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Abbreviations: LUTS: lower urinary tract symptoms; **OAB:** overactive bladder

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Abbreviated prescribing information of Betmiga® prolonged-release tablets

Version: 003 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 antimuscarinic 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 in 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 12% 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 maculo, Rash papular, 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.

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The Cover Shot

The practice of clinical cardiology, in particular that of interventional cardiology, is skill demanding. Specific training on refined procedures is a prerequisite for the proper management of cardiac patients, who are often fairly ill especially if precipitating factors co-existed. Just before the outbreak of the COVID pandemic, I was in North Shore, Hawaii, watching the 50th World Championship of the Billabong Pipe Master Event. The surfers are all well-experienced in riding the waves inside the pipe-line formed by the big wave as it curved forward from the ocean onto the shoreline. Sometimes instead of forming a water-pipe, a gigantic wave of height a few times taller than the surfer, would be chasing from behind and throwing the competitor off at any time if he does not stay fully alert. Similarly the interventionist must stay alert all the time when performing his procedure. And despite the many skills that he has commanded through his intensive training, complications do occur and are ready to throw him off - and off for the patient as well. A word of warning !

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Editorial

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"We celebrate the past to awaken the future." -- John F. Kennedy

This year, the Hong Kong College of Cardiology (HKCC) is celebrating its 30th anniversary. While we celebrate the growth of the College, we constantly remind ourselves of our mission to promote education in cardiovascular medicine. In these past three decades, we witnessed remarkable advances in various frontiers of cardiology. As Editor for this issue of the Hong Kong Medical Diary, we gladly share with readers several of these important developments.

For more than three decades, anti-platelet therapy has been shown to improve outcomes in patients with coronary artery disease. As coronary stents were further developed and revolutionised the treatment of coronary artery disease, there was a continuous evolution of anti-platelet regimens to optimise clinical outcomes in patients with different clinical profiles.

About three decades ago, the treatment of heart failure evolved from diuretic and digoxin to regimens targeting at the neurohormonal system when angiotensin-converting enzyme inhibitors (ACEI) was first shown to reduce mortality. Since then, there have been further breakthroughs in both pharmacological and non-pharmacological treatment of heart failure.

In patients with atrial fibrillation, the benefit of anticoagulant for thromboembolism prophylaxis has been known for three decades. The latest focus has shifted to the role of screening atrial fibrillation for early identification of asymptomatic cases for anticoagulant therapy. Whether this will lead to similar benefits is a subject of interest and controversy.

"Bed rest" was the old wisdom for managing cardiovascular diseases decades ago. Contemporary approaches highlight the benefit of early mobilisation and exercise-based cardiac rehabilitation. Recommendations for exercise for various cardiac conditions were recently formulated by the international authority.

In the development of cardiac surgery in Hong Kong, the first heart transplant performed 30 years ago marked an important milestone. In the subsequent years came a remarkable journey that led to another milestone, which was the development of minimally invasive cardiac surgery, particularly for valvular heart diseases and congenital heart diseases.

These topics will be elaborated in this issue. You are invited to join us in witnessing the astounding development in cardiology over these three decades and to share the joy of HKCC's 30th anniversary.

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Antiplatelet Therapy for Coronary Artery Disease: Evolution in Three Decades

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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 30 September 2022.

For more than three decades, in patients with various atherosclerotic cardiovascular diseases (ASCVD), antiplatelet therapy has been shown to reduce recurrent vascular events by about 25%.[1] This was most studied with aspirin, which has long been the mainstay of treatment for coronary artery disease (CAD). Clopidogrel was compared with aspirin in the CAPRIE trial in patients with prior myocardial infarction (MI), prior ischemic stroke, or symptomatic peripheral arterial disease (PAD). Clopidogrel was shown to result in a lower rate of the composite outcome of ischemic stroke, MI or vascular death in comparison to aspirin, but the benefit was only modest and driven mainly by a reduction of events in PAD, but not MI, subgroups.[2] In patients with stable CAD, aspirin thus remains the recommended standard therapy, clopidogrel being an alternative in patients intolerant to aspirin.[3,4]

DUAL ANTI-PLATELET THERAPY (DAPT): TOWARDS MORE ANTI-PLATELET ACTIVITIES, FOR WHOM?

The CHARISMA trial randomised patients with either documented ASCVD or multiple risk factors to DAPT with clopidogrel plus aspirin versus aspirin alone.[5] Patients requiring revascularisation and patients judged to require DAPT (such as a recent acute coronary syndrome) were excluded. Overall, there were no significant differences in the rates of myocardial infarction, stroke or cardiovascular death.[5] The above findings do not support the use of DAPT in stable chronic CAD.[3,6]

Instead, DAPT is the standard therapy for patients having undergone percutaneous coronary intervention (PCI) or patients with acute coronary syndrome (ACS).

For PCI, the introduction of coronary stents more than 30 years ago significantly improved the acute procedural success rate and long-term results as compared to plain balloon angioplasty, but exposed a new risk of stent thrombosis. Various drug regimens were studied to prevent the occurrence of stent thrombosis, including aspirin alone, DAPT and aspirin plus warfarin.[7] DAPT was found to be most effective, and a period of DAPT after PCI became the standard of care.

For ACS patients, the CURE study randomised patients with non-ST elevation ACS to DAPT with aspirin plus clopidogrel (for 3 to 12 months) versus aspirin alone.[8] DAPT resulted in a significant reduction in the primary composite endpoint of cardiovascular death, non-fatal MI or stroke, at the expense of a higher rate of major bleeding, but not life-threatening bleeding. In 64% of study patients who received medical therapy alone without PCI, a similar beneficial effect was observed.[8] DAPT is thus recommended for ACS, whether treated medically or with PCI, for a period of 12 months.[6,9]

DAPT REGIMEN: FROM CLOPIDOGREL TO MORE POTENT P2Y12 INHIBITORS

The earlier studies that indicated the benefit of DAPT for ACS and PCI were based on a regimen combining aspirin and clopidogrel, the latter being a P2Y12 receptor inhibitor. With the development of more potent P2Y12 inhibitors, namely ticagrelor and prasugrel, these newer P2Y12 inhibitors were compared with clopidogrel as part of the DAPT regimen in patients with ACS. In the PLATO trial, ACS patients both intended for PCI and planned for conservative treatment were enrolled. Ticagrelor as compared to clopidogrel resulted in a significant reduction in primary composite endpoints (cardiovascular death, MI or stroke),[10] a benefit which was also observed in the non-PCI subgroup.[11] Ticagrelor was associated with a higher risk of non-CABG (coronary artery bypass grafting) bleeding, but not overall incidence of major bleeding.[10] For prasugrel, it was also shown to improve outcomes as compared to clopidogrel in the TRITON-TIMI 38 trial which enrolled ACS patients scheduled for PCI.[12] However, for ACS patients undergoing conservative treatment, prasugrel was not demonstrated to be of benefit in the TRILOGY ACS trial.[13]

Thus, DAPT with aspirin together with a potent P2Y12 inhibitor is recommended for ACS patients. Either ticagrelor or prasugrel can be considered for patients undergoing PCI, while ticagrelor is more favoured for patients planned for conservative treatment.[9]

Currently there is limited evidence to support the use of ticagrelor and prasugrel in patients with stable CAD or after elective PCI for stable CAD, though in the latter scenario the drugs may be considered in individual

patients if the coronary anatomy is deemed high risk for stent thrombosis after PCI.[4]

DAPT DURATION AFTER PCI: LONGER THE BETTER, OR SHORTER THE BETTER?

About two decades ago, the invention of drug-eluting stent (DES) revolutionised PCI as it demonstrated a better outcome as compared to its precursor bare-metal stent (BMS), particularly in the reduction of incidence of in-stent restenosis. DES has become the default stent used in current practice. The development of DES, however, brought about an important issue about the optimal duration of DAPT after PCI. DES slowly releases drugs that inhibit the proliferation of vascular smooth muscle cells in response to vascular injury from stent deployment, a process that causes restenosis. This mechanism of DES also causes delayed reendothelialisation, resulting in an uncovered stent scaffold that predisposes to stent thrombosis.

When the first-generation sirolimus-eluting stent (Cypher®) and paclitaxel-eluting stent (Taxus®) were released in the early 2000s, DAPT for three months and six months respectively were recommended, largely based on the protocol adopted in index studies of the stents.[14] Subsequent reports raised concerns about higher risk of late and very late stent thrombosis with these first-generation DES.[15,16] The recommendation for DAPT duration after PCI for stable CAD patients was changed to 12 months in the 2011 American guideline,[17] and 6 to 12 months in 2010 European guideline.[18]

However, this recommendation was largely empirical and not based on strong evidence. Many studies were carried out to look for the optimal duration of DAPT, either shorter or longer.

The rationale for a shorter DAPT duration is that newer generation DES were developed, which have thinner stent strut, biocompatible or biodegradable polymer, and improved anti-proliferative drug release kinetics. These resulted in improved arterial healing and were shown to have lower risk of stent thrombosis.[19] Moreover, prolonged DAPT was associated with higher risk of bleeding.[8] More importantly, the occurrence of bleeding after PCI was shown to be an independent predictor of mortality.[20] Several studies compared a shorter three to 6-month with 12-month of DAPT after PCI with newer generation stents. Patients treated with three to six-month of DAPT had the benefit of lower rates of major bleeding as compared with one year of DAPT, while the rates of stent thrombosis, myocardial infarction or mortality were similar.[21-23] While these findings supported a shorter DAPT duration after PCI in general, studies on ACS population raised concerns about higher risk of MI or stent thrombosis with shortened DAPT in ACS setting.[24,25] As such, six-month is the recommended default DAPT duration after PCI for stable CAD, while that for ACS is one year.[6,23]

However, the "default" durations need to be modified on individual basis. There were studies looking into whether a longer DAPT duration of more than one year after DES would reduce ischemic events not necessarily related to stenting. DAPT trial was the largest and most representative one, randomising patients to 12-month DAPT versus an extended period of up to 30 months. It showed a reduction in MI with prolonged DAPT, but an increased risk of bleeding and a borderline significant increase in total mortality.[26] Meta-analyses which included other studies on prolonged DAPT showed similar findings of reduced risk of MI and stent thrombosis with prolonged DAPT of more than one year but at the expense of higher incidence of bleeding, with some studies indicating a higher mortality.[27-30] Thus, routine extension of DAPT duration is not recommended.[6,23]

However, the DAPT trial showed that, in the setting of acute MI, the benefit of prolonged DAPT in reducing ischemic event was higher though the increased risk of bleeding remained.[31] A similar finding was inferred from another secondary prevention trial that studied the effect of prolonged DAPT (with aspirin and ticagrelor at 90mg bd or 60mg bd) in patients with a history of MI more than one year previously, with or without PCI, plus one additional high risk clinical feature. Low dose ticagrelor significantly reduced the incidence of MI and stroke, and showed a trend towards reducing cardiovascular death, but increased the risk of major bleeding.[32] Putting together, prolonged DAPT for more than one year, with either clopidogrel or low dose ticagrelor, may be considered after ACS if the patient is considered high thrombotic risk, provided that the patient has low bleeding risk.[6,23] In stable CAD patients with these risk profiles, extending DAPT with aspirin and clopidogrel beyond six months may be considered.[6,23]

Conversely, for patients with high bleeding risk (HBR), it is recommended to shorten the DAPT duration to three or even one month for stable CAD and to six months for ACS.[6,23] There were actually limited data from randomised controlled trials to guide the optimal duration of DAPT in this HBR patient group, but studies have demonstrated the feasibility and safety of short DAPT duration of one to three months following implantation of specific new-generation stents in HBR patients.[33-37]

SHORTENED DAPT BY DROPPING ASPIRIN: A NEW PARADIGM

For decades, aspirin has been the backbone of anti-platelet regimen, and DAPT traditionally means addition of a P2Y12 inhibitor which will be discontinued after the duration of DAPT is completed. In search of a better balance between reducing ischemic risk and reducing bleeding risk, a new strategy has evolved in which a short duration of DAPT is followed by keeping P2Y12 monotherapy and dropping aspirin. The rationale is that in the presence of strong P2Y12 inhibitor, aspirin provides little additional inhibition of platelet aggravation and may even attenuate the efficacy of P2Y12 inhibitor, yet aspirin carries additional bleeding risk.[38]

Four randomised studies demonstrated the benefits of this strategy,[39-42] with two studies using clopidogrel or mostly clopidogrel after one- or three-month

DAPT respectively for relatively low ischemic risk all-comers,[39,40] one using ticagrelor after three-month DAPT for high ischemic risk patients,[41] and one using ticagrelor after three-month DAPT for ACS patients.[42] These studies showed that this aspirin-free strategy after one- or three-month of DAPT significantly reduced bleeding events without increase in thrombotic events.[39-42] Another trial using a hard composite endpoint of death or new Q-wave MI at two years was negative.[43] Putting together, meta-analyses that include all these five trials confirmed the benefit of this strategy in reducing bleeding risk without increasing thrombotic risk.[44,45] The benefit was also observed in ACS patients, but ticagrelor was the P2Y12 inhibitor used in most of these patients.[44] A word of caution came from another study using clopidogrel monotherapy after one to two months of DAPT in ACS setting. It showed a numerical increase in cardiovascular events despite the reduction in bleeding events.[46] This raised concern in adopting clopidogrel for P2Y12 monotherapy after short DAPT in ACS setting.

"MODULATING" DAPT BY ESCALATION OR DE-ESCALATION OF P2Y12 INHIBITORS: ANOTHER STRATEGY BEYOND DAPT DURATION

To individualise DAPT strategy balancing a patient's ischemic risk and bleeding risk, other than modifying DAPT duration and deciding on dropping P2Y12 inhibitors or dropping aspirin afterwards, another developed strategy is to modulate DAPT by escalating or de-escalating the intensity of P2Y12 inhibitors during DAPT.

De-escalation can be considered if a patient is initiated on a potent P2Y12 inhibitor, notably in ACS setting, but he is deemed at high bleeding risk. The rationale for de-escalation is that the thrombotic risk is highest in the first months after ACS then declines thereafter whereas the bleeding risk remains relatively stable over time.[47]

On the other hand, escalation to more potent P2Y12 inhibition can be considered if a patient is indicated for aspirin plus clopidogrel as default, notably in chronic CAD setting, but he is deemed at high ischemic risk.

Both escalation and de-escalation can be "guided" or "unguided".

The principle for the "guided" approach is that clopidogrel not only has less potent platelet inhibition as compared to ticagrelor and prasugrel, but also has wide inter-individual variability in response due to genetic polymorphisms of the hepatic cytochrome P450 2C19 enzyme required to transform clopidogrel into its active metabolite.[47] Thus, assessment of individual response to clopidogrel can potentially "guide" the need to escalate from clopidogrel and the safety of de-escalate from potent P2Y12 inhibitors to clopidogrel. This assessment can be done by platelet function testing for platelet reactivity during treatment or genetic testing for "loss-of-function" (LoF) genotypes.

On the other hand, the "unguided" approach refers to escalation or de-escalation solely based on clinical judgement of a patient's thrombotic risk and bleeding risk.

De-escalation in ACS setting, both guided and unguided, are supported by clinical trials. TROPICAL-ACS study and POPULAR GENETIC study investigated de-escalation guided by platelet function test and genotype testing respectively, both studies showing around 60% of patients being eligible for de-escalation.[48,49] Both studies demonstrated non-inferiority of guided de-escalation strategy regarding ischemic outcomes.[48,49] Bleeding events were significantly reduced in one study[49] numerically reduced in the other.[48] The benefit of unguided de-escalation one month after ACS was shown by TOPIC, HOST-REDUCE-POLYTECH-ACS and TALOS-AMI studies, using de-escalating strategies from potent P2Y12 inhibitors to clopidogrel or from standard dose prasugrel to half dose prasugrel.[50-52] All three studies demonstrated benefit in reducing bleeding events without an increase in thrombotic events, supporting a more easily applicable approach of unguided de-escalation strategy.[50-52]

The role of escalation in chronic CAD setting, on the other hand, is less well established. Several studies evaluated the benefit of escalation guided by either platelet function test or genotype testing, showing no consistent benefit.[47] However, a meta-analysis of these studies showed that guided escalation strategy was associated with a reduction in ischemic events including MI, stent thrombosis and stroke.[53] For unguided escalation strategy for chronic CAD, as discussed in a previous section, there is no clinical data supporting its use, though it can be considered on individual basis.

LONG TERM P2Y12 INHIBITOR MONOTHERAPY (INSTEAD OF ASPIRIN) REVISITED

As discussed in the previous section, the CAPRIE trial conducted more than two decades ago showed that clopidogrel was only of marginal benefit as compared with aspirin for chronic treatment of CAD,[2] and aspirin remained the standard therapy.[3,4] A recent study, the HOST-EXAM study, revisited clopidogrel monotherapy in the chronic maintenance phase 6-18 months after PCI. As compared to aspirin monotherapy, clopidogrel monotherapy significantly reduced both composite thrombotic endpoint and major bleeding.[54] A latest meta-analysis on trials that compared aspirin with P2Y12 inhibitors (using clopidogrel or ticagrelor in different trials) in various ASCVD (including CAD, cerebrovascular diseases and PAD) showed that P2Y12 inhibitor monotherapy for secondary prevention is associated with a significant reduction in atherothrombotic events, without an increased risk of major bleeding.[55]

OTHER ISSUES

Beyond the scope of this article is the regimen of anti-platelet therapy when a patient has a concomitant need for long-term anticoagulation, the role of dual pathway inhibition by adding low dose anticoagulant to anti-

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*In place of an ACEi or ARB **ACEi**=angiotensin-converting enzyme inhibitor; **ARB**=angiotensin II receptor blocker; **HF**=heart failure; **MOA**=mechanism of action

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ENTRESTO tablets Important note: Before prescribing, consult full prescribing information. **Presentation: ENTRESTO 50 mg film-coated tablets** Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex). **ENTRESTO 100 mg film-coated tablets** Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium salt complex) **ENTRESTO 200 mg film-coated tablets** Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium salt complex). **Indications:** Treatment of symptomatic chronic heart failure (NYHA class II-IV) in adult patients with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization due to heart failure. **Dosage and administration: Adults:** •The recommended starting dose of ENTRESTO is 100 mg twice daily. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 200 mg twice daily, as tolerated by the patient. •A starting dose of 50 mg twice daily is recommended for patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), and should be considered for patients previously taking low doses of these agents. **•Geriatric patients:** The dose should be in line with the renal function. **•Pediatric patients:** ENTRESTO has not been studied. Use of ENTRESTO is not recommended. **•Renal impairment:** No dose adjustment is required in patients with mild renal impairment (Estimated Glomerular Filtration Rate (eGFR) 60-90 ml/min/1.73 m²); A starting dose of 50 mg twice daily is recommended in patients with moderate renal impairment(eGFR 30-60 ml/min/1.73 m²); A starting dose of 50 mg twice daily and caution is recommended in patients with severe renal impairment (eGFR <30 ml/min/1.73 m²). Not recommended for patients with end-stage renal disease. **•Hepatic impairment:** No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh A classification). A starting dose of 50 mg twice daily is recommended in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. In patients with severe hepatic impairment use of ENTRESTO is not recommended. **•Method of administration** For oral use. May be administered with or without food. **Contraindications:** •Hypersensitivity to the active substance, sacubitril, valsartan, or to any of the excipients. •Concomitant use with ACE inhibitors. ENTRESTO must not be administered until 36 hours after discontinuing ACE inhibitor therapy. •Known history of angioedema related to previous ACE inhibitor or ARB therapy. •Concomitant use with aliskiren in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m²). • Second and third trimester of pregnancy. •Hereditary or idiopathic angioedema •Severe hepatic impairment, biliary cirrhosis and cholestasis **Warnings and precautions:** **•Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS):** ENTRESTO must not be administered with an ACE inhibitor due to the risk of angioedema. ENTRESTO must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with ENTRESTO is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of ENTRESTO. • The combination of ENTRESTO with direct renin inhibitors such as aliskiren is not recommended. The combination of ENTRESTO with aliskiren-containing products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m²). • ENTRESTO contains valsartan, and therefore should not be co-administered with another ARB containing product. **•Hypotension:** If hypotension occurs, temporary down-titration or discontinuation of ENTRESTO is recommended. Dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered. Sodium and/or volume depletion should be corrected before starting treatment with ENTRESTO. **•Impaired renal function:** •Evaluation of patients with heart failure should always include assessment of renal function. Down titration of ENTRESTO should be considered in patients who develop a clinically significant decrease in renal function. Caution should be exercised when administering ENTRESTO in patients with severe renal impairment (eGFR <30 ml/min/1.73 m²). **•Hyperkalemia:** Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution. If clinically significant hyperkalemia occurs, measures such as adjustment of concomitant medicinal products, temporary down-titration or discontinuation should be considered. Monitoring of serum potassium is recommended especially in patients with risk factors such as renal impairment, diabetes mellitus, hypoaldosteronism, receiving a high potassium diet or mineralocorticoid antagonists. If serum potassium level is >5.4 mmol/l discontinuation should be considered. **•Angioedema:** If angioedema occurs, ENTRESTO should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. ENTRESTO must not be re-administered. Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if ENTRESTO is used in these patients. ENTRESTO must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. Black patients may have increased susceptibility to develop angioedema. **•Patients with renal artery stenosis:** Caution is required in patients with renal artery stenosis and monitoring of the renal function is recommended. **•Patients with NYHA functional classification IV:** Caution should be exercised. **•B-type natriuretic peptide (BNP):** BNP is not a suitable biomarker of heart failure in patients treated with ENTRESTO. **•Hepatic impairment:** Caution is recommended when using ENTRESTO in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. ENTRESTO is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification). **Pregnancy:** The use of ENTRESTO is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy. **Breast-feeding:** It is not known whether ENTRESTO is excreted in human milk. Because of the potential risk for adverse drug reactions in breastfed newborns/infants, ENTRESTO is not recommended during breastfeeding. **Adverse drug reactions:** ***Very common (≥1/10):*** Hyperkalemia, hypotension, renal impairment. ***Common (≥1/100 to <1/10):*** Anaemia, hypokalemia, Hypoglycaemia, Dizziness, Cough, Headache, Syncope, Vertigo, Orthostatic hypotension, Diarrhoea, Nausea, Gastritis, Renal failure (renal failure, acute renal failure), Fatigue, Asthenia ***Uncommon (≥1/1,000 to <1/100):*** Hypersensitivity, Dizziness postural, Pruritis, Rash, Angioedema. **Interactions:** ***•Concomitant use contraindicated:*** aliskiren in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m²). Use with ACE inhibitors: ENTRESTO must not be started until 36 hours after taking the last dose of ACE inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of ENTRESTO. ***•Concomitant use not recommended:*** ARB containing products ***•Caution when used concomitantly*** with OAT1B1 and OATP1B3 substrates(e.g. statins), PDE5 inhibitors (e.g. sildenafil), lithium, potassium-sparing diuretics (triamterene, amiloride) , mineral corticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium, other agents that may lead to increased serum potassium level (e.g. heparin), non-steroidal anti-inflammatory agents (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 Inhibitors), inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine),OAT1 (e.g. tenofovir, cidofovir) or MPR2 (e.g. ritonavir), furosemide, nitrates (e.g. nitroglycerine), metformin. **Packs:** 50mg: 28's; 100mg: 28's and 56's; 200mg: 56's. Not all pack sizes may be marketed. **Legal classification:** P1S1S3. **Ref:** EMA Nov 2015. **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

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platelet therapy for patients with high ischemic risk, the various parameters defining bleeding and ischemic risks, and the consideration in special populations such as elderly, chronic kidney disease and diabetes mellitus. These issues are discussed in published guidelines and reviews.[4,9,47,56] Another issue is how to refine DAPT regimen in our local population, given the evidence that East Asian populations are more susceptible to bleeding than thrombotic events, the so-called East Asian paradox.[57]

GAP IN EVIDENCE

While clinical evidence suggests that DAPT regimen can be tailored in several ways according to the bleeding risk and ischemic risk of a patient, there is no randomised controlled trial comparing the various strategies. Limited evidence came from a recent network meta-analysis comparing shortened DAPT with de-escalation in ACS setting. The study showed that short DAPT reduced bleeding while de-escalation decreased net adverse cardiovascular events (combining bleeding and ischemic events), suggesting that short DAPT could be a better approach for patients with high bleeding risk, while de-escalation might be a more suitable option for patients with high thrombotic risk.[58]

CONCLUSION

Over the past decades, the regimen of anti-platelet therapy has been constantly evolving, in parallel with the advance in coronary intervention in the management of CAD. The "standard" for DAPT is aspirin plus clopidogrel for six months for chronic CAD having undergone PCI, aspirin plus a potent P2Y12 inhibitor for 12 months after ACS with or without PCI. More importantly, clinical evidence calls for a personalised approach to tailoring DAPT regimen according to a patient's ischemic risk and bleeding risk. DAPT can be prolonged or shortened, the latter followed by either dropping P2Y12 inhibitor or dropping aspirin. Alternatively, modulating DAPT intensity can be done by escalating or de-escalating the potency of P2Y12 inhibitor, the latter can be guided or unguided. In terms of long-term therapy, aspirin monotherapy remains the current standard, but more data are accumulating regarding the use clopidogrel monotherapy.

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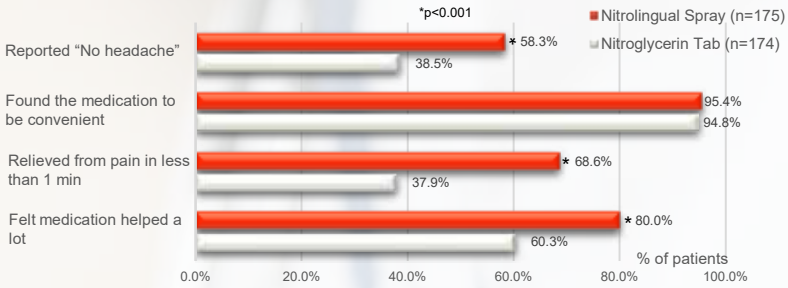
Why does Nitrolingual®-Spray outweigh NTG Tablet?

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
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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.

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*All doses are expressed in the form of elemental iron.


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-achrestic anaemia, 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

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VIFOR PHARMA

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Antiplatelet Therapy for Coronary Artery Disease: Evolution in Three Decades" by Dr Kin-lam TSUI 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 30 September 2022. 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. **Aspirin has been a standard drug for patients with atherosclerotic cardiovascular diseases (ASCVD) since more than 30 years ago.**
2. **For patients with stable coronary artery disease (CAD) managed by medical therapy without percutaneous coronary intervention (PCI), dual anti-platelet therapy (DAPT) is more effective than aspirin monotherapy and thus is the regimen of choice.**
3. **For acute coronary syndrome (ACS), DAPT for 12 months is recommended, disregard of whether the patient is treated medically or by PCI.**
4. **Ticagrelor is more potent than clopidogrel and is used with aspirin as a standard DAPT regimen for ACS patients.**
5. **Ticagrelor monotherapy is one of the standard regimens for stable CAD.**
6. **"DAPT" conventionally means a period of aspirin plus a P2Y12 inhibitor (e.g. clopidogrel/ticagrelor) followed by long-term aspirin monotherapy.**
7. **After PCI, instead of prescribing a "standard" DAPT regimen for all patients, a patient's regimen should be individualised after assessing his bleeding risk and thrombotic risk.**
8. **Clopidogrel may have a lower antiplatelet effect in some patients related to genetic predisposition.**
9. **For an ACS patient who is put on a potent DAPT regimen, namely aspirin plus ticagrelor, de-escalating of DAPT to aspirin plus clopidogrel can be considered after a period when there is a concern about bleeding risk, but only after confirming the patient has the adequate antiplatelet response to clopidogrel.**
10. **East Asian populations are more susceptible to thrombotic than bleeding events, an observation referred to as the East Asian paradox.**

ANSWER SHEET FOR SEPTEMBER 2022

Please return the completed answer sheet to the Federation Secretariat on or before 30 September 2022 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Antiplatelet Therapy for Coronary Artery Disease: Evolution in Three Decades

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

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Answers to August 2022 Issue

Nutritional Supplementation Before, During and After Pregnancy

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

Repatha® (evolocumab)

Go lower and longer for better outcomes

Lowering LDL-C with Repatha® offers increased CV risk benefits over time[1]

Reductions in the key secondary composite endpoint of CV death, MI or stroke in the FOURIER study*:

In the first year (0-12 months) — 16% RRR (HR: 0.84 (95% CI: 0.74–0.96))

Beyond the first year (12–36 months) — 25% RRR (HR: 0.75 (95% CI: 0.66–0.85))

Repatha® has demonstrated consistent safety over a 5-year treatment period[2]

Safety and tolerability outcomes in the 5-year OSLER-1 study:

- Safety profile comparable to placebo
- No neutralizing antibodies detected

Repatha® is supported by well-established worldwide clinical experience[3,4]

Since launch, >1,000,000 patients have benefited from the sustained efficacy and consistent safety of Repatha®,[3] including >41,000 patients in clinical trials[4]

*The composite of CV death, MI or stroke was a key secondary endpoint of the study; data presented are from prespecified exploratory analysis.[1]

FOURIER study design: The FOURIER study was a double-blind, randomized, placebo-controlled, event-driven trial in 27,564 adult subjects with established CVD and with LDL-C 1.8 mmol/L and/or non-HDL-C 2.6 mmol/L despite high- or moderate-intensity statin therapy. Subjects were randomly assigned to receive Repatha® (140 mg every 2 weeks or 420 mg once monthly) or placebo. The median follow-up duration was 26 months.[1] The risk of the primary efficacy endpoint (a composite endpoint of time to CV death, MI, hospitalization for unstable angina, stroke, or coronary revascularization) was reduced by 15% (HR: 0.85; 95% CI: 0.79–0.92; p<0.001).[1]

OSLER-1 study design: OSLER-1 was an open-label, 4-year extension study following a 1-year randomized treatment period.[2] 1,125 subjects enrolled in one of five phase 2 studies of Repatha® were randomized to SOC or SOC plus Repatha® 420 mg monthly during the randomized period; 1,151 patients progressed to the all-Repatha® period (420 mg monthly, plus SOC) for year 2 and beyond.[2] The primary objective was characterization of the long-term safety and tolerability of Repatha®; subjects were followed for up to 5 years.[2]

Abbreviations
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; RRR, relative risk reduction; SOC, standard of care.

Repatha® (Evolocumab) Abbreviated Prescribing Information
Presentation: Solution for injection; pre-filled autoinjector 140 mg/mL. **Indications:** 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 adult patients unable to reach LDL C goals with the max tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in adult patients who are statin-intolerant or for whom statin is contraindicated. Homozygous familial hypercholesterolaemia: In combination with other lipid-lowering therapies in adults and adolescents ≥12 years. Established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease): In adult as an adjunct to correction of other risk factors: In combination with max tolerated dose of 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 statin is contraindicated to reduce cardiovascular risk by lowering LDL-C levels. **Dosage:** Primary hypercholesterolaemia or mixed dyslipidaemia: Recommended dose 140 mg every 2 weeks or 420 mg once monthly; both doses are clinically equivalent. Homozygous familial hypercholesterolaemia: Initial recommended dose 420 mg once monthly. After 12 weeks, can be up titrated to 420 mg once every 2 weeks if clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their schedule. Established atherosclerotic cardiovascular disease: Recommended dose 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent. No dose adjustment is necessary in elderly patients (age ≥65 years), patients with renal impairment or with mild hepatic impairment. **Method of use:** S/c injection into the abdomen, thigh or upper arm region. Sites should be rotated and injections should not be given where skin is tender, bruised, red, or hard. Must not be administered i/v or i/m. The 420 mg dose should be administered consecutively using 3 pre-filled autoinjectors within 30 mins. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Precautions:** Patients with moderate hepatic impairment: A reduction in total evolocumab exposure observed may lead to a reduced effect on LDL C reduction; close monitoring may be warranted. Used with caution in patients with severe hepatic impairment. Needle cover of pre-filled autoinjector is made from dry natural rubber (a derivative of latex), which may cause severe allergic reactions. Interactions: ~20% increase in the clearance of evolocumab was observed in patients co-administered statins. No statin dose adjustments are necessary when used in combination with evolocumab. **Pregnancy:** Should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab. **Side effects:** Common: Influenza, nasopharyngitis, upper respiratory tract infection, hypersensitivity, rash, nausea; back pain, arthralgia; injection site reactions such as bruising, erythema, haemorrhage, pain, swelling.

Please read the full prescribing information prior to administration and full prescribing information is available upon request. HKREPPI04.

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Advancement in Heart Failure Management Over the Past 30 Years

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INTRODUCTION

Heart Failure is an important burden to the healthcare system due to its high prevalence affecting 1-2% of the population and high mortality of more than 50% at 5 years.[1,2] Over the past 30 years, efforts have been made to fight the war against the emerging heart failure epidemic and there has been a significant advancement in heart failure management, with resultant improvements in morbidity and mortality.

PHARMACOTHERAPIES

More than 30 years ago, the role of angiotensin-converting-enzyme inhibitor (ACEI) in the management of heart failure was established by the first landmark Consensus Trial published in 1987. Since then, multiple high-quality studies confirmed the pivotal roles of beta-blockers, angiotensin-receptor antagonist, and mineralocorticoid receptor antagonist in managing heart failure and the use of these drugs has been incorporated in international guidelines for managing heart failure.[3,4] The pharmacotherapies for heart failure continued to evolve and in 2010, the SHIFT study, which involved 6,558 patients, demonstrated the use of selective sinus-node inhibitor when compared to placebo resulted in a lower composite of cardiovascular death or hospital admission for worsening heart failure (Hazard Ratio (HR) 0.82, 95% CI: 0.75-0.90, p<0.0001) mainly driven by hospital admissions for worsening heart failure (HR 0.74, 95% CI: 0.66-0.83; p<0.0001) and deaths due to heart failure (HR 0.74, 95% CI: 0.58-0.94, p=0.014).[5]

In 2014, angiotensin receptor neprilysin inhibitor (ARNI) was studied in the PARADIGM-HF study, which involved 8,442 patients, and was demonstrated to be superior in reducing risks of death and hospitalisation when compared to standard treatment enalapril (HR 0.80, 95% CI: 0.73-0.87, p<0.001).[6] This subsequently led to the recommendation that ARNI was preferred to ACEI in treatment for heart failure with reduced ejection fraction in the latest heart failure guidelines.[7,8]

The inhibitors of sodium-glucose cotransporter 2 (SGLT2) were a class of drugs initially developed to treat diabetes mellitus and was subsequently confirmed to be useful for patients with heart failure with reduced ejection fraction regardless of diabetes status in the landmark study DAPA-HF trial and EMPEROR-Reduced Trial published in 2019 and 2020, respectively.[9,10] A pooled meta-analysis of the DAPA-HF trial and EMPEROR-Reduced Trial, which together involved 8,474 patients, demonstrated a 13% reduction in all-cause death (HR 0.87, 95% CI: 0.77–0.98, p=0.018), 14% reduction in cardiovascular death (HR 0.86, 95% CI: 0.76-0.98, p=0.027), a 26% relative reduction in the combined risk of cardiovascular death or first hospitalisation for heart failure (HR 0.74, 95% CI: 0.68-0.82, p<0.0001), as well as a 25% decrease in the composite of recurrent hospitalisations for heart failure or cardiovascular death (HR 0.75, 95% CI: 0.68–0.84, p<0.0001).[11]

In 2021, the EMPEROR-Preserved trial was published and was the first clinical trial in patients with heart failure with preserved ejection fraction, which met its primary endpoint of reduced composite of cardiovascular death or hospitalisation for heart failure (HR 0.79; 95% CI: 0.69-0.90, p<0.001).[12]

In 2020, the oral soluble guanylate cyclase stimulator was demonstrated in the VICTORIA trial, which included 5,050 patients, to lower composite of death from cardiovascular causes or first hospitalisation for heart failure among patients with high-risk heart failure, defined as patients with elevated plasma B-type natriuretic peptide (BNP) or NT-proBNP level together with either recent heart failure hospitalisation within six months or recent need for intravenous diuretics within three months (HR 0.90, 95% CI: 0.82-0.98, p=0.02).[13]

In 2021, for the first time a drug that directly enhances cardiac systolic function by selectively activating cardiac myosin was demonstrated to improve clinical outcomes. In the GALACTIC-HF trial, which included 8,256 patients, the use of selective cardiac myosin activator among patients with heart failure with reduced ejection fraction less than or equal to 35% resulted in a lower incidence of composite of a heart-failure event or death from cardiovascular causes (HR 0.92, 95% CI, 0.86-0.99, p=0.03).[14] All these latest developed pharmacotherapies, except the selective cardiac myosin activator, have been registered and available for managing heart failure in Hong Kong.

DEVICE THERAPIES

Besides advancements in pharmacotherapy, cardiac implantable electronic devices were also evaluated in the management of heart failure. Heart failure patients are at risk of sudden cardiac death, especially due to ventricular arrhythmias. In 1996, the MADIT study showed reduced mortality with the use of implantable cardioverter defibrillator (ICD) in patients with ischemic cardiomyopathy (HR 0.46; 95% CI: 0.26-0.82, p=0.009)

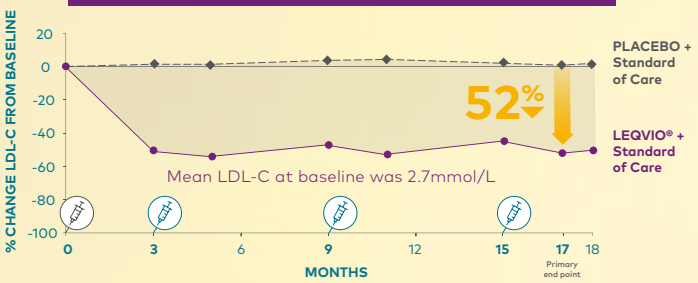
LEQVIO®
(inclisiran) injection 284 mg/1.5 mL

2 DOSES A YEAR*
FOR EFFECTIVE AND SUSTAINED LDL-C REDUCTION[1†]

FDA APPROVED[2]

EMA APPROVED[3]

In ORION-10 (N=1,561), LEQVIO® demonstrated LDL-C reduction in patients with established **ASCVD**[1,4]



Patients in both study arms were on a maximally tolerated statin.[1,4]

In ORION-10 clinical trial, LEQVIO® demonstrated LDL-C reduction in ASCVD patients:[4]

52% EFFECTIVE LDL-C REDUCTION

Between-group difference of -52.3% (95% CI: -55.7%, -48.8%; P<0.001) refers to the difference between the placebo group (1.0%) and the LEQVIO® group (-51.3%) at month 17.

*LEQVIO® is dosed initially, again at 3 months, and then once every 6 months.[1]
†LDL-C reduction was maintained during each 6-month dosing interval.[1]

Study design: ORION-10 was a multicenter, double-blind, randomized, placebo-controlled 18-month clinical trials. Patients with established ASCVD were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy and required additional LDL-C reduction. The ORION-11 trial, in addition to patients with ASCVD, included adults who were ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol

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Leqvio® Important note: Before prescribing, consult full prescribing information. **Presentation: Solution for injection:** Each pre-filled syringe contains 1.5 mL of solution containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium). **Indications:** Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) 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 LDLC 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. **Dosage and administration:** *Recommended dose:* 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months. *Missed dose:* • If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule. • If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months. *Treatment Transition from PCSK9 Inhibitor Monoclonal Antibody:* Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain LDL C lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor. **Special populations:** *Renal impairment:* No dose adjustments are necessary for patients with mild, moderate or severe renal impairment or patients with end stage renal disease. There is limited experience with inclisiran in patients with severe renal impairment. Inclisiran should be used with caution in these patients. *Hepatic impairment:* No dose adjustments are necessary for patients with mild (Child Pugh class A) or moderate (Child Pugh class B) hepatic impairment. No data are available in patients with severe hepatic impairment (Child Pugh class C). Inclisiran should be used with caution in patients with severe hepatic impairment. *Pediatric patients (below 18 years):* The safety and efficacy of inclisiran have not been established. *Geriatric patients (65 years of age or above):* No dose adjustment is necessary. **Method of administration:** Intended for administration by a healthcare professional. For subcutaneous injection into the abdomen, alternative injection sites include the upper arm or thigh. Injections should not be given into areas of active skin disease or injury such as sunburns, skin rashes, inflammation or skin infections. Leqvio should be inspected visually for particulate matter prior to administration. Each pre-filled syringe is for single use only. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and precautions:** ***Haemodialysis:*** Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing. **Pregnancy, lactation, females and males of reproductive potential *Pregnancy:*** There are no or limited amount of data from the use of inclisiran in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy. ***Lactation:*** It is unknown whether inclisiran is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of inclisiran in milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from inclisiran therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. ***Infertility:*** No human data. No effects on animal fertility. **Adverse drug reactions:** ***Common (≥1 to <10%):*** Adverse events at the injection site (includes injection site reaction, injection site pain, injection site erythema, and injection site rash). **Interactions:** Not a substrate, inhibitor or inducer of CYP450 enzymes or common drug transporters. Not expected to have clinically significant interactions with other medications. Drug-drug interaction assessments demonstrated a lack of clinically meaningful interactions with either atorvastatin, rosuvastatin or other statins. **Packs:** Solution in pre-filled syringe: 1's **Legal classification:** P1S1S3 Last revision: Sep 2021 Ref: EU Dec 2020

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and subsequently the SCD-HeFT trial in 2005 showed ICD reduce mortality in heart failure patients including both ischemic and non-ischemic aetiology (HR 0.77; 97.5% CI: 0.62-0.96, p=0.007).[3,4]

In addition, the role of cardiac resynchronisation therapy (CRT) in managing heart failure was first established by the COMPANION trial in 2004, which showed a reduction in time to death from or hospitalisation for any cause with the use of CRT (HR 0.81; 95% CI: 0.69-0.96, p=0.014). Subsequently, the CARE-HF trial in 2005 showed CRT reduced the time to death from any cause or unplanned hospitalisation for a major cardiovascular event (HR 0.63; 95% CI: 0.51-0.77, p<0.001); the MADIT-CRT trial in 2009 showed reduced death from any cause or a nonfatal heart-failure event (HR 0.66; 95% CI:0.52-0.84, p=0.001); as well as the RAFT study in 2010 showed reduced death from any cause or hospitalisation for heart failure (HR 0.75; 95% CI: 0.64-0.87, p<0.001).[3,4]

As a result ICD and CRT were recognised as standard heart failure therapies for suitable patients to reduce morbidity and mortality. According to local data, there was a significant increase in the utilisation of ICD with mean 128 ICD device implantations per year before 2010 vs mean 324 implantations per year after 2011 in Hong Kong (p<0.001), and there was also a significant increase in the utilisation of CRT devices from mean 91 CRT device implantations per year before 2010 vs mean 143 implantations per year after 2011 in Hong Kong (p=0.012).

HEART TRANSPLANT AND LEFT VENTRICULAR ASSIST DEVICES FOR STAGE D HF

Some patients with chronic heart failure will inevitably progress to stage D advanced heart failure. Heart transplantation has been the gold standard therapy for eligible patients with advanced heart failure. The first heart transplant in Hong Kong was performed in 1992 and 237 heart transplants have been performed since then till 2021.[15] This year is the 30th anniversary of both our first heart transplant patient and Hong Kong Heart Transplant Service. The overall post-heart transplant survival rates were 86.6% and 68.8% at one- and ten-year respectively with a median survival of 18.5 years in Hong Kong, which was comparable to the survival rates of 84.0% and 56.8% at one- and ten-year as well as median survival of 11.9 years reported by the International Society of Heart and Lung Transplantation registry.[15]

However, due to limited donor supply and high-risk nature of stage D heart failure, patients on the heart transplant waiting list faced a very high mortality of around 20% per year while on heart transplant waiting list in the past.[15] Furthermore, many patients with advanced heart failure were not eligible for heart transplantation due to various reasons such as comorbidities and advanced age. As a result, there has been an unmet need to support these patients besides long term inotropic palliative care.

Since the first landmark study REMATCH trial published in 2001, there has been a significant advancement in technology and experience of left ventricular assist device (LVAD) both as a bridge to transplant (BTT) and destination therapy (DT). In the latest MOMENTUM 3 trial, patients who received the latest design of fully magnetically levitated centrifugal-flow LVAD were significantly better when compared to patients who received the previous generation axial-flow LVAD in terms of survival, free of disabling stroke and reoperation to replace or remove a malfunctioning device at two years (relative risk 0.84; 95% CI: 0.78-0.91, p<0.001).[16] This signifies improvements in technology and design of the LVAD can result in smaller, more reliable, durable and effective LVAD devices with fewer complications.

To date, there have been more than 26,000 patients who have received LVAD implantation world-wide.[17] Since the first LVAD implantation in 2010, more than 140 LVAD implantations have been performed in Hong Kong and more than 90% of the cases were for BTT, while the remaining were for DT. It has been demonstrated that the use of BTT LVAD was associated with 79% risk reduction of waiting list mortality; survival after BTT LVAD was similar to those who received heart transplantation up to eight years in Hong Kong.[15]

In addition, efforts have been made to expand the potential heart transplant donor pool by utilising the organ care system (OCS), which enables ex-vivo perfusion and assessment of traditional marginal heart donor which would have otherwise been rejection in the past. Its use has been previously reported to be safe and effective in accessing acceptability of these marginal donor hearts without compromising post-heart transplantation outcomes.[18,19] Hong Kong has been the first Asian city utilising OCS for marginal heart assessment and has successfully increased heart donor availability by 20% since 2020.

CONCLUSION

In conclusion, there have been many major rapid advancements in different aspects of heart failure management over the last 30 years and it will continue to evolve in response to the emerging heart failure epidemic.

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Dermatology Quiz

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Specialist in Dermatology & Venereology

Dr Lai-yin CHONG

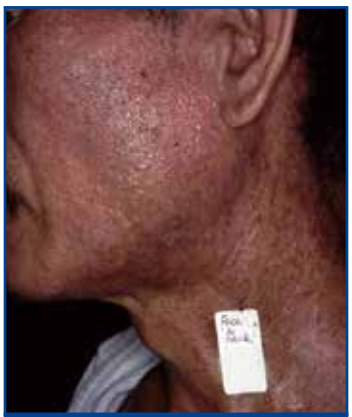

Fig.1: Brownish greasy hyperkeratotic lesions over the face

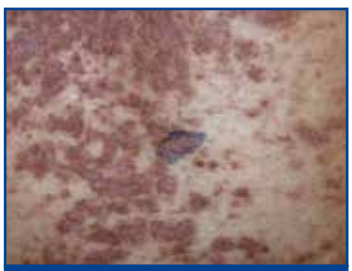

Fig.2: Close up at the back

This 50-year-old man developed these brownish greasy hyperkeratotic lesions since his teenage years (Fig.1 &2). These lesions gradually increased in extent and distributed over his face, anterior chest, upper back and dorsa of both hands and feet. He had itchiness and malodor from these skin lesions, especially after sun exposure and sweating, resulting in psychosocial disturbances in his life. His past health was otherwise good. There was no family history.

Questions

1. What is your clinical diagnosis and what are the differential diagnoses?
2. What important diagnostic clues should be looked for in the physical examination?
3. How do you confirm the diagnosis?
4. How do you treat this disease?

(See P.44 for answers)

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MAT-HK-2200588-1.0/07-2022

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Screening for Atrial Fibrillation - Where Are We Now?

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Dr Ho-chuen YUEN

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia. The prevalence of AF in Hong Kong was found to be 0.77% in a community screening programme in 2016 and it was expected to increase substantially, especially in the older population, in the years to come.[1] Patients with AF have a fivefold increase in the risk of ischaemic stroke. It was estimated that around 33% of ischaemic stroke patients suffered from AF. In over 25% of patients with AF-related stroke, stroke was the first manifestation of previously undiagnosed AF.[2] The ischaemic stroke risk in AF patients can be reduced by more than 60% with the use of oral anticoagulant therapy. This gives an urge to screen for AF in order to see if we can reduce ischaemic stroke in patients with unknown AF.

There are different guidelines from various parts of the world on the topic of AF screening. In 2022, the United States Preventive Service Task Force concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for AF in asymptomatic adults ages >= 50 years.[3] However, the 2020 European Society of Cardiology AF Guidelines gave a class I recommendation that opportune screening for AF is recommended by pulse taking or ECG rhythm strip in patients ages >= 65 years and a class IIa recommendation that systematic ECG screening should be considered to detect AF in patients >= 75 years or those at high risk of stroke.[4] To get a better understanding on AF screening, we have to answer three main questions: 1) Is AF screening effective in identifying people with previously undiagnosed AF and what screening tool and intensity are the best? 2) Is there any difference between clinical AF and screen-detected AF in terms of ischaemic stroke risk? 3) Is it beneficial to treat screen-detected AF with anticoagulant therapy?

IS AF SCREENING EFFECTIVE IN IDENTIFYING PEOPLE WITH PREVIOUSLY UNDIAGNOSED AF AND WHAT SCREENING TOOL AND INTENSITY ARE THE BEST?

There are a great variety of devices that can be used to detect subclinical AF. These devices range from wearable cardiac monitoring devices such as smartwatches to invasive implantable devices such as implantable loop recorders. Screening intensity, which can be divided into one-time, intermittent or continuous, also varies with different devices. In the past, one-time standard surface ECG (typically 12-lead) was most-commonly used in earlier studies of AF screening. The development of portable ECG devices (typically 1-lead) makes frequent intermittent ECG screening more feasible. In addition, implantable loop recorders can provide continuous monitoring of heart rhythm for up to three years.

Over the past two decades, there have been various randomised controlled trials using various screening methods to see if more people with undiagnosed AF could be picked up with AF screening. Table 1 shows the details of some of the main studies. The SAFE study published in 2005 used pulse taking and a single time-point 12-lead ECG to screen for AF in the population aged 65 or above. It showed a small but significant increase in AF detection rate (0.5% absolute increase) in the screened population when compared to the population without screening.[5] However, the recently published VITAL-AF study, which again tested the effectiveness of AF screening in population aged 65 or above but used a handheld single-lead ECG as a screening tool, did not detect any significant increase in AF detection rate.[6] One important point to note is that the rate of newly diagnosed AF in the non-screened arm of the SAFE study (1.04%) was substantially less than that observed in the non-screened arm of the VITAL-AF study (1.59%). The authors of the VITAL-AF study suggested the negative result in their study could be a result of increased AF detection through usual care in contemporary primary care practice.

The STROKESTOP and REHEARSE-AF studies utilised handheld ECG devices for intermittent screening for a certain period of time. Both studies showed a significantly higher AF detection rate in the screened arms. The STROKESTOP study detected 1% absolute increase while the REHEARSE-AF study revealed 2.8% absolute increase in AF detection rate.[7,8] The screened group received a two-week continuous ECG patch monitor to wear at baseline and at three months in the SCREEN-AF study and showed a higher AF detection rate (4.8% absolute increase).[9] The LOOP study randomly assigned high-risk older patients without known AF to get implantable loop recorders or usual care. In the group with loop recorders, they defined AF episodes lasting six minutes or longer as significant. AF was detected in 32% of those with the loop recorder group versus 12% in the usual care group, yielding 20% absolute increase in AF detection rate.[10] There seems to be enough evidence that these screening strategies, performed intermittently or continuously if not one-

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Study design: [2] An international multicentre phase III trial conducted at 72 centres in 12 European countries to assess the reliability, cycle control, side effects and effects on blood pressure (BP) and body weight of the monophasic formulation of 20 µg ethinylestradiol/150 µg desogestrel. 1684 sexually active, healthy women were accepted into the study. All women took the pill in a 21/7 regimen. Data was obtained over 25 970 cycles.[3] A randomized, multicentre study carried out at 52 centres in France to compare the cycle control and tolerability of 2 oral contraceptives containing 20 µg ethinylestradiol and either 150 µg desogestrel or 75 µg gestodene. 1016 healthy adult women aged between 18-45 received the desogestrel (n = 509) or the gestodene (n = 507) preparation in a 21/7 regimen for 6 treatment cycles. [4] An open, parallel group comparison study, carried out at 19 centres in 4 European countries to compare cycle control, bleeding patterns and efficacy of two low-dose combined oral contraceptives. 453 healthy women aged 18-35 years were randomized to receive a 24/4 regimen of 3 mg drospirenone/20 µg ethinylestradiol (n=230) or a 21/7 regimen of 150 µg desogestrel/20 µg ethinylestradiol (n=223). Daily bleeding was recorded over 7 treatment cycles. [5] An open, randomized, double-blind, multicentre phase III study, carried out at 67 centres in 6 European countries to compare contraceptive efficacy, cycle control, and tolerability of a 23-day regimen with 20 µg ethinylestradiol and 75 µg GSD and a 21-day regimen with 20 µg ethinylestradiol and 150 µg desogestrel. 890 healthy women aged 18-35 years were randomized to receive a 23-day regimen of 20ug ethinylestradiol /75 ug gestodene (n=445 for 2975 cycles) or a 21/7 regimen of 20 ug ethinylestradiol and/150 ug desogestrel (n=445 for 2912 cycles).

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Selected Safety Information

Indications: contraception. **Dosing and administration:** Tablet for oral use. Each tablet contains 0.150 mg desogestrel and 0.020 mg ethinylestradiol. The tablets must be taken in the order directed on the strip every day at about the same time. One tablet is to be taken daily for 21 consecutive days. Each subsequent strip is started after a 7-day tablet-free interval. **Contraindications:** Combined hormonal contraceptives should not be used in the following situations. Should any of the conditions appear for the first time during COC use, the product should be stopped immediately. · Presence or risk of venous thromboembolism (VTE) - Venous thromboembolism – current VTE (on anticoagulants) or history of (eg deep venous thrombosis [DVT] or pulmonary embolism [PE]). - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency. - Major surgery with prolonged immobilization. - A high risk of venous thromboembolism due to the presence of multiple risk factors. · Presence or risk of arterial thromboembolism (ATE) – Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infaction) or prodromal conditions (e.g. angina pectoris). - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA). - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia, and antiphospholipid (anticardiolipin-antibodies, lupus anticoagulant). - History of migraine with focal neurological symptoms. - A high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk factor such as: - Diabetes mellitus with vascular symptoms - Severe hypertension – Severe dyslipoproteinaemia · Presence or history of pancreatitis associated with severe hypertriglyceridaemia. · Presence or history of severe hepatic disease as long as liver function values have not returned to normal. · Presence or history of liver tumours (benign or malignant). · Known or suspected sex steroid-influenced malignancies (e.g., of the genital organs or the breasts). · Endometrial hyperplasia. · Undiagnosed vaginal bleeding. · Hypersensitivity to the active substances or to any of the excipients. · Mercilon® is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir. **Precautions or warnings:** The suitability of Mercilon® should be discussed with the woman considering below conditions. Risk of venous thromboembolism (VTE); risk of arterial thromboembolism (ATE); development of cervical cancer; breast cancer; transaminase (ALT) elevations due to hepatitis C treatment, hypertriglyceridaemia,, hypertension, jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss; (hereditary) angioedema; Crohn's disease and ulcerative colitis; chloasma. **Adverse events:** Some women may experience mild side effects while taking the drug. Common undesirable effects are depressed mood, mood altered, headache, nausea, abdominal pain, breast pain, breast tenderness, and weight increased. Like all medicines, Mercilon® can have side effects, although not everybody gets them. Tell your doctor if you notice any unwanted effect, especially if severe or persistent, or if there is a change in your health that you think might be caused by the Pill.

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time, identify older people with previously undiagnosed AF more effectively than usual care. Intermittent or continuous screening strategies probably get more yield than one-time strategy.

Table 1: Summary of the differences in AF detection rate between screened and non-screened groups in randomised controlled trials using different screening approaches (Developed by the author)

	Sample size (no. of subjects)	Mean age	Screening approach	The absolute increase in AF detection rate
SAFE 2005 [5]	9,869	75.3	One-time 12-lead ECG	0.5% (significant difference)
VITAL-AF 2022 [6]	30,715	74	One-time handheld single-lead ECG	0.13% (P=0.38, non-significant difference)
SCREEN-AF 2021 [9]	856	80	Continuous: two-week continuous ECG patch x two times (three months apart)	4.8% (significant difference)
REHEARSE-AF 2017 [8]	1,001	72.6	Intermittent: twice-weekly screening x 12 months	2.8% (significant difference)
STROKESTOP 2021 [7]	27,577	75 or 76	Intermittent: twice-daily screening x two weeks	1.0% (significant difference)
LOOP 2021 [10]	6,004	74.7	Continuous: loop recorder	19.6% (significant difference)

IS THERE ANY DIFFERENCE BETWEEN CLINICAL AF AND SCREEN-DETECTED AF IN TERMS OF ISCHAEMIC STROKE RISK?

In the older days, most AF we found was clinical AF with standard surface ECG documentation. However, we are facing more and more subclinical AF nowadays because of the increasing use of implantable cardiac devices and portable cardiac monitoring devices. The issue is further complicated by technological advances in consumer-oriented cardiac monitoring devices such as smartwatches. Whether subclinical AF carries the same ischaemic stroke risk as clinical AF remains unknown.

Currently, most studies on the ischaemic stroke risk of subclinical AF focus on patients with intracardiac implantable devices, including pacemakers and defibrillators. Pacemakers and defibrillators carry the ability to monitor the burden of AF or atrial tachycardia (AT) continuously. The TRENDS study is a prospective observational study enrolling patients with >= 1 stroke risk factor(s) receiving pacemakers or defibrillators. It showed that the thromboembolic rate was low when compared with patients with traditional AF and similar risk factors. The AF/AT burden had a significant impact on the thromboembolic risk. The data from this study suggested that AT/AF burden >= 5.5 hours within the past 30 days doubled the risk of thromboembolism when compared to zero AF/AT burden.[11]

The ASSERT study enrolled patients aged 65 or above, with hypertension and no history of AF, in whom a pacemaker or defibrillator had recently been implanted. Subclinical AF was defined as AF lasting >= 6 minutes in this study. Subclinical AF was found to be associated with an increased risk of ischemic stroke or systemic embolism with a hazard ratio of 2.49 in a 2.5-year follow-up.[12] Subsequent analyses demonstrated that most of the thromboembolism events occurred in patients with AF lasting > 24 hours.[13] It is now believed that high-burden and long-duration subclinical AF is associated with an increased risk of ischaemic stroke. The stroke risk of low-burden and short-duration subclinical AF detected by pacemakers or defibrillators is less well-understood.

IS IT BENEFICIAL TO TREAT SCREEN-DETECTED AF WITH ANTICOAGULANT THERAPY?

We do know that oral anticoagulant therapy has been proven to be effective in reducing the risk of ischaemic stroke in clinical AF.[14] However, the risk-benefit ratio of anticoagulant therapy in treating screen-detected AF remains to be elucidated. An observational study showed that treating screen-detected AF with anticoagulant therapy had an outcome similar to treating clinical AF.[15] It is just hypothesis-generating and we definitely need randomised controlled trials to clarify this finding.

The LOOP and STROKESTOP studies were designed to evaluate the health outcomes of AF screening. In the LOOP study, investigators enrolled patients aged 70 to 90 (mean age 74.7 years) who had at least one stroke-risk factor and randomised them to get implantable loop recorders or usual care. In the group with loop recorders, anticoagulation was recommended if AF episodes lasted six minutes or longer. After a median follow-up of 65 months, the LOOP authors found that despite detecting almost three times more AF (AF detection rate: 32% in the loop recorder group versus 12% in the usual care group) and a nearly threefold higher use of anticoagulant therapy, use of implantable loop recorder did not show significant reduction in stroke or systemic embolism.[9] The STROKESTOP study recruited people aged 75 and 76 and randomised them to be invited to screening, which consisted of intermittent ECG readings taken twice daily for two weeks, or not. In the screened group, 7,165 (51.3%) of the 13,979 people invited to screening chose to participate in the screening programme. Treatment with oral anticoagulants was offered if AF was detected or untreated. After a median follow-up of 6.9 years, investigators found that the screened group had a small but significant reduction in the primary endpoint, which consisted of ischaemic or haemorrhagic stroke, systemic embolism, bleeding requiring hospitalisation, and all-cause mortality (hazard ratio: 0.96). The reduction was mainly driven by a reduction in ischaemic stroke in those people who agreed to undergo screening when compared to the control group in the as-treated analysis (hazard ratio: 0.76).[6]

The difference in study outcomes between the LOOP and STROKESTOP studies probably lies in their

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參考資料：1. Hong Kong Product Circular (ATOZET®). 2. Cannon, C.P. et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med.* 2015;372 (25):2387-2397. 3. Bays, H.E. *et al.* Efficacy and safety of ezetimibe added on to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia. *Am J Cardiol.* 2013;112:1885-1895. 4. Averna, M et al. Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: A statement from a European Atherosclerosis Society Task Force. Atherosclerosis 325 (2021) 99–109

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* A composite of CV death, non-fatal MI, hospital admission for UA, coronary revascularization (≥30 days after randomization), or non-fatal stroke

Study Design: The **IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)** was a randomized, double-blind study involving 18,144 patients who had been hospitalized for an ACS within the preceding 10 days and had LDL-C levels of 1.3-2.6mmol/L if they were receiving LLT or 1.3-3.2mmol/L if they were not receiving. The combination of ezetimibe (10mg) and simvastatin (40mg) was compared with simvastatin (40mg) alone and placebo. The primary endpoint was a composite of CV death, non-fatal MI, unstable angina requiring rehospitalization, coronary revascularization ≥30 days after randomization, or non-fatal stroke. The median follow-up was 6 years.

CV=cardiovascular; MI=myocardial infarction; UA=unstable angina; IMPROVE-IT=IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; ACS=acute coronary syndrome; LDL-C=low-density lipoprotein cholesterol; LLT=lipid-lowering therapy

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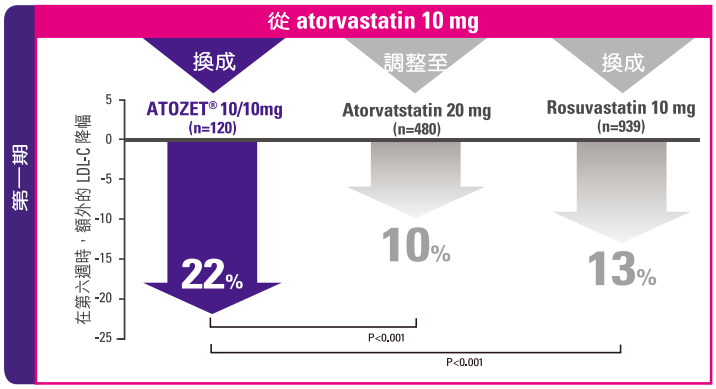

Hypercholesterolemic patients (n =1,547) at high atherosclerotic cardiovascular disease risk with low-density lipoprotein cholesterol (LDL-C) levels ≥100 and ≤160 mg/dl while treated with atorvastatin 10 mg/day entered a multicenter, randomized, double-blind, active-controlled, clinical trial using two 6-week study periods. Period I compared the efficacy/safety of (1) adding ezetimibe 10 mg (ezetimibe) to stable atorvastatin 10 mg, (2) doubling ator-vastatin to 20 mg, or (3) switching to rosuvastatin 10 mg. Subjects in the latter 2 groups who persisted with elevated LDL-C levels (≥100 and ≤160 mg/dl) after period I, entered period II; subjects on atorvastatin 20 mg had ezetimibe added to their atorvastatin 20 mg, or uptitrated their atorvastatin to 40 mg; subjects on rosuvastatin 10 mg switched to atorvastatin 20 mg plus ezetimibe or uptitrated their rosuvastatin to 20 mg.
The primary efficacy end point variable was the percent change from treated baseline in LDL-C levels at the end of period I

Selected Safety information on ATOZET®

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different approaches in screening for AF. The LOOP study used continuous heart rhythm monitoring by loop recorders and defined AF episodes lasting six minutes or above as significant while the STROKESTOP study adopted intermittent ECG recordings taken twice daily for two weeks as the screening strategy. Continuous ECG monitoring provided by a loop recorder is very sensitive and can pick up very short and infrequent AF episodes. The LOOP study tells us that using six minutes of AF as the threshold for anticoagulant therapy may not be beneficial. Where to draw the line for significant AF which warrants treatment requires more research. Intermittent ECG screening used in STROKESTOP study seems to pick up more clinically meaningful AF.

CONCLUSION

Although screening can detect more cases of previously unknown AF, uncertainty about the effects of such detection on health outcomes remains. However, whether we like it or not, AF screening is happening in our daily practice nowadays because of the exponential growth of smartwatches and smartphone apps capable of heart rhythm monitoring. There is currently no study exploring the stroke risk associated with AF detected by consumer-oriented devices. Research on this subject matter is warranted given the rising popularity of these convenient wearable cardiac monitoring devices. We should not forget the potential dangers of AF screening. Abnormal screening results may generate unnecessary anxiety. ECG misinterpretation may also cause overdiagnosis and overtreatment and anticoagulant therapy is not without risk.

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Exercise Recommendations in Patients with Cardiovascular Disease

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A sedentary lifestyle is associated with increased risks of cardiovascular disease, diabetes mellitus and mortality.[1] Regular exercise improves the quality of life[1] and prolongs survival.[2-3] Moderate intensity exercise for more than three hours per week and vigorous-intensity exercise of 20 minutes for >= 3 times per week were associated with 27% and 32% reduction in mortality respectively.[3]

Among patients with coronary artery disease, an exercise-based cardiac rehabilitation programme is associated with a reduction of cardiovascular mortality and an improvement of quality of life.[4] In patients with heart failure, an exercise-based cardiac rehabilitation programme has been shown to improve quality of life and reduce all-cause and heart failure hospitalisation.[5]

The current American[6] and European[7] guidelines recommend that adults should perform at least 150 to 300 minutes of moderate-intensity aerobic exercise or 75 to 150 minutes of high-intensity aerobic exercise, combined with 2-3 sessions of muscle-strengthening resistance training per week.

However, concern about the risk of exercise-related adverse cardiovascular events and lack of systematic training often become physicians' major obstacles in optimising exercise prescription for patients with cardiovascular diseases.

In reality, the absolute risk of exercise-related sudden cardiac death (SCD) and adverse cardiovascular events are very low in population-based studies. The risk of exercise-related SCD ranged from 0.31 to 2.1 per 100,000 person-years. The reported risk of exercise-associated myocardial infarction was 0.75 per 100,000 person-years.[8] Among athletes, the reported incidence of SCD was 1.21 per 100,000 person-years[9], which was much lower than that in the general population (50-100 SCD per 100,000 person-years).[10] Event in patients with coronary artery disease, the reported risk of adverse cardiovascular events during supervised exercise-based cardiac rehabilitation programme was extremely low - one cardiac arrest per 116,906 patient-hours, one myocardial infarction per 219,970 patient-hours, one fatality per 752,365 patient-hours, and one major complication per 81,670 patient-hours of participation.[11]

The current review summarises the 2020 European Society of Cardiology Guidelines on sports cardiology and exercise in patients with cardiovascular disease.[7]

The review consists of two parts. Part I summarises the definition of recreational and competitive athletic activities, grading of exercise intensity, and classification of the intensity of various sports disciplines, general exercise recommendations, pre-participation cardiovascular disease screening recommendations and risk stratification in patients with coronary artery disease with regard to exercise prescription. Part II summarises the exercise prescription recommendations in patients with cardiovascular diseases, with special emphasis on patients with hypertension, coronary artery disease, heart failure, cardiomyopathy, myocarditis, pericarditis and cardiac arrhythmia. Due to word limitations, certain cardiovascular conditions (patients with aortic diseases, congenital heart diseases, cardiac implantable electronic devices and post-heart transplant patients) are not covered in this review.

PART I

Definition of Athletic Activities

An athlete is defined as an individual engaging in regular sports training and official sports competitions. A recreational athlete engages in sports for pleasure and leisure-time activity, whereas a competitive athlete is highly trained with a greater emphasis on performance and winning. Elite athletes (i.e. national team, Olympians, and professional athletes) generally exercise >=10 hours/week. Competitive athletes [i.e. high school, college, and older (master) club level athletes] generally exercise >=6 h/week. Recreational athletes generally exercise >=4 h/week.

Grading of Exercise Intensity

Exercise intensity could be graded into low, moderate, high and very high according to maximum oxygen consumption, maximum heart rate, heart rate reserve, rate of perceived exertion and training zone (Table 1). Maximum oxygen consumption has to be assessed using cardiopulmonary exercise testing (CPET) and is less applicable in general exercise prescription outside the settings of cardiac rehabilitation or professional athletic training. Maximum heart rate could be calculated by subtracting age from 220. Heart rate reserve could be calculated by subtracting resting heart rate from maximum heart rate (MHR). Using the MHR classification, moderate intensity is defined as 55-74% of MHR. High intensity is defined as 75-90% of MHR. Exercise intensity could also be classified according to training zone. Low-intensity exercise is below the

aerobic threshold. Moderate-intensity exercise is above the aerobic threshold but not reaching the anaerobic threshold. High-intensity exercise is close to anaerobic threshold. Very high-intensity exercise is above the anaerobic threshold.

Table 1: Indices of exercise intensity for endurance sports from maximal exercise testing and training zones (Adapted from Pelliccia A et al. ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.)[7]

Intensity of exercise	VO2 max (%)	HR max (%)	HRR (%)	RPE Scale	Training Zone
Low	< 40	< 55	< 40	10-11	Aerobic
Moderate	40-69	55-74	40-69	12-13	Aerobic
High	70-85	75-90	70-85	14-16	Aerobic + lactate
Very high	> 85	> 90	> 85	17-19	Aerobic + lactate + anaerobic

HRmax = maximum heart rate; HRR = heart rate reserve; RPE = rate of perceived exertion; VO2max = maximum oxygen consumption.

Classification of the Intensity of Various Sports Disciplines:

Sports disciplines could be classified according to predominant components (skill, power, mixed and endurance) and intensity of exercise. (Table 2)

Table 2: Sporting discipline in relation to the predominant component (skill, power, mixed, and endurance) and intensity of exercise (Adapted from Pelliccia A et al. ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.)[7]

GENERAL EXERCISE RECOMMENDATIONS

The following are the current guideline recommendations on exercise prescription in healthy adults:

1. At least 150 minutes of moderate-intensity aerobic exercise per week, or 75 minutes of vigorous-intensity aerobic exercise per week, or an equivalent combination is recommended for all healthy adults. (Class I; Level of recommendation (LOE) A)

2. A gradual increase in moderate-intensity aerobic exercise to 300 minutes per week or vigorous-intensity aerobic exercise to 150 minutes per week is recommended for additional benefits in healthy adults. (Class I; LOE A)

3. Resistance training for 3 days per week is recommended.

4. Multiple sessions of exercise spreading throughout 4-5 days a week and preferably every day is recommended (Class I; LOE B)

I. Recommendation on pre-participation cardiovascular disease screening necessary before starting an exercise programme

In general, routine pre-participation cardiovascular disease screening is not necessary for low-to-moderate-cardiovascular-risk young adults who intend to participate in recreational sports. Further clinical evaluation and/or cardiovascular disease screening should be considered in competitive athletes or in individuals with high CVD risk who intend to engage in intensive exercise programme or competitive sports.

1. In healthy individuals < 35 years of age and individuals > 35 years of age with low to moderate cardiovascular disease (CVD) risk, participation in all recreational sports should be considered without further cardiovascular assessment. (Class II a; LOE C)

2. In sedentary individuals > 35 years of age with high or very high CVD risk, clinical evaluation and maximal exercise testing should be considered for prognostic purposes among those who intend to engage in an intensive exercise programme or competitive sports. (Class II a; LOE C)

3. In individuals > 35 years of age without coronary artery disease who have very high CVD risk (e.g., SCORE > 10%, strong family history of familial hypercholesterolemia) and want to engage in high or very high-intensity exercise, risk assessment with functional imaging, coronary computed tomography angiogram or carotid/femoral artery ultrasound may be considered. (Class II b ; LOE B)

4. In sedentary adults aged 65 years or older who wish to participate in high-intensity activity, a full clinical assessment including a maximal exercise test should be considered. (Class II a; LOE C)

5. For competitive athletes, cardiovascular screening with family history, symptoms, physical examination, and 12-lead resting ECG should be considered. (Class II a; LOE C)

II. Risk stratification in individuals with atherosclerotic coronary artery disease with regard to exercise-induced adverse cardiac events

Individuals with atherosclerotic CAD and the following features are regarded as at high risk of developing exercise-induced cardiac events (Table 3):

Table 3 : High risk features of exercise-induced cardiac events in patients with atherosclerotic coronary artery diseases (Adapted from Pelliccia A et al. ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.)[7]

Critical coronary stenosis > 70% in a major coronary artery or > 50% in the left main stem on coronary angiography and/or FFR < 0.8 and /or iFR< 0.9
Basal left ventricular ejection fraction <= 50% and wall motion abnormalities
Inducible myocardial ischemia on maximal exercise testing
NSVT, polymorphic or very frequent ventricular premature beats, at rest and during maximal stress
Recent ACS +/- PCI or surgical revascularisation < 12 months

PART II

Part II summarises the exercise prescription recommendations in patients with cardiovascular diseases, with special emphasis on patients with hypertension, coronary artery disease, heart failure, cardiomyopathy, myocarditis, pericarditis and cardiac arrhythmia.

Patients with Obesity, Hypertension, Dyslipidemia or Diabetes

Sports/exercise should be considered to reduce cardiovascular risk, to improve blood pressure control, or improve insulin sensitivity in patients with obesity, hypertension and diabetes mellitus respectively:

- Resistance training >= three times per week, in addition to moderate or vigorous aerobic exercise (at least 30 minutes, 5-7 days per week) in obese individuals (BMI >= 30 kg/m2 or a waist circumference > 80 cm for females or > 94 cm for males) (Class I; LOE A)
- Resistance training >= three times per week in addition to moderate or vigorous aerobic exercise (at least 30 minutes, 5-7 days per week) in patients with well-controlled hypertension (Class I; LOE A)
- Resistance training >= three times per week in addition to moderate or vigorous aerobic exercise (at least 30 min, 5-7 days per week) in patients with diabetes mellitus. (Class I; LOE A)

In patients with well-controlled hypertension but with high risk and/or target organ damage, and in patients with uncontrolled hypertension (Systolic blood pressure >160 mmHg) (until blood pressure has been controlled), high-intensity exercise is not recommended. (Class III; LOE C)

Patients with Coronary Artery Disease (CAD)

Sports/exercise should be considered in the following settings in patients with CAD:

- Exercise-based cardiac rehabilitation in all patients with coronary artery disease (CAD) to reduce cardiac mortality and rehospitalisation (Class I; LOE A)
- Exercise-based cardiac rehabilitation in parallel with low to moderate intensity recreational exercise for 8-12 weeks after a cardiac event, starting soon after discharge after acute coronary syndrome (ACS), cardiac surgery or percutaneous coronary intervention (PCI)
- Competitive or leisure sports activities (with some exceptions such as older athletes and sports with extreme CV demands) in CAD individuals at low risk of exercise-induced adverse events (Class II a; LOE C)

Competitive sports in asymptomatic CAD individuals at high risk of exercise-induced adverse events or those with residual ischemia are not recommended (except for individually recommended skill sports) (Class III; LOE C). Leisure time exercise below angina and ischemic thresholds in CAD individuals at high risk of exercise-induced adverse events may be considered. (Class IIb; LOE C)

Congestive Heart Failure (CHF)

Sports/exercise should be considered in patients with CHF under the following settings:

- Exercise-based cardiac rehabilitation in stable individuals with heart failure with reduced ejection fraction (HFrEF)/heart failure with mid-ranged ejection fraction (HFmrEF) to improve exercise capacity, and quality of life, and reduce the frequency of hospital readmission (Class I; LOE A) #
- Sports participation in individuals with heart failure who are at low risk, in stable condition for at least one month after receiving optimal medical treatment and functional class I status (based on a complete assessment and exclusion of all contraindications) (Class IIa; LOE C)
- Moderate-intensity endurance and resistance training combined with lifestyle modification and optimal medical treatment of cardiovascular risk factors in individuals with heart failure with preserved ejection fraction (HFpEF) (Class I; LOE C)

A maximal exercise test (preferably cardiopulmonary exercise test-CPET) is important to assess functional capacity, exercise-induced arrhythmias or haemodynamic abnormalities and for prescription of exercise intensity, based on VO2peak, or on resting and maximal heart rate during exercise [e.g., Heart rate reserve or Borg's rating of perceived exertion (RPE)].

Sports/exercise may be considered in patients with CHF under the following settings:

- Low-intensity non-competitive sports in stable optimally treated individuals with HFrEF (II b; LOE C)

- Low to moderate intensity non-competitive skill, power, mixed or endurance sports in stable asymptomatic and optimally treated individuals with heart failure with mid-ranged ejection fraction (HFmrEF) and HFrEF (II b; LOE C)

- High-intensity non-competitive sports in selected stable asymptomatic and optimally treated individuals with HFmrEF, with an age-matched exercise capacity beyond average (adapted to the capabilities of the individuals) (Class II b; LOE C)

- High-intensity interval training (HIIT) in low-risk individuals with HFmrEF/HFrEF who want to return to high-intensity aerobic and mixed endurance sports (Class II b; LOE C)

- Competitive sports in selected stable individuals with HFpEF and normal maximal exercise testing (Class II b; LOE C)

Vigorous-intensity resistance training and endurance exercise are not recommended in individuals with heart failure with reduced left ventricular ejection fraction (HFrEF), irrespective of symptoms. (Class III; LOE C). Exercise is not recommended in chronic heart failure (HF) individuals with hypotension or hypertension at rest or during exercise, unstable cardiac disease, deteriorating symptoms of HF, myocardial ischaemia despite therapy (exercise may be permitted up to ischaemic threshold), or severe and sub-optimally treated pulmonary disease.

Optimal exercise training dosing for patients with chronic heart failure could be prescribed according to the following recommendation. (Table 4)

Table 4: Optimal exercise training dosing for patients with chronic heart failure (Adapted from Pelliccia A et al. ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease.)[7]

	Aerobic exercise	Resistance exercise
Frequency	3-5 days/week (optimally daily)	2-3 days/week (balance training daily)
Intensity	40-80% of VO2 peak	BORG Rate of Perceived Exertion < 15 (40-60% of one repetition maximum)
Duration	20-60 minutes	10-15 repetitions in at least 1 set of 8-10 different upper and lower body exercise
Mode	Continuous or interval	-
Progression	A progressively increasing training regimen should be prescribed with regular follow-up controls (at least every 3-6 months) to adjust the duration and the level of the exercise to the reached level of tolerance	

Valvular Heart Disease (VHD)

Sports/Exercise should be considered in patients with VHD under the following settings:

- All recreational or competitive sports in individuals with mild aortic stenosis, mild aortic regurgitation, and mild mitral regurgitation (if desired) (Class I; LOE C)

- All recreational or competitive sports in individuals with mild mitral stenosis (MVA 1.5-2.0 cm^2) with resting systolic pulmonary arterial pressure < 40 mmHg and normal exercise test (Class I; LOE C)

- Low to moderate intensity recreational sports in individuals with moderate aortic stenosis with LVEF >= 50%, good functional capacity and normal BP response during exercise test (II a C)

- All recreational and competitive sports in individuals with moderate aortic regurgitation, with a non-dilated LV with LVEF>50% and normal exercise stress test (Class II a; LOE C)

- All recreational and competitive sports in individuals with moderate mitral regurgitation who fulfill all the following criteria: (II a C)
  - LVEDD < 60 mm or < 35.3 mm/m^2 in men and < 40 mm/m^2 in women
  - LVEF>= 60%
  - Resting systolic pulmonary arterial pressure <50 mmHg
  - Normal exercise test

Competitive or recreational sports/exercise of moderate and high intensity are not recommended in individuals with severe mitral stenosis (mitral valve area < 1 cm^2), severe aortic stenosis, severe aortic regurgitation with LVEF <= 50% and/or exercise-induced arrhythmia. (Class III ; LOE C). Competitive sports participation is not recommended in individuals with severe mitral regurgitation and LVEF < 60%. (Class III ; LOE C)

Cardiomyopathies

Participation in 150 minutes of low-intensity exercise per week in individuals with arrhythmogenic cardiomyopathy and low-to-moderate-intensity recreational exercise in individuals with dilated cardiomyopathy (regardless of the EF, in the absence of limiting symptoms, and exercise-induced ventricular arrhythmia) should be considered. (Class II a; LOE C)

Vigorous-intensity recreational and competitive exercises are not recommended in patients with hypertrophic cardiomyopathy (HCM) #, left ventricular non-compaction (LVNC) * and dilated cardiomyopathy and any of the high-risk features (Class III; LOE C), and arrhythmogenic cardiomyopathy (ACM) (including genotype positive/phenotype negative patients) (Class III; LOE B).

High-risk features in HCM: Cardiac symptoms or history of cardiac arrest or unexplained syncope, moderate ESC risk score (>= 4%) at five years, LVOT gradient at rest > 30 mmHg, abnormal BP response to exercise, exercise-induced arrhythmia). *High-risk features in LVNC: Cardiac symptoms, LVEF < 40% and /or frequent and/or complex ventricular arrhythmia on ambulatory Holter or exercise testing. High-risk

features in DCM: Cardiac symptoms or history of cardiac arrest or unexplained syncope, LVEF < 45%, frequent and/or complex ventricular arrhythmia on ambulatory Holter or exercise testing, extensive late-gadolinium enhancement > 20% on cardiac MRI or high-risk phenotype (Lamin A/C or filamin C)

Myocarditis/Pericarditis

Return to all forms recreational or competitive sports could be considered 3-6 months after diagnosis, in asymptomatic myocarditis individuals, with normal troponin and biomarkers of inflammation, normal LV systolic function on echocardiography and CMR, no evidence of ongoing inflammation or myocardial fibrosis on CMR, good functional capacity, and absence of complex ventricular arrhythmia on ambulatory Holter monitoring or exercise testing. (Class IIa; LOE C) Return to all forms recreational or competitive sports 30 days to three months after diagnosis should be considered in completely recovered acute pericarditis individuals (depending on clinical severity) (Class I; LOE C)

Sports/Exercise are not recommended in patients with myocarditis/pericarditis under the following settings:

- Leisure time or competitive sports in individuals with a probable or definitive diagnosis of recent myocarditis or pericarditis, while active inflammation is present (Class III; LOE C)
- Moderate to high-intensity exercise within the first 3-6 months of acute myocarditis, 1-3 months of acute pericarditis (Class III; LOE B)
- High-intensity leisure exercise or competitive sports in myocarditis individuals with residual myocardial scar and persistent left ventricular dysfunction (Class III; LOE C)
- Moderate to high-intensity exercise in individuals with constrictive pericarditis (Class III; LOE C)

Cardiac Arrhythmia

Among patients with genotype-positive/phenotype-negative long QT syndrome (i.e., QTc < 470/480 ms in men/women), shared decision-making regarding sports participation should be considered taking into account the type and setting of sports (individual vs. team), type of mutation, and extent of precautionary measures. (Class IIa; LOE C).

In patients with paroxysmal supraventricular tachycardia without preexcitation and patients with ventricular ectopics without the familial or structural underlying disease (with periodic evaluation), all competitive and leisure-time sports are recommended. (Class I; LOE C)

Sports/Exercise are not recommended in patients with cardiac arrhythmia under the following settings:

- Intensive sports within two half-lives of anti-arrhythmic (i.e., up to two days) in atrial fibrillation (AF)/atrial flutter patients who took pill-in-the-pocket flecainide or propafenone (Class III; LOE C)
- High-impact sports or sports with high risk of trauma in patients with AF who are anticoagulated (Class III; LOE A)
- High-intensity recreational and competitive sports in long QT syndrome (LQTS) patients (even when on beta-blockers) with a QTc > 500 ms or in genetically confirmed LQTS individuals with a QTc >= 470 ms (in men) or >= 480 ms (in women) (Class III; LOE B)
- Competitive sports in LQTS individuals (with or without implantable cardioverter defibrillator) with prior cardiac arrest or arrhythmic syncope (Class III; LOE C)
- Exercise associated with increase in body core temperature > 39 degree Celsius in individuals with Brugada syndrome or phenotypically negative mutation carrier (Class III; LOE C)
- Sports/exercise in individuals with a history of exercise-induced ventricular tachycardia (not specifically limited to individuals with catecholaminergic polymorphic ventricular tachycardia).

Management of cardiac arrhythmia with respect to exercise/sports participation

- In atrial fibrillation patients, the use of class I antiarrhythmic drugs as monotherapy is not recommended, without proof of adequate rate control of atrial fibrillation/atrial flutter during vigorous exercise. (Class III; LOE C). Participation in sports without antiarrhythmic therapy should be considered in AF individuals without structural heart disease, and in whom AF is well tolerated. (Class IIa; LOE C). Atrial fibrillation ablation is recommended in exercising individuals with recurrent symptomatic AF, and/or in those who do not want drug therapy. (Class I; LOE B). Prophylactic cavo-isthmus dependent atrial flutter ablation should be considered in atrial fibrillation patients who intend to participate in intensive exercise and in whom class I drug therapy is initiated. (Class II a; LOE C)
- Among patients with atrial flutter, cavo-tricuspid isthmus ablation should be considered in those who want to engage in intensive exercise. (Class II a; LOE C)
- In patients with an accessory pathway, ablation of the accessory pathway in competitive and recreational athletes with pre-excitation and documented arrhythmias. (Class I; LOE C). An electrophysiology study is recommended to evaluate the risk for sudden death in competitive/professional athletes with asymptomatic pre-excitation. (Class I; LOE B)

- In competitive athletes with paroxysmal supraventricular tachycardia without pre-excitation, curative ablation should be considered. (Class IIa; LOE C)

- In all exercising patients with long QT syndrome with prior symptoms or prolonged QTc, therapy with beta-blocker at the target dose is recommended. (Class I; LOE B)

SUMMARY

The cardiovascular and general health benefits of exercise far outweigh its risks. Regular exercise in both healthy individuals and most patients with cardiovascular diseases improves the quality of life, reduces mortality and cardiovascular hospitalisation. There are certain patients with cardiovascular disease in whom exercise restriction is recommended: including but not limited to patients with uncontrolled hypertension, unstable coronary artery disease, unstable heart failure, cardiomyopathies with high-risk features, uncontrolled cardiac arrhythmia, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, acute myocarditis and acute pericarditis. Rather than limiting the physical activities of patients with cardiovascular disease (CVD), our role as physicians and cardiologists is to optimise medical or interventional therapies and stabilise patient's cardiovascular conditions, in order to allow the initiation and continuation of the individualised, disease-specific systematic exercise training programme.

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Certificate Course for General Practitioners, Nurses and Health Care Providers who are interested in Cardiology

• Course No. C386 • CME/CNE Course

Certificate Course in

Cardiology 2022

(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong College of Cardiology

Objectives:

This course is designed for General Practitioners, Nurses and Health Care Providers who are interested in Cardiology. A series of lectures covering up-to-date cardiology knowledge and skill in day-to-day clinical practice.

Date	Topics	Speakers
13 Oct 2022	Interpretation of the electrocardiograph Include: - Electrocardiographic interference: Fact or artefact. - The spectrum of ambulatory electrocardiographic monitoring - The electrocardiographic footprints of Wenckebach AV block - The electrocardiograph identification of rhythms requiring cardiac pacing - Identification and interpretation of the normal pacing electrocardiograph	Prof. Harry George Mond Specialist Physician The Royal Melbourne Hospital Associate Professor University of Melbourne Honorary Adjunct Associate Professor Monash University
20 Oct 2022	Overview and application of cardiac Imaging and functional tests in the management of coronary artery disease	Dr. Law Kwan Kin Specialist in Cardiology
27 Oct 2022	Diagnosis of heart failure and management	Dr. Cheng Yue Hong Associate Consultant Pok Oi Hospital Honorary clinical assistant professor CUHK
3 Nov 2022	Cardiovascular disease prevention by diet modification	Dr. Ko Kwok Chun, Jason Specialist in Cardiology
10 Nov 2022	Managing patients on aspirin for primary prevention. Is aspirin a one size fit all therapy?	Dr. Chow Hoi Fan Specialist in Cardiology
	COVID-19: Cardiac manifestation in adults	Dr. Lo Ka Yip, David Specialist in Cardiology
17 Nov 2022	Clinical approach to palpitations and syncope in paediatric patients	Dr. Kwok Sit Yee Consultant Cardiologist Hong Kong Children's Hospital

Dates : 13, 20, 27 October & 3, 10, 17 November 2022 (Thu) (Every Thursday)
Time : 7:00 pm – 8:30 pm
Duration of Session : 1.5 hours (6 sessions)
Course Feature : Video lectures (with Q&A platform for participants to post the questions)
Language Media : English (Supplemented with Cantonese)
Quiz for Doctors : DOCTORS are required to complete a quiz after the completion of each lecture
Course Fee : HK$1,000
Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Deadline : 6 October 2022
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel: 2527 8898 Fax: 2865 0345 Email : vienna.lam@fmshk.org

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Development of Minimally Invasive Cardiac Surgery in Hong Kong

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Dr Daniel TL CHAN

INTRODUCTION

The history of cardiac surgery is relatively short, as compared to other surgical specialties. Cardiac surgery was considered to be beyond the limits of propriety and acceptability in the 19th century, as reflected by a statement made by a surgeon at a meeting of the Vienna Medical Society in 1881 – "No surgeon who wished to preserve the respect of his colleagues would ever attempt to suture a wound of the heart."[1] Operating on the heart was limited to saving victims of cardiac trauma. The survival rate of 40% during the 1890s was remarkable for that period.[2]

Extracardiac procedures were the mainstay of cardiac surgery before 1950. Multiple favourable case reports of patent ductus arteriosus ligation, coarctation repair, Blalock-Taussig shunt for congenital diseases and closed commissurotomy for mitral stenosis for adult rheumatic heart disease aroused an interest in developing different innovative approaches. Cardiac surgery blossomed after the development of the cardiopulmonary bypass machine in 1952, an intraoperative technique which allowed cardiac surgeons to correct a variety of cardiac conditions on a bloodless and motionless surgical field.

Since then, the role of cardiac surgery in managing coronary artery diseases, valvular heart diseases, aortic diseases, congenital heart diseases and heart failure problems has been firmly established. Although mortality and morbidity have been improving in recent decades, cardiac surgery is still labelled as 'high risk', 'big wound surgery', 'traumatic', etc. Most patients and even health care workers would be daunted by its invasiveness.

MINIMALLY INVASIVE CARDIAC SURGERY (MICS)

Over the years, cardiac surgeons have worked hard to find minimally invasive ways to perform various heart surgeries. As a matter of fact, our heart is well protected by a rigid chest wall. A median sternotomy is required to have a clear view of the heart. Further complicating the issue is the need for the cardiopulmonary bypass to allow surgeons to work on an arrested heart. (Fig. 1) This is the reason why cardiac surgery has probably been the last surgical specialty to adopt minimally invasive videoscopic techniques. The attractiveness of videoscopic-assisted minimally invasive surgery developed by general surgeons, gynaecologists and thoracic surgeons in the early 1980s aroused the interest of cardiac surgeons to move towards a smaller wound.

There have been various approaches that claimed to be minimally invasive at that time. To unify and simplify the philosophy of minimally invasive cardiac surgery, The Society of Thoracic Surgeons of the U.S.A. defined minimally invasive cardiac surgery (MICS) in 2003 as 'any procedure not performed with a full sternotomy AND cardiopulmonary bypass support'. In addition, Dr Carpentier and Dr Loulmet recommended the degree of surgical invasiveness of MICS into four levels in 1998 (Table 1).[3] There was a robust investigation of safety and benefits of MICS in the late 1990s and early 2000s. The benefits of MICS compared to conventional sternotomy are summarised in Table 2.[4]

Table 1: Level of surgical invasiveness (Adapted from Soltesz E, Cohn L. Minimally Invasive Valve Surgery. Cardiology in Review: May 2007)

Classification	Invasiveness
Level I	Incision of 10-12cm Direct vision Standard or slight modified cardiopulmonary bypass Standard instruments
Level II	Incision of 6-8cm Direct vision or video-assisted Modified cardiopulmonary bypass Long instruments
Level III	Incision of 4-6cm Video-directed or robotic-assisted Modified cardiopulmonary bypass Special instruments
Level IV	Port-assess Video-directed or robotic-assisted Modified cardiopulmonary bypass Special instruments

Table 2: Benefits of MICS compared to conventional approach (Adapted from P. Modi, et al. Minimally invasive mitral valve surgery: a systematic review and meta-analysis. European Journal of Cardio-thoracic Surgery. 2008(34))

Improved quality of life
Faster recovery and return to normal life
Smaller incision, better cosmetic results, and superior psychological acceptance
Reduction in tissue damage
Reduction in blood transfusion
Reduction in risk of infection
Reduction in pain
Lower global cost

Fig. 1. Clinical photo of a sternotomy and supporting cardiopulmonary bypass machine (Personal collection)

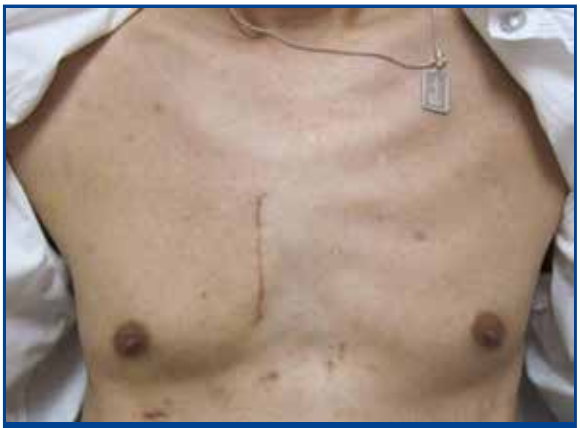

Fig. 2. Clinical photo of a right parasternal wound for mitral valve repair (Personal collection)

Fig. 3. A photo of the East Carolina University Heart Center, North Carolina, U.S.A. and their robotic training facility (Personal collection)

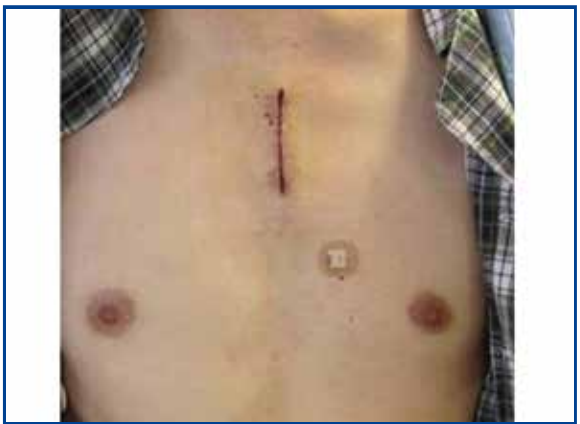

Fig. 4. A clinical photo of a hemi-sternotomy wound (Personal collection)

Fig. 5. A snapshot of the minimally invasive cardiac surgery meeting at Queen Mary Hospital in 2014. Live surgery by Dr KM Chiu and simultaneous lecture by Prof Chitwood (Personal collection)

Fig. 6. Clinical photos showing current MICS approaches at QMH: A) Robotic-assisted surgery and post-op wound. B) Endoscopic-assisted surgery and the wound at one month follow-up (Personal collection)

Fig. 7. Clinical photo showing the QMH Heart Team performing: A) Trans-apical TAVI in a hybrid operating theatre. B) J-valve for severe aortic regurgitation and C) NeoChord procedure for severe mitral valve regurgitation (Personal collection)

KICK START OF MICS IN HONG KONG

In 2007, our enthusiasm for MICS was led by Dr Timmy Au, consultant surgeon and former chief of service. He adopted a right-sided parasternal vertical incision for mitral valve repair. With a half-sized wound and less bone disruption, the surgery went uneventful and the patient was discharged after one week. (Fig. 2) This approach continued to expand to include different indications such as atrial septal defect repair, mitral valve replacement, etc. However, this approach has been criticised for the breaking of the right 3rd and 4th ribs, sacrificing the right internal mammary artery and being more painful than sternotomy wound.[5]

To overcome these problems, we had to advance to a higher level of MICS (Table 1). Level 2 or 3 MICS required the use of a thoracotomy wound without rib cutting. The site of cannulation for cardiopulmonary bypass needed to be moved to the peripheral vessels so as to create more room for operation. A small operating wound required enhanced vision from endoscopy, special surgical instruments and altered anaesthetic and cardiopulmonary bypass strategies. In order to adopt these changes and start a new surgical technique, attending conferences, reading books and journals are important but definitely not enough. Overseas training under experts is mandatory.

Professor Randolph Chitwood is one of the pioneers and the most experienced MICS surgeon in the world. He provided the authors with the necessary hands-on training in the East Carolina University, North Carolina, U.S.A. in 2011. (Fig. 3) It was a fruitful year of training under Professor Chitwood and his team. From more than 100 MICS experience, not only routine and successful operations could be learned, but most importantly the skills in the management of complications were also acquired.

After the authors gained overseas experience, more MICS approaches were undertaken at Queen Mary Hospital after 2012. Hemi-sternotomy for aortic valve replacement and sub-arterial ventricular septal defect repair was performed. (Fig. 4) Right thoracotomy for atrial septal defect and mitral valve replacement followed. We had the pleasure to hold a live case MICS meeting, with the support from the Hospital Authority commissioned training fund in 2014. During the meeting, Professor Chitwood and Dr KM Chiu from Taiwan performed two MICS cases along with the Queen Mary team. (Fig. 5) This wonderful experience strengthened the whole team including surgeons, cardiac anaesthetists, nurses and perfusionists, and encouraged us to work further on minimally invasive approaches.

This enriching experience allowed us to move to level III MICS, which involves a smaller wound, non-rib spreading and a total endoscopic approach that offers less post-operative pain and better cosmesis for our patients. Currently, the standard MICS would be either carried out by endoscopic-assisted or robotic-assisted surgery through a 4-5cm thoracotomy wound. (Fig. 6) Selection criteria were also broadened. Initially, young, straightforward pathology and slim body habitus were the basic suitability requirements. Over time, older patients with complex problems or even redo surgeries can be performed via MICS.

The number of MICS has increased dramatically since 2014. Up to 2021, more than 600 MICS has been performed in Queen Mary Hospital including mitral valve, aortic valve, congenital heart diseases and other concomitant procedures. The mortality in this group was 0.65% and major complications including renal failure and stroke were < 1%.[6] MICS has evolved from a new approach to a standard treatment nowadays. We would make recommendations to patients to undergo MICS whenever their clinical conditions are suitable.

CATHETER-BASED SURGERY

A 3-4cm thoracotomy probably is the smallest wound size in open-heart surgery. The use of cardiopulmonary bypass, although very safe nowadays, creates certain invasiveness and risk in the surgery. In order to further minimise the invasiveness of cardiac surgery, we need to explore endovascular or transcatheter procedures. A good example is transcatheter aortic valve implantation (TAVI). It was first successfully performed in an aortic stenosis patient in 2001 and raised huge interest in this technique. Numerous investigators reported the feasibility of this technique, promptly acknowledged its superiority in treating high-risk patients, and now even confirmed its non-inferiority to standard aortic valve replacement in moderate and low-risk patients.

TAVI programme for aortic stenosis commenced in 2012 at Queen Mary Hospital and up to now almost 400 cases have been performed. Although the development was fast and fruitful, the most successful achievement was the formation of a 'Heart Team' - comprising cardiac surgeons, cardiologists, cardiac anaesthesiologists and specialty nurses. The combined experience and expertise brought us to a new horizon of hybrid treatment of different cardiac diseases. Cardiac surgeons are not just a 'backup' for disastrous situations, but are also actively involved in performing catheter procedures. The setting up of the Heart Team has allowed the TAVI programme to involve patients who have difficult vascular access or complex clinical scenario.

The Heart Team members always strive for applying new technologies and obtaining better patient outcomes. In 2018, our team went to Mainland China, Germany and the Netherlands for training in the use of various new devices. A second-generation TAVI device named J-Valve was introduced. Its special clipping features can complement the current TAVI device in treating aortic regurgitation. Another catheter-based mitral valve repair system called the NeoChord device was also implemented for selected patients. Both novel devices involved a trans-apical approach and a heart team collaboration.(Fig. 7) Since then, wider patient coverage with more minimally invasive options has been achieved.

THE FUTURE PROSPECTIVE

The treatment profile of cardiac diseases is shifting towards catheter-based treatment. No less than 30 new devices are under investigations worldwide. However, conventional cardiac surgery is still the gold standard in many aspects. The attractive minimalism of catheter treatment may not be equal to optimal treatment. One of the examples is using TAVI in young and fit aortic stenosis patients. Recent meta-analysis suggested the benefits of TAVI are superseded by higher mortality and re-intervention after six months as compared to surgical aortic valve replacement.[7] Nevertheless, the choice of a suitable treatment for a particular patient is the utmost important role of cardiac surgeons nowadays. Catheter training and experience have to be incorporated into training curriculums in order to keep up with the constantly evolving trend.

CONCLUSION

Minimally invasive surgery is a philosophy aiming to minimise the damage caused by surgery. It was adopted late in cardiac surgery due to the need of a good exposure and cardiopulmonary bypass. However, the evolution was fast with endoscopic and robotic technologies in the last two decades. Transcatheter treatment was a strong force that pushed the development even faster. Cardiac surgeons had to work hard to keep up with technologies, so as to play a key role in operating, selecting patients, ensuring quality and working as a team player in Heart Team.

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The Joy of Collecting

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Most kids love collecting. Even toddlers collect tiny diecast model cars, especially boys as early as one to 1½ old. Young girls perhaps are less passionate about collecting cars and they seem to be content with holding onto one or more rag dolls or other stuffed toys, teddy bears, for instance. Young children collect because collecting gives them a sense of identity and a sense of accomplishment! As their collection grows, their superiority complex grows, the more they want to possess more than their friends! There is educational value as well, as the process of collecting toys helps a child satisfy his or her curiosity, and some experts are of the opinion that collecting helps a child learn, satisfy his or her curiosity and it may even be therapeutic as it relieves stress, and fine-tunes their motor skills and hand-eye-coordination.

Many adults collect art and antiques for a variety of reasons. Some do so because it fulfils the need for relaxation, enhances one's sense of accomplishment and enriches one's quality of life. Many of my learned medical colleagues are big-time collectors. I began collecting antique Chinese objets d'art about 30 years ago, after receiving one jade pendant as a gift from a close friend who had been collecting Chinese jades for decades. He took me to antique shops on Saturday afternoon, and I began to purchase a few jade pieces at antique shops on Hollywood Road. I had little knowledge about ancient Chinese jade or other antiques then, but each item acquired prompted me to find out the story behind each antiquity, along with the history of a particular item. I therefore bought a lot of books written on the subject and became a frequent visitor to local museums.

I began museum hopping every time I travelled to major cities in China, like the National Museum of China and the Museum of History, the Shanghai Museum, Shaanxi Museum etc. I enjoyed going to Cardiology Meetings anywhere because I could slip away for half a day or so to major museums in China, Europe and the United States. My favourite ones are the British Museum Oriental Section, the Harvard Sackler Museum and the Winthrop Collection, where one can see many fine pieces of great Chinese Antique Jade Artefacts. I began to learn more and more about antique Chinese jade by reading as well as going to these museums. I was determined to know as much as the antique shop owners, if not more. They obviously do possess tremendous knowledge about the antiques in their shops simply by learning in their trade and by sheer experience, but their primary objective is to sell, and as quickly as possible. However, as a buyer, my objective is to acquire an antique item in order to enhance my appreciation of the antique item. For that matter, I try not to fall into the trap of buying a non-authentic piece!

Almost 30 years ago, a senior cardiologist colleague took me to an antique shop in Beijing Antique Market right after a cardiological conference, where a few Song Dynasty Ceramics caught our eyes. With much trepidation and some encouragement from my colleague, I could not resist the chance of buying a monochrome glazed ceramic ware (Fig. 1). I began to do some research by reading plenty of books written by experts on the subject. The more I read, the more I began to appreciate the aesthetic sophistication of Song Ceramic wares: Ru (汝), Guan (官), Ge (哥), Jun (均), Ding (定), which were, by Royal Appointment, patronised by the Imperial court, and much praised and appreciated by scholars and collectors in subsequent dynasties, even today! It was in Beijing and Shanghai where I also acquired a few antique wooden Zitan"紫檀" and Huanghuali "黃花梨" wooden medicine boxes, Guanpixiang "官皮箱", brushpots "筆筒", and I have loved every piece since! I dared not buy antique Zitan and Huanghuali large furniture, because I simply had difficulty storing them. I wish I did and I sometimes regret having missed the opportunity of acquiring Zitan or Huanghuali yoke back 南官帽椅 armchairs, Huanghuali long-tables with everted ends 翹頭案 etc. Now they are too expensive for me!

Fig. 1: Monochrome glazed ceramic ware (Personal collection)

I have tried to stick to the following principles when I purchase an antique, though I must admit I sometimes falter:

- Never buy any item beyond my means

- Try hard not to rush into buying before studying an item according to the conformation, texture and surface characteristic (for instance, the characteristic iridescence consistent with the age of a jade artefact which had been buried for centuries), the carving and workmanship
- Try not to believe in everything the vendor tells me
- Read a lot of books written on the subject, just like I do when I am confronted with a difficult medical problem!

ANCIENT CHINESE JADE

Now I must go back to write more about ancient Chinese jade, which remains my principal area of interest. Ancient Chinese jade is fascinating. The word 'jade' comes from the Spanish term "piedra de ijada", which means colic stone or stone of the flank, as even the ancient Greek/Latin men believed that jade carried a mythical healing power, especially for kidney and loin ailments, colicky pain from kidney or ureteral stone as presumably the Greeks and Romans loved drinking a lot of wine! In ancient China, people believed that wearing jade could ward off evil spirits and could cure diseases, and the royal and rich class of people placed jade items in burial sites, believing and hoping they could have a better next life. To some extent, jade reflects many Chinese beliefs and values, and jade has been intertwined with the philosophy of ancient rulers and scholars.

The earliest jade artefacts were excavated and more recently, scientifically so in the last century. It is now established that jade artefacts existed pre-historically, as evidenced by excavated finds in:

- Hongshan Culture 紅山文化 (BC 4000 to BC 2500)
- Liangzhu Culture 良渚文化 (BC 3500 to BC 2100)
- Longshan Culture 龍山文化 (BC 3000 to BC 2000)

A large number of jade artefacts from the prehistoric or late Neolithic period have been found according to the specific region. Those excavated from the Northeastern part of China, i.e. the western part of Liaoning to the easternmost part of Inner Mongolia are called Hongshan jade. Fig. 2 shows a typical and perhaps iconic jade dragon "玉豬龍" which is believed to be a symbol of fertility and wealth. Another Hongshan jade is the jade eagle "玉鷹" (Fig. 3) . The eagle is symbolic of the mythical bird, the only animal that could fly and hence act as a messenger between heaven and earth. Such was presumably the ancient belief of people in ancient China!

Fig. 2: Iconic Hongshan jade dragon "玉豬龍" (Personal collection)

Fig. 3 :Hongshan Jade Eagle "玉鷹" (Personal collection)

A good example of a Liangzhu jade is shown in Fig. 4. It is a Liangzhu Cong "良渚琮" an icon for Liangzhu and believed to represent the earth. It is square on the outside and round on the inside. The Liangzhu people believed that the earth was flat and square, while the sky was round. Fig. 5 shows a plaque with the Liangzhu emblem: a mythical god-humanoid figure on top representing divine power while a beast-like being lies below. Some researchers believe this represents the tripartite relationship between divine power ruling human beings in the middle while all other animals are at the bottom rank.

Fig. 4: Liangzhu Cong "良渚琮" (Personal collection)

Fig. 5: Plaque with the Liangzhu emblem (Personal collection)

From excavated jade artefacts, we are now able to see rapid development in jade over the centuries as members of the royal family, as well as the rich and noble class, were very fond of collecting and wearing a jade of their liking. A scholarly gentleman always carried a jade pendant "君子無故，玉不去身" to remind him of the five virtues of jade: benevolence, righteousness, courtesy, wisdom, faith (仁, 義, 禮, 智, 信) which were exactly those expected of a true gentleman.

I am not going to repeat what I wrote in the two articles published in the Hong Kong Medical Diary in 2008 and 2011, but I do want to share with the reader some of my collected "personal treasures" of the Western Zhou (1100 BC to 771 BC), Spring and Autumn (770BC to 475 BC), Warring States to Han 475 BC to AD 220 which are definitely my favourites.

This is a Shang to Western Zhou bowl (Fig. 6) with a cover lid. Two dragons are seen at the base and three frogs are on the lid. The workmanship is simply amazing. The next jade shown in Fig. 7 is a Warring-States winged wine cup "玉羽觴". One is expected to politely hold the two wings on each side of the cup when saluting a king or host to show respect. The next jade is an exquisite round jade container with a covering lid and a base. The round box sits neatly on the tri-legged base, while the lid fits perfectly with the container. Five dragons are seen on top of the cover lid, and another three on base, each below a taotie "饕餮" motif (Fig. 8). This, in my opinion, totally reveals the superior craftsmanship of the Warring States to the Western Han era. I once tried to see if the cover lid fitted well with the container by pouring water into the latter, putting the lid on top, then turning it upside down and shaking it a few times, and no water dripped out. Another jade container (Fig. 9) is seen with a lid

cover, and this was probably designed for storing valuable jewellery or herbal pills! A Han Dynasty jade spoon is shown in Fig. 10, and a jade Yi "玉匜" with a spout for pouring medicine into the mouth (Fig. 11).

Fig. 6: Shang to Western Zhou bowl with a cover-lid (Personal collection)

Fig. 7: Warring-States period winged cup "玉羽觴" (Personal collection)

Fig. 8: Exquisite Han round jade container with a covering lid and a base (Personal collection)

Fig. 9: Valuable Han jewelry or herbal pills jade container (Personal collection)

Fig. 10: Han Dynasty jade spoon (Personal collection)

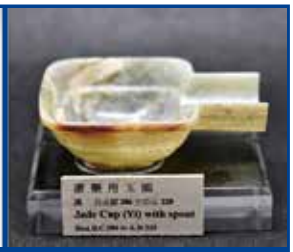

Fig 11: "玉匜" jade spoon with a spout for pouring medicine into the mouth (Personal collection)

The Bi-Xie "辟邪" in Fig. 12 is not made of jade but rather turquoise, which is also considered a precious stone, much coveted by collectors even today, and one can compare this with another made of Xinjiang white jade (Fig. 13).

Fig. 12: Turquoise Bi-Xie "辟邪" (Personal collection)

Fig 13: Xinjiang White jade Bi-Xie "辟邪" (Personal collection)

I will skip Six Dynasties, Sui, Tang and Song to Ming/Qing Dynasty jade. However, I do want to show a Ming Huanghuali Medicine Box (Fig. 14), which was purchased in Beijing, and an Arabic Medicine Grinder, which I bought in Morocco, Fig. 15. Lastly, an interesting wooden box covered with tortoiseshell skin dedicated to Yan Fu "嚴復" is shown in Fig. 16. Yan Fu translated many books of the western world, e.g. Thomas Huxley's Evolution of the Species, (天演論) based on the "On the Origin of Species" by Charles Darwin" into Chinese, and he was one of the founders of Beijing University (or the precursor of), Fudan University and Tsinghua university in the early part of the 20th century.

My journey into collecting antiques has been a fruitful learning experience, and this passion of mine has not dwindled. One important thing I have learnt after 30 years is that I remain a humble student!

Fig. 14: Ming Huanghuali Medicine Box (Personal collection)

Fig. 15: Arabic Medicine Grinder (Personal collection)

Fig. 16: Wooden box covered with tortoiseshell skin dedicated to Yan Fu "嚴復" (Personal collection)

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				★Zoom Live Two Common GI Problems In Frail Elderly - Online ★Certificate Course on Renal Medicine 2022 (Video Lectures) **1**	**2**	**3**
★LI SHU PUI SYMPOSIUM 2022: 100 Years of Medical Service in Hong Kong - Yesterday, Today and Tomorrow **4**	**5**	★Certificate Course in Ophthalmology 2022 (Video Lectures) **6**	★Zoom Live Optimal Management for Asthma Patients - from Evidence to Action - Online ★Certificate Course on Respiratory Medicine 2022 (Video Lectures) **7**	★Zoom Live Combination of Antidepressant and Opioid Antagonist - New Role in Weight Management - Online ★Certificate Course on Renal Medicine 2022 (Video Lectures) ★Zoom Live Webinar Update on the Management of Atopic Dermatitis **8**	★Zoom Live Patient Counselling on Family Planning - Online **9**	**10**
11	**12**	★Zoom Live Updates in Stroke Management - Online ★Certificate Course in Ophthalmology 2022 (Video Lectures) **13**	★The Hong Kong Neurosurgical Society Monthly Academic Meeting -To be confirmed ★Certificate Course on Respiratory Medicine 2022 (Video Lectures) **14**	★Certificate Course on Renal Medicine 2022 (Video Lectures) **15**	★Zoom Live Update on the Management of Moderate to Severe Orthopedic Pain - Online **16**	**17**
18	★Zoom Live COVID-19 Vaccination Safety And Effectiveness For Pregnant And Lactating Women - Online **19**	★In-person / Zoom HKMA-GHK CME Programme 2021-2022 Topic: Updated Therapy In Gynecological Cancers and Hysterectomy (Physical + Online) ★Certificate Course in Ophthalmology 2022 (Video Lectures) **20**	★Certificate Course on Respiratory Medicine 2022 (Video Lectures) **21**	★Zoom Live Certificate Course for GPs 2022 - Updates on Management of Heptitis B - Online ★Zoom Live Optimal Management of BPH - Online ★Certificate Course on Renal Medicine 2022 (Video Lectures) ★FMSHK Executive Committee Meeting **22**	★Zoom Live Acute Diarrhea Management In Pediatric Patients - Online **23**	**24**
25	**26**	**27**	★Certificate Course on Respiratory Medicine 2022 (Video Lectures) **28**	★Certificate Course on Renal Medicine 2022 (Video Lectures) ★Zoom Live Covid-19 Vaccination in Adolescents and Children - the Hong Kong Experience **29**	★Zoom Live COVID-19 Vaccination for Infants, Children and Adolescents - Online **30**	

Date / Time	Function	Enquiry / Remarks
1 THU 2:00 PM	**Zoom Live** **Two Common GI Problems In Frail Elderly – Online** Organiser: Hong Kong Medical Association Speaker: Dr James Ka-hay LUK	HKMA CME Dept. 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Renal Medicine 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Ronald LIN & Dr Chun-hay TAM	Ms Vienna LAM Tel: 2527 8898
4 SUN 8:50 AM	**LI SHU PUI SYMPOSIUM 2022: 100 Years of Medical Service in Hong Kong – Yesterday, Today and Tomorrow** Organiser: Hong Kong Sanatorium & Hospital LSP Lecture Speaker: Prof Gabriel LEUNG Venue: Ballroom, JW Marriott Hotel Hong Kong or Zoom Webinar	Hong Kong Sanatorium & Hospital www.hksh.com/lsp2022
6 TUE 7:00 PM	**Certificate Course in Ophthalmology 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr LAM Stacey Carolyn & Dr Bonnie Nga-kwan CHOI	Ms Vienna LAM Tel: 2527 8898
7 WED 2:00 PM	**Zoom Live** **Optimal Management for Asthma Patients - from Evidence to Action – Online** Organiser: HKMA-Central, Western & Southern Community Network Speaker: Dr KWOK Yuk-lung	Ms Daphne LO 3108 2514 1 CME Point
7:00 PM	**Certificate Course on Respiratory Medicine 2022 (Video Lectures)** Organiser:The Federation of Medical Societies of Hong Kong Speaker: Dr Ka-ping CHAN	Ms Vienna LAM Tel: 2527 8898
8 THU 2:00 PM	**Zoom Live** **Combination of Antidepressant and Opioid Antagonist - New Role in Weight Management – Online** Organiser: HKMA-KLN East Community Network Speaker: Dr Michelle Yin-ting NG	Ms Daphne LO 3108 2514 1 CME Point
7:00 PM	**Certificate Course on Renal Medicine 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Jason IP & Dr Gensy Mei-wa TONG	Ms Vienna LAM Tel: 2527 8898
7:30 PM	**Zoom Live Webinar** **Update on the Management of Atopic Dermatitis** Organiser: Hong Kong Chinese Medical Association Ltd. Speaker: Dr Kacey Kwun-cheung HAU	HKCMA Ms Stone Tse 2527 8898 1 CME Point
9 FRI 2:00 PM	**Zoom Live** **Patient Counselling on Family Planning - Online** Organiser: HKMA-Shatin Community Network Speaker: Dr CHAN On-yee	Ms Candice TONG 3108 2513 1 CME Point
13 TUE 2:00 PM	**Zoom Live** **Updates in Stroke Management – Online** Organiser: HKMA-YTM Community Network Speaker: Prof Alexander Yuk-lun LAU	Ms Candice TONG 3108 2513 1 CME Point
7:00 PM	**Certificate Course in Ophthalmology 2022 (Video Lectures)** Organiser:The Federation of Medical Societies of Hong Kong Speaker: Dr Frank Hiu-ping LAI	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: Dr XIAO Xiao	Dr Calvin MAK 1.5 CME Point 2595 6456
7:00 PM	**Certificate Course on Respiratory Medicine 2022 (Video Lectures)** Organiser:The Federation of Medical Societies of Hong Kong Speaker: Dr Macy LUI	Ms Vienna LAM Tel: 2527 8898
15 THU 7:00 PM	**Certificate Course on Renal Medicine 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Ms Cherry Pui-yee LAW & Dr Desmond Yat-hin YAP	Ms Vienna LAM Tel: 2527 8898
16 FRI 2:00 PM	**Zoom Live** **Update on the Management of Moderate to Severe Orthopedic Pain - Online** Organiser: HKMA-KLN City Community Network Speaker: Dr LEE Sung-yee	Ms Candice TONG 3108 2513 1 CME Point
19 MON 2:00 PM	**Zoom Live** **COVID-19 Vaccination Safety And Effectiveness For Pregnant And Lactating Women - Online** Organiser: Hong Kong Medical Association Speaker: Dr Ernest Hung-yu NG	HKMA CME Dept. 3108 2514 1 CME Point
20 TUE 2:00 PM	**In-person / Zoom** **HKMA-GHK CME Programme 2021-2022** **Topic: Updated Therapy In Gynecological Cancers and Hysterectomy (Physical + Online)** Co-organiser: Hong Kong Medical Association & Gleneagles Hong Kong Hospital Speaker: Dr NG Tong-yow Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong	HKMA CME Dept. 3108 2507 1 CME Point
7:00 PM	**Certificate Course in Ophthalmology 2022 (Video Lectures)** Organiser:The Federation of Medical Societies of Hong Kong Speaker: Dr MOHAMED Shaheeda & Dr Nancy Shi-yin YUEN	Ms Vienna LAM Tel: 2527 8898
21 WED 7:00 PM	**Certificate Course on Respiratory Medicine 2022 (Video Lectures)** Organiser:The Federation of Medical Societies of Hong Kong Speaker: Dr Alvin CHOI	Ms Vienna LAM Tel: 2527 8898

Date / Time	Function	Enquiry / Remarks
22 THU 2:00 PM	**Zoom Live** **Certificate Course for GPs 2022 - Updates on Management of Heptitis B - Online** Co-organisers: HKMA-KLN East Community Network, HA-United Christian Hospital & HK College of Family Physicians Speaker: Dr SAKHRANI Navin	Ms Judy YU 3949 3043 1 CME Point
2:00 PM	**Zoom Live** **Optimal Management of BPH - Online** Organiser: HKMA-HK East Community Network Speaker: Dr CHENG Kwun-chung	Ms Candice TONG 3108 2513 1 CME Point
7:00 PM	**Certificate Course on Renal Medicine 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Andrew LUK & Dr Joseph Ho-sing WONG	Ms Vienna LAM Tel: 2527 8898
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong Venue: Council Chamber, 4/F,DukeWindsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
23 FRI 2:00 PM	**Zoom Live** **Acute Diarrhea Management In Pediatric Patients – Online** Organiser: Hong Kong Medical Association Speaker: Dr TSANG Wing-yan	HKMA CME Dept. 3108 2507 1 CME Point
28 WED 7:00 PM	**Certificate Course on Respiratory Medicine 2022 (Video Lectures)** Organiser:The Federation of Medical Societies of Hong Kong Speaker: Dr Johnny Wai-man CHAN	Ms Vienna LAM Tel: 2527 8898
29 THU 7:00 PM	**Certificate Course on Renal Medicine 2022 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Maggie MA & Dr Wing-fai PANG	Ms Vienna LAM Tel: 2527 8898
7:30 PM	**Zoom Live** **Covid-19 Vaccination in Adolescents and Children - the Hong Kong Experience** Organizer : Hong Kong Chinese Medical Association Ltd Speaker : Prof LAU Yu-lung	HKCMA Ms Stone Tse 2527 8898 1 CME Point
30 FRI 2:00 PM	**Zoom Live** **COVID-19 Vaccination for Infants, Children and Adolescents – Online** Organiser: Hong Kong Medical Association Speaker: Dr Emily Chi-wan HUNG	HKMA CME Dept. 3108 2507 1 CME Point

Certificate Course for Medical and Healthcare Professionals ● **Course No. C385** ● **CME/CNE Course**

Short Course in

Clinical Toxicology 2022

(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society for Emergency Medicine and Surgery

Date	Topics	Speakers
11 October 2022	Poisons in Food and Water	Dr. NG Hon Wah Tseung Kwan O Hospital
18 October 2022	Toxicities of Chinese Medicine	Dr. FUNG Hin Tat Tuen Mun Hospital
25 October 2022	Common Pharmaceutical Drug Poisonings	Dr. LEUNG Siu Chung, Patrick Department of Emergency Medicine School of Clinical Medicine The University of Hong Kong
1 November 2022	Poisons in the Household	Dr. CHAN Chi Keung Hong Kong Poison Information Centre
8 November 2022	Abusive Drug	Dr. CHOW Tin Yat Hong Kong Poison Information Centre
15 November 2022	Venomous Animals in Hong Kong	Dr. WONG Oi Fung North Lantau Hospital

Dates : 11, 18, 25 October & 1, 8, 15 November 2022 (Every Tuesday)
Time : 7:00 pm – 8:30 pm
Course Feature : Video lectures (with Q&A platform for participants to post the questions)
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$1,000
Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel: 2527 8898 Fax: 2865 0345 Email : vienna.lam@fmshk.org

Online Application from website: http://www.fmshk.org

Answers to Dermatology Quiz

Answers:

1. Darier disease (Keratosis follicularis)

   Darier disease is an autosomal dominant genodermatosis characterised by greasy hyperkeratotic papules in the seborrhoeic area, typical nail abnormalities, and mucous membrane lesions.

   The differential diagnoses include Seborrhoeic dermatitis, Familial benign pemphigus (Hailey-Hailey Disease), Acrokeratosis verruciformis of Hopf, and Transient acantholytic dermatosis.

2. Nail changes provide important diagnostic clues. A sandwich of red and white longitudinal bands, together with a V-shaped nick at the free margin of the nail, is the most pathognomonic nail finding in this disease. Palmar pits are also useful supporting features in the diagnosis.

3. Skin biopsy should be done to establish the diagnosis. Acantholysis (loss of epidermal adhesions) and dyskeratosis (abnormal premature keratinisation) are the two typical findings in histopathology. If available, gene sequencing can confirm the diagnosis by demonstrating *ATP2A2* mutations.

4. Unfortunately, there is no cure for this genodermatosis. Genetic counselling should be provided concerning its hereditary pattern. Most patients have a family history of this autosomal dominant disease. However, a negative family history, such as in this patient, does not exclude the diagnosis as it may represent sporadic mutations.

   Psychological counselling is often necessary as psychosocial consequences from the appearance and odour of the lesions are common, often associated with neuropsychiatric abnormalities as well.

   Sun protection should be advised as ultraviolet light often aggravates the symptoms of itchiness and pain.

   Treatment of secondary infections should be prompted as there is increased susceptibility to cutaneous bacterial and viral infections, especially the herpes simplex virus.

   Emollients with urea or lactic acid can reduce scaling and hyperkeratosis, thus alleviate the symptoms.

   Oral retinoids such as acitretin or isotretinoin have been the most effective medical treatment in this disease. Though not curative, they can significantly improve the lesions.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology and Venereology

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

Annual Scientific Meeting 2022

Innovations in Disease Diagnosis and Management

Date: 16 October 2022 (Sunday) **Time:** 09:00 - 17:00 **Format:** Hybrid
Venue: 3/F & 4/F, Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Tsim Sha Tsui, Kowloon
(Pending COVID situation, limited seats available)

Save the date!
We look forward to seeing you soon!

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↓31% **All-cause mortality vs placebo**
(HR 0.69; 95% CI, 0.53, 0.88; p=0.004)[2]

↓29% **Composite of CV death or hHF vs placebo**
(HR 0.71; 95% CI, 0.55, 0.92; p=0.009)[2]

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