis and renal dysfunction • Immune-Mediated Skin Adverse Reactions (SJS, TEN, exfoliative dermatitis or bullous pemphigoid) Other immune-mediated adverse reactions • Infusion-related reactions • As with all therapeutic proteins, there is the potential for immunogenicity. • **For detailed adverse events, please consult the full prescribing information.**

Before prescribing KEYTRUDA®, please consult the full prescribing information.

Reference:
1. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; for the KEYNOTE-189 investigators. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med.* 2018; 378(22):2078–2092. **2.** Hong Kong Product Circular (KEYTRUDA, MSD) **3.** Gadgeel S, et al. KEYNOTE 189: Updated Overall Survival and Progression After the Next Line of Therapy With Pembrolizumab plus Chemotherapy With Pemetrexed and Platinum vs Placebo plus Chemotherapy for Metastatic Nonsquamous Non-Small-Cell Lung Cancer. Poster Presented at the 2019 American Society of Clinical Oncology Annual Meeting; May 31 to June 4, 2019; Chicago, IL, USA

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HK-KEY-00040 07/19

Patients with type 2 diabetes
should expect more after metformin

REALISE THE POTENTIAL

UP TO

80%

ACHIEVED ADA TARGET OF HbA_{1c}

<7%

VS OTHER DIABETES TREATMENT[1,2,7,8,9#]

OZEMPIC®

The only once-weekly treatment unifying superior efficacy and CV benefits[1-5]

SUPERIOR GLYCAEMIC CONTROL[1,2*]

Up to 1.8% HbA_{1c} reduction[2]

SUPERIOR AND SUSTAINED WEIGHT LOSS[1-3*]

Up to 6.5kg weight reduction [2]

PROVEN CV BENEFITS [1,3 †]

26% CV risk reduction[1,3§]

§ When added to SOC, which included oral antidiabetic treatment, insulin, antihypertensives, diuretics and lipid-lowering therapies.[3]

Other diabetes treatments refer to sitagliptin, dulaglutide, exenatide ER, liraglutide, canagliflozin and glargine U100. Target refers to American Diabetes Association target of HbA_{1c} <7%.

† In SUSTAIN 6, Ozempic® reduced CV risk (CV death, nonfatal myocardial infarction [MI] or nonfatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care.[1]

* Results apply to Ozempic® across SUSTAIN trials, which included placebo, DPP4-I, SGLT-2I, GLP-1 RA and basal insulin.[1,2]

For adults with type 2 diabetes with established ASCVD or indicators of high ASCVD risk

2019 ADA/EASD consensus report recommends a GLP-1 RA therapy with proven CV benefit[6]

CV=cardiovascular; CVD=cardiovascular disease; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes;
GLP-1 RA=glucagon-like peptide-1 receptor agonist.

Abbreviated prescribing information Ozempic® (semaglutide), Ozempic 0,25 mg solution for injection in pre-filled pen; Ozempic 0,5 mg solution for injection in pre-filled pen; Ozempic 1 mg solution for injection in pre-filled pen,**Consult Summary of Product Characteristics before prescribing.Presentation:** Ozempic 0,25 mg & 0,5 mg solution for injection: Each pre-filled pen contains 2 mg semaglutide in 1,5 ml solution. Ozempic 1 mg solution for injection: One pre-filled pen contains 4 mg semaglutide in 3,0 ml solution. **Uses:** Ozempic® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise as Monotherapy: when metformin is considered inappropriate due to intolerance or contraindications. Combination therapy: in addition to other medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see the full Summary of Product Characteristics. **Dosage and Administration:** The starting dose is 0,25 mg Ozempic® once weekly. After 4 weeks the dose should be increased to 0,5 mg once weekly. After at least 4 weeks with a dose of 0,5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. Ozempic® is to be administered once weekly at any time of the day, with or without meals. Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. Ozempic® should not be administered intravenously or intramuscularly. When Ozempic® is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued unchanged. When Ozempic® is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia. **Elderly:** No dose adjustment is required based on age. Therapeutic experience in patients aged ≥75 years of age is limited. **Renal impairment:** No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience in patients with severe renal impairment is limited. Not recommended for use in patients with end-stage renal disease. **Hepatic impairment:** No dose adjustment is required for patients with hepatic impairment. Experience in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with Ozempic®. **Paediatric population:** The safety and efficacy of Ozempic® in children and adolescents below 18 years have not yet been established. No data are available. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** Ozempic® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Ozempic® is not a substitute for insulin. There is no experience in patients with congestive heart failure NYHA class IV and Ozempic® is therefore not recommended in these patients. The possibility of gastrointestinal adverse reactions should be considered when treating patients with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration, which could cause a deterioration of renal function. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Ozempic® should be discontinued; if confirmed, Ozempic® should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Patients treated with Ozempic® in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. Consider reducing the dose of sulfonylurea or insulin when initiating treatment with Ozempic®. In patients with diabetic retinopathy treated with insulin and Ozempic®, an increased risk of developing diabetic retinopathy complications has been observed. Caution should be exercised when using Ozempic® in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. **Interactions:** Ozempic® delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Ozempic® should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption. No dose adjustment of paracetamol, oral contraceptives (ethinylestradiol and levonorgestrel), atorvastatin, warfarin, digoxin or metformin is necessary when administered with Ozempic®. For further details of these interaction studies, please see the Summary of Product Characteristics. **Pregnancy and lactation:** Ozempic® should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs during treatment, Ozempic® should be discontinued. Ozempic® should not be used during breast-feeding. Effect of Ozempic® on fertility in humans is unknown. **Driving or using machines:** When Ozempic® is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. **Undesirable Effects:** The most frequently reported adverse reactions with Ozempic® in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. Adverse reactions by system organ class and absolute frequencies identified in all phase 3a trials listed here as Very common (≥1/10): Hypoglycaemia when used with insulin or sulfonylurea, nausea, diarrhoea; Common (≥1/100 to <1/10): Hypoglycaemia when used with other OADs, decreased appetite, dizziness, diabetic retinopathy complications, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastro-oesophageal reflux disease, eructation, flatulence, cholelithiasis, fatigue, increased lipase, increased amylase, weight decreased; Uncommon (≥1/1,000 to <1/100): dysgeusia, increased heart rate, injection site reactions; Rare (≥1/10,000 to <1/1,000): anaphylactic reaction.

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