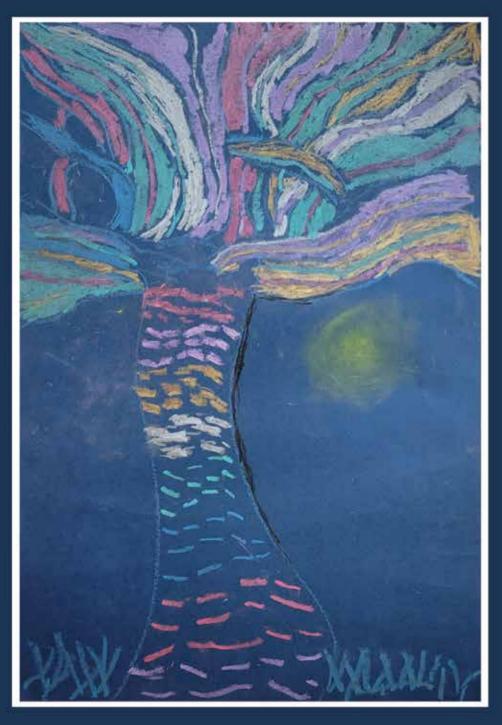


## THE HONG KONG 香港醫訊 MEDICAL DIARY

VOL.28 NO.11 November 2023

## Clinical Pharmacology







## STRUGGLING TO CONTROL ELEVATED LDL-C? \*







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† vs placebo on top of maximally tolerated statins, with or without other oral lipid-lowering therapies. An up to 17% LDL-C reduction on top of maximally-tolerated statin therapy with around 50% of studied patients on high intenisty statins. An up to 28% LDL-C reduction was observed in patients on no statin, very low-intensity or low-intensity statin therapy, with or without other non-statin lipid lowering therapies. ‡ vs placebo on top of maximally tolerated statins.7

1. Nilemdo Hong Kong Package Insert Mar 2023. 2. Nustendi Hong Kong Package Insert Mar 2023. 3. Goldberg AC et al. JAMA. 2019; 322(18): 1780-1788. 4. Ray KK et al. N Engl J Med. 2019; 380: 1022-1032. 5. Laufs U et al. JAm Heart Assoc. 2019; 8:e011662. 6. Ballantyne CM et al. Atherosclerosis. 2018; 277: 195-203. 7. Ballantyne CM et al. Eur J Prev Cardiol. 2020; 27(6): 593-603.

#### Abbreviated Prescribing Information

Nilemdo (bempedoic acid) tablets 180 mg. Indications: Nilemdo is an adenosine triphosphate-citrate lyase (ACL) inhibitor indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. Dosage and Administration: Administer 180 mg orally once daily with or without food. Contraindications: None.

Warnings and Precautions: Hyperuricemia: May increase blood uric acid levels. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. Tendon Rupture: Nilemdo is associated with an increased risk of tendon rupture or injury. Discontinue Nilemdo at the first sign of tendon rupture. Avoid Nilemdo in patients who have a history of tendon disorders or tendon rupture. Pregnancy and lactation. Adverse Reactions: Most common: upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. Others include tendon rupture, gout, benign prostatic hyperplasia, atrial fibrillation. **Drug Interactions:** Simvastatin: Avoid concomitant use of Nilemdo with simvastatin greater than 20 mg. Pravastatin: Avoid concomitant use of Nilemdo with pravastatin greater than 40 mg. Version: Mar 2023.

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Dr Will YH CHAN

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#### The Cover Shot



The front cover features "The Tree of Life", drawn by Matthew, aged 9. Many of the modern drugs that we use today are derived from plants-digoxin from Digitalis purpurea or the common foxglove; phlorizin in the apple bark is a natural sodium glucose co-transporter inhibitor. Aspirin or acetyl-salicylic acid was derived from salicin in the willow bark. Plants may hold the key to new drugs that are waiting to be discovered. We have recently witnessed a series of climate catastrophes from wildfires that have burnt down islands, cities that floods have swept away. This lone tree is a symbolic reminder of our duty to protect our fragile environment and safeguard it for future generations.

The Tree of Life
Mr Matthew CHIU



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#### **Editorial**

#### **Prof Elaine CHOW**

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Issue Editor



We have experienced an unprecedented pandemic on a global scale that has touched everyone's lives. As we recover from the COVID-19 pandemic, we reflect on the lessons learnt. The pandemic has forced us to re-examine the complex interrelationships between man, nature and science. Vaccines and drugs against COVID-19 were developed, tested, approved, and applied clinically at previously unthinkable speeds. At the same time, we observed scepticism and mistrust in science, pharma and politics while vast quantities of health-related information, sometimes false, were propagated through the internet and social media at lightning speed.

Clinical pharmacology rests at the interface between drug discovery, drug development and implementation. Armed with knowledge of the pharmacology and mechanisms of actions of new compounds, it is the duty of clinical pharmacologists to make sure drugs are adequately tested for safety in humans. However, it is still taking months to years for most new drugs to become accessible to the patient. We have seen growing numbers of guidelines and consensus documents that quickly recommend new treatments. Nevertheless, the "implementation gap" remains significant in many areas of medicine. Considerations of costeffectiveness and equitable access to drugs are also within the remit of clinical pharmacologists.

In this issue, Prof Juliana Chan will discuss the importance of clinical trials and how everyday clinicians should be involved in research, without which medicine cannot advance. The ultimate benefits to the patient, clinicians and the healthcare system outweigh short-term time and cost investments. While statins are probably the single most important drug accounting for the significant decline in cardiovascular disease in the past decade, we now have alternatives such as bempedoic acid and newer modalities that push lipid-lowering to new boundaries. Prof Brian Tomlinson will take us through the latest advances in lipidlowering therapies. Similarly, we have seen glucagon-like-peptide 1 based therapies evolve from single to potent multi-agonists, which can achieve up to 20 % body weight loss. Dr Paul Lee will share some landmark trials and safety data for this emerging class of antiobesity drugs. Finally, Dr Will Chan will highlight the anti-arrhythmic potential of many commonly encountered drugs and management tips.

As the Editor of this issue, I hope this collection of articles will inspire our readers on the relevance of clinical pharmacology to all walks of medicine. "The Tree of Life", featured the front cover of this issue, reminds us of the plant-based origins of many of our drugs. It also reminds us of our duty to educate and nurture future generations. Last but not least, I would like to thank all the authors for their contributions and industrial partners for their unfailing support.





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### **Recent Advances in Lipid Therapy**

#### **Prof Brian TOMLINSON**

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Prof Brian TOMI INSON

Prof Elaine CHOW

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 November 2023.

#### INTRODUCTION

Several new therapeutic agents have been developed to target lipid disorders in recent years. These include not only oral treatments and combinations of oral drugs, but also the new approaches with monoclonal antibodies (mAbs) and RNA based therapeutics with antisense oligonucleotide (ASO) and small interfering RNA (siRNA) compounds (Fig. 1)¹.

Low-density lipoprotein cholesterol (LDL-C) remains the primary target for lipid treatment<sup>2</sup>, but it has been recognised that the remnant cholesterol carried in triglyceride-rich lipoproteins (TRLs) also contributes to atherosclerosis and lipolysis of triglycerides may result in inflammatory or thrombotic effects3. Non-highdensity lipoprotein cholesterol (non-HDL-C) includes the cholesterol carried in TRLs and is considered an alternative or secondary target for treatment. Triglyceride levels of < 1.7 mmol/L (150 mg/dL) are considered to indicate lower cardiovascular (CV) risk, and this corresponds to a remnant cholesterol level of 0.8 mmol/L so the target for non-HDL-C can be calculated by adding 0.8 mmol/L to the LDL-C target (Table 1)<sup>4</sup>. Apolipoprotein B (apoB) levels provide an alternative treatment target which is more representative of the total number of atherogenic particles.

## Table 1. Corresponding non-high-density lipoprotein cholesterol and apolipoprotein B levels for commonly used low-density lipoprotein cholesterol goals<sup>4,5</sup>.

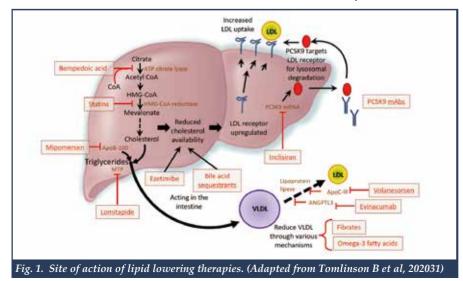
| Cardiovascular risk | LDL-C                     | Non-HDL-C                 | Apolipoprotein B |
|---------------------|---------------------------|---------------------------|------------------|
| Moderate            | 2.6 mmol/L<br>(100 mg/dL) | 3.4 mmol/L<br>(131 mg/dL) | 100 mg/dL        |
| High                | 1.8 mmol/L<br>(70 mg/dL)  | 2.6 mmol/L<br>(100 mg/dL) | 80 mg/dL         |
| Very high           | 1.4 mmol/L<br>(55 mg/dL)  | 2.2 mmol/L<br>(85 mg/dL)  | 65 mg/dL         |

Non-HDL-C = non-high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

For triglycerides, < 1.7 mmol/L (150 mg/dL) is considered to indicate lower risk.

## TREATMENT FOR LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Statins remain the first line treatment to reduce LDL-C and CV risk, and if moderate or high dose statin is not sufficient to achieve LDL-C goals, lipid guidelines recommend adding ezetimibe<sup>5</sup>. Statins are a very safe group of medications. The serious side effect of severe myopathy or rhabdomyolysis is very uncommon. It is usually associated with the use of excessive doses inappropriate for the patient or drug interactions, which occur mainly with simvastatin and other



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drugs which inhibit cytochrome P450 (CYP) 3A4/5 and interact with simvastatin and to a lesser extent atorvastatin6. Gemfibrozil inhibits drug transporters, CYP2C8 and glucuronidation pathways and interacts with most statins. Cyclosporine shows greater interactions through CYP enzymes and transporters. An appropriate maximum dose of statin should be chosen for individual patients. Plasma concentrations of rosuvastatin are twice as high in Chinese and Japanese patients compared to Caucasians, and the 40 mg dose of rosuvastatin was not approved in Japan, China or Korea and we suggest it should be avoided in all Chinese populations. For simvastatin, there is a recommendation from the clinical pharmacogenomics implementation consortium to perform genotyping for solute carrier organic anion transporter family member 1B1 (SLCO1B1) if doses of more than 20 mg are expected to be used, but this is not often done<sup>7</sup>. It may be safer and more effective to add ezetimibe to a moderate intensity statin dose rather than using the maximum approved statin dose.

Treatments to reduce LDL-C that have the final effect of increasing expression of the LDL receptors (LDLRs) include statins, ezetimibe, and proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors (Table 2). Recently, bempedoic acid has been approved in the U.S. and Europe. Bempedoic acid Inhibits ATP-citrate lyase (ACLY), an enzyme upstream of 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase, the target of statins, in the cholesterol synthesis pathway. It is administered as an oral prodrug that is activated in the liver, but not in skeletal muscle, by very long-chain acyl-CoA synthetase-1 (ACSVL1). It is, therefore, unlikely to cause muscle problems. It was shown to reduce CV events in statin intolerant patients in the CLEAR Outcomes study, and it can reduce LDL-by C by about 30 %, or 20 %, on top of statins<sup>8</sup>. Its major role may be to treat statin intolerant patients, although true intolerance to statins is relatively uncommon. It is available in a combination tablet with ezetimibe, and this could be used as an addition to statin before adding the more expensive injectable PCSK9 therapies if a further modest reduction in LDL-C is required to reach the target.

| Table 2. | Effects of lipid lowering treatments on low- |
|----------|--|
| density  | lipoprotein cholesterol <sup>4</sup> .       |

| uensity tipoprotein chotesterois.                         |                                |
|---|--------------------------------|
| Treatment   | Average LDL-C<br>reduction (%) |
| Moderate intensity statin                                 | 30 %                           |
| High intensity statin                                     | 50 %                           |
| High intensity statin plus ezetimibe                      | 65 %                           |
| PCSK9 inhibitor   | 60 %                           |
| PCSK9 inhibitor plus high intensity statin                | 75 %                           |
| PCSK9 inhibitor plus high intensity statin plus ezetimibe | 85 %                           |

LDL-C = low-density lipoprotein cholesterol

With the addition of the PCSK9 inhibitors, almost all patients can reach the LDL-C targets apart from those with homozygous familial hypercholesterolaemia (HoFH). The mAbs, evolocumab and alirocumab, can reduce LDL-C by 60 % on average and have few adverse effects apart from occasional mild injection site reactions. The siRNA inclisiran is also effective in reducing LDL-C by an average of 50 %, and it can be

given at six monthly intervals after the first two doses, which should improve adherence to therapy<sup>9</sup>. There are no adverse safety signals identified with inclisiran so far, and the ORION-4 CV outcome study should be completed within the next few years.

Patients with HoFH should be offered treatment with high intensity statin, ezetimibe and PCSK9 inhibitors. They will generally require additional treatments such as LDL apheresis, lomitapide or mipomersen. Lomitapide inhibits microsomal triglyceride transfer protein in the liver and intestine and reduces the output of chylomicrons and VLDL particles, which in turn may result in accumulation of triglycerides in the intestine and the liver and cause gastrointestinal and liver adverse effects<sup>10</sup>. Recent data suggest these adverse effects can be managed by dosage reduction and tolerability becomes satisfactory, but the drug is extremely expensive. Mipomersen is a second generation ASO targeting apoB. It is not well tolerated with severe injection site reactions and flu like symptoms, and it is not generally available nowadays.

Evinacumab is a fully human mAb which targets angiopoietin-like protein 3 (ANGPTL3). It was found to be effective in reducing LDL-C in patients with HoFH, including those with no functional LDLRs. ANGPTL3 inhibits lipoprotein lipase (LPL) and also endothelial lipase, and it appears to reduce LDL-C in patients without active LDLRs by an endothelial lipase-dependent uptake of apoB-containing particles into the liver. It has been approved for HoFH in Europe and the U.S. but is also extremely expensive. ANGPTL3 inhibitors may reduce HDL-C, which may limit their wider application.

#### TREATMENT FOR HYPERTRIGLYCERIDAEMIA

Patients with elevated triglycerides can be divided into those with severe hypertriglyceridaemia with plasma triglycerides ≥ 10 mmol/L (900 mg/dL) in European guidelines or  $\geq 500 \text{ mg/dL}$  ( $\geq 5.6 \text{ mmol/L}$ ) in American guidelines, where the major immediate risk is for acute pancreatitis, or those with lower levels where the TRLs contribute to CV risk<sup>11</sup>. It is important to address diet and lifestyle, and managing underlying conditions, particularly diabetes and obesity, should be optimised for all patients with high triglycerides. For those with severe hypertriglyceridaemia, treatments with fibrates and/or omega-3 fatty acids are recommended to reduce the triglyceride levels to < 500 mg/dL to reduce the risk of pancreatitis. Several formulations of omega-3 fatty acids are approved for this, including combinations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and it may be necessary to increase the dose up to 4 g/day. Most fibrates will also effectively reduce triglycerides by up to 50 % or more.

In the most severe cases, such as familial chylomicronaemia syndrome (FCS), due to homozygous loss-of-function mutations in the gene for LPL or associated proteins, it may not be possible to achieve adequate control of triglyceride levels to reduce the risk of acute pancreatitis and new drugs are in development to target this.



Volanesorsen is an ASO targeting apoC-III, and in patients with FCS it reduced apoC-III levels by 84 % and triglycerides by 77 % 12. A mild degree of thrombocytopenia was a common adverse event. Volanesorsen appears to work through a pathway which is independent of LPL, and reducing apoC-III appears to facilitate the uptake of lipid particles through the LDL family of receptors including LDLRrelated protein 1 (LRP1) and possibly hepatic heparan sulfate proteoglycan receptors, such as syndecan-113. Volanesorsen was approved in Europe for FCS but not in the U.S. Other drugs targeting apoC-III are in development including olezarsen which is a triantennary N-acetylgalactosamine (GalNAc) conjugated ASO targeting apoC-III, and the siRNA ARO-APOC3. These may have a wider indication than volanesorsen, but apoČ-III inhibition may increase LDL-C in some patients.

For patients with milder degrees of hypertriglyceridaemia, the European lipid guidelines recommend treating the LDL-C to goal initially with statins and other LDL-C lowering treatments if necessary. In primary prevention patients or high-risk patients who are at LDL-C goals with triglycerides > 2.3 mmol/L (> 200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins<sup>5</sup>. In high-risk patients with persistently elevated triglycerides of 1.5 - 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, the addition of omega-3 fatty acids (icosapent ethyl 2 x 2 g daily) is recommended.

In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes study) trial in diabetic patients not initially on statin treatment, fenofibrate showed CV benefits in some subgroups, including those with low HDL-C14. It also reduced the need for laser treatment for diabetic retinopathy by 31 % and amputation events by 34 %15,16. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study in patients with diabetes on simvastatin, fenofibrate only showed benefits in the subgroup with HDL-C  $\leq$  34 mg/dL and triglycerides  $\geq$  204 mg/dL17. In the ACCORD Follow-On Study (ACCORDION) after treatment cessation, the benefit of fenofibrate persisted in this subgroup with dyslipidaemia<sup>18</sup>.

The PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) study with pemafibrate 0.2 mg twice daily was designed to test the effect of a fibrate in the patients predicted to benefit who had type 2 diabetes with triglyceride levels 200 - 499 mg/dL (2.26 - 5.64 mmol/L) and HDL-C levels  $\leq$  40 mg/dL (1.03 mmol/L) with LDL-C levels at target on moderate or high intensity statin therapy¹9. The trial was stopped early because CV events had no benefit. Triglycerides and very-low-density lipoprotein (VLDL) cholesterol were reduced by about 26 % and apoC-III by 28 %, but LDL-C increased by 12.3 %, apoB increased 4.8 % and there was no change in non-HDL-C.

This result reflects genetic studies showing that triglyceride-lowering genetic variants in LPL and LDL-C-lowering variants in LDLR lower the risk of coronary heart disease per unit difference in apoB, and the clinical benefit of lowering triglyceride and LDL-C levels may

be proportional to the absolute change in apoB<sup>20</sup>. A meta-regression analysis of clinical trials of lipid-lowering drugs, including the ACCORD and FIELD studies with fenofibrate, showed the risk ratio for major vascular events was related to reduction in non-HDL-C with triglyceride lowering treatments<sup>21</sup>. Therefore, with no change in non-HDL-C and a small increase in apoB in the PROMINENT study, it might be predicted there would be no CV benefit.

The main effect of pemafibrate in the PROMINENT study appears to be the activation of LPL with increased conversion of VLDL to LDL particles without increasing the overall clearance of apoB containing particles from the circulation. This may be related to the phenotype of the patients involved and the background therapy with moderate or high intensity statin. Pemafibrate was developed to be more selective than other fibrates and to avoid the elevations in creatinine and liver enzymes sometimes seen with fibrates, and it differs from other fibrates, such as fenofibrate, in various ways<sup>22,23</sup>. Therefore, it may not be appropriate to extrapolate the results from trials with pemafibrate to other fibrates.

The benefit of fenofibrate in addition to statin has been assessed in recent population-based cohort studies in Korea. In the ECLIPSE-REAL (Evaluation of Cardiovascular events on Korean dyslipidemic Patients with fenofibrate treatment in the REAL world) propensity matched cohort study of adults with metabolic syndrome, participants receiving statin plus fenofibrate had 26 % reduction in composite cardiovascular events compared to those using statin only treatment and in those with low HDL-C ( $\leq$  0.88 mmol/L) or high triglycerides ( $\geq$  2.23 mmol/L) the reduction was 36 %<sup>24</sup>.

In another propensity-matched study from the same group in Korea, statin-plus-fenofibrate therapy was associated with a significant 12 % lower risk of diabetic retinopathy progression compared to statin monotherapy in patients with type 2 diabetes and metabolic syndrome<sup>25</sup>.

Another population-based cohort study from Korea investigated the effects of fenofibrate add-on to statin treatment in participants who had already used statins and had high triglyceride levels ( $\geq 150~\text{mg/dL}$ ) $^{26}$ . Compared to fenofibrate non-users, fenofibrate users had a significant 17 % reduction in all-cause death and 7 % reduction in CV disease, and the benefits were consistent in those with diabetes and the 73 % without diabetes. The benefits were greater in those who used fenofibrate for over a year.

Recent trials with omega-3 fatty acids showed a significant 25 % reduction in a composite of CV events in high-risk patients with a purified formulation of EPA (icosapent ethyl 4 g daily) in REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial)<sup>27</sup>, but no benefit with a combined carboxylic acid formulation of EPA and DHA 4 g daily in STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia)<sup>28</sup>.



Questions have been raised regarding the choice of placebo in these studies, which was mineral oil in REDUCE-IT and corn oil in STRENGTH<sup>29</sup>. In an analysis of the Copenhagen General Population Study (CGPS) to mimic the active and comparator groups in REDUCE-IT and STRENGTH, it was concluded that the contrasting results of these studies could partly be explained by a difference in the effect of comparator oils (mineral vs corn), but not of active oils (EPA vs EPA + DHA), on lipid traits and C-reactive protein<sup>30</sup>.

Current guidelines recommend icosapent ethyl in patients who have reached LDL-C targets on statins but have elevated fasting triglyceride levels in the range of 1.5 to 5.6 mmol/L (135 to 499 mg/dL), as seen in the REDUCE-IT study.

#### **CONCLUSIONS**

Treatment to target LDL-C levels is the mainstay of lipid management. Statins are still the first line therapy, and ezetimibe or PCSK9 inhibitors should be added if LDL-C goals are not achieved. Bempedoic acid provides another option that has recently been approved. For elevated triglycerides, fibrates and/or omega-3 fatty acids can be used if the levels are very high (> 10 mmol/ L). Icosapent ethyl is recommended for lower levels of fasting triglycerides. Fenofibrate may be an alternative, especially in patients with diabetes and retinopathy, but it would be prudent to check that non-HDL-C or apoB are reduced if a fibrate is added to reduce CV risk. For the very rare condition of HoFH, treatments with lomitapide or evinacumab may be available in some countries and for the equally rare condition of FCS, volanesorsen has been approved in Europe.

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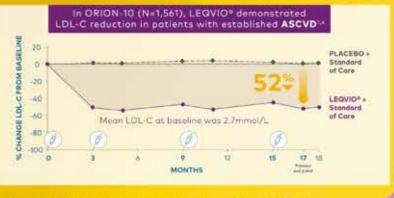
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\*LDE-C reduction was maintained during each 6-month.

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#### **MCHK CME Programme Self-assessment Questions**

Please read the article entitled "Recent Advances in Lipid Therapy" by Prof Brian TOMLINSON and Prof Elaine CHOW 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 November 2023. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary. (Address: Duke of Windsor Social Service Bldg., 4/Fl., 15 Hennessy Rd., Wan Chai. Enquiry: 2527 8898)

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

- 1. A low-density lipoprotein cholesterol (LDL-C) target of less than 1.4 mmol/L is appropriate for patients at a very high cardiovascular risk.
- 2. Non-HDL-C and apolipoprotein B levels are alternative treatment targets for lipid lowering therapies.
- 3. High intensity statin plus ezetimibe may achieve an average reduction of LDL-C by 65 %.
- 4. The clinical pharmacogenomics implementation consortium recommends genotyping for solute carrier organic anion transporter family member 1B1 (SLCO1B1) before starting atorvastatin in all patients.
- 5. Bempedoic acid is an oral prodrug activated in the liver but not in skeletal muscle.
- 6. Rosuvastatin 40 mg daily is contraindicated in East Asians.
- 7. The siRNA inclisiran must be given monthly in patients with homozygous familial hypercholesterolemia (HoFH).
- 8. Both fenofibrate and pemafibrate have been shown to reduce cardiovascular events in randomised controlled trials.
- 9. Volanesorsen targets angiopoietin-like protein 3 (ANGPTL3) and is effective in treating homozygous FH.
- 10. Fibrates and omega-3 fatty acids are approved for reducing the risk of pancreatitis in patients with severe hypertriglyceridaemia.

#### **ANSWER SHEET FOR NOVEMBER 2023**

Please return the completed answer sheet to the Federation Secretariat on or before 30 November 2023 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

### **Recent Advances in Lipid Therapy**

#### Prof Brian TOMLINSON

BSc (Lond), MBBS (Lond), MD (Lond), FRCP (Lond, Edin, Glasg), FHKCP, FACP, FHKAM (Medicine)

Professor, Faculty of Medicine, Macau University of Science and Technology, Macau SAR, China

#### Prof Elaine CHOW

3. T

1. F

2. T

MBChB, MRCP, FRCP (Lond), FHKAM

Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong

4. F

5. T

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| Answers to October 2023 Issue |                      |                |
| Advances in Pleural Medicine  |                      |                |

6. F

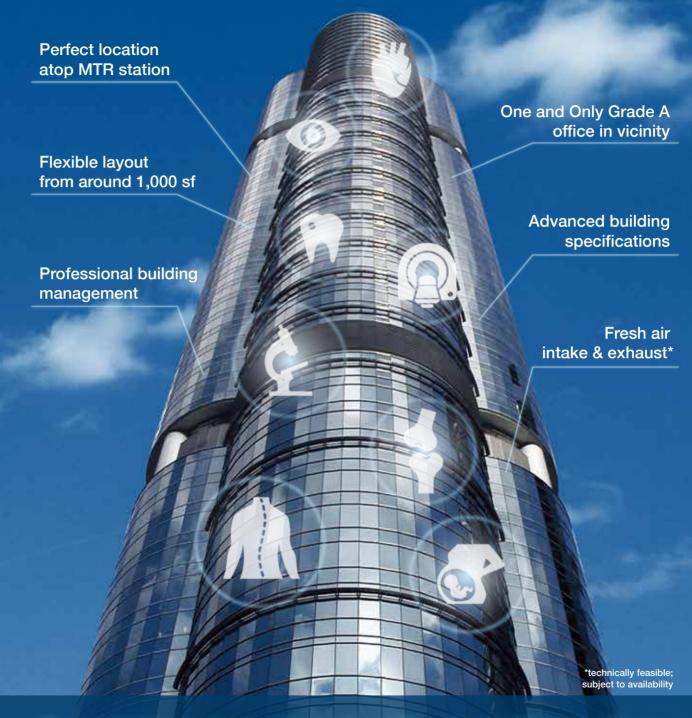
8. T

9. T

7. T

10. F





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# Understanding Clinical Trials to Implement Datadriven Integrated Care - A Perspective of Clinical Pharmacologist and Endocrinologist

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Prof Juliana CN CHAN

Draf Andras VO IIIV

#### INTRODUCTION

Complexity is a key feature in internal medicine. For the same disease, different people can have different clinical presentations. For the same clinical presentation, different people can have different underlying causes. For the same treatment, different people can have different responses. While there are now many diagnostic and therapeutic technologies, doctors are trained to bring out the best of these technologies through their understanding of human biology, clinical medicine and appropriate use of different technologies, notably drugs, for prevention and treatment purposes through good medical practice.

#### GOOD MEDICAL PRACTICE

According to the General Medical Council of the United Kingdom, good medical practice describes what it means to be a good doctor:

- Make the care of his/her patient his/her first concern
- Be competent and keep his/her professional knowledge and skills up to date
- Take prompt action if he/she thinks patient safety is being compromised
- Establish and maintain good partnerships with his/ her patients and colleagues
- Maintain trust in the profession by being open, honest and acting with integrity<sup>1</sup>

Good medical practice starts with comprehensive history taking and physical examination followed by relevant investigations to create a priority list of differential diagnoses, taking into consideration the clinical context. Making a correct diagnosis puts the patient on the right path of receiving the right intervention to achieve the right outcomes. This should be supplemented by patient empowerment, including the nature of the diagnosis, aetiologies, prognosis and treatment options with benefit-risk ratios to promote informed decision-making.

## PRACTICE ENVIRONMENT AND DOCTOR-PATIENT RELATIONSHIP

Globally and in Hong Kong, 70 % of all deaths are due to noncommunicable diseases (NCDs). The latter is

defined by the World Health Organization as cancer, respiratory disease, cardiovascular disease and diabetes. These patients require chronic care, including regular assessments, drugs and education to prevent silent deterioration, which can lead to multiple morbidities with recurrent hospitalisations and premature death. To achieve this, a stable and good doctor-patient relationship supported by allied healthcare workers with access to technologies in an environment conducive to good medical practice is critically important<sup>2</sup>.

## CLINICAL PHARMACOLOGY AND QUALITY PHARMACEUTICAL CARE

Drugs are one of the most important armaments physicians use to help their patients<sup>3</sup>. The premise for developing clinical pharmacology as a subspecialty in internal medicine is to promote the appropriate use of medicine in order to maximise benefits and minimise harm. According to the British Pharmacology Society, clinical pharmacology encompasses all aspects of the relationship between drugs and humans. It is the only medical specialty that focuses on the safe, effective and economical use of medicines with an aim to sustain and advance best healthcare relevant to all specialities<sup>4</sup>.

## DRUG DISCOVERY AND TRANSLATION

Traditionally, many clinical pharmacologists work in the academia with clinical expertise in a subject, e.g. hypertension. They are practising physicians and teach undergraduate and postgraduate students while conducting early and late phase clinical trials in healthy volunteers and patients, essential for the development of a novel drug. Drug development begins with the discovery of a disease pathway and related proteins, which form drug targets for the synthesis of molecules/compounds or peptides/proteins aimed at correcting the disease pathway.

Since 1993, the Human Genomic Project led by the United States National Institute of Health has sequenced the genomes of thousands of individuals, which have provided the basis for many genetic studies aimed at discovering single nucleotide polymorphisms (SNPs) or sequences associated with different human diseases<sup>5</sup>. These discoveries are interpreted in the context of phenotypes (i.e. observable traits), which have to be



defined by physicians with a good understanding of the clinical course of a particular disease. These complex databases, including phenotypes and multiomic data, are analysed jointly by scientists with expertise including but are not limited to human biology, clinical medicine, chemistry and bioinformatics. The ultimate goal is to improve our understanding of causes, trajectories and consequences of diseases as well as discover druggable pathways with minimal off-target side effects for possible translation to therapeutic agents, accompanied by biomarkers for diagnostic, classification and prognostic purpose. These drug targets need to undergo pre-clinical and clinical evaluation for registration by a regulatory agency. Once marketed, these drugs will undergo continuing evaluation by gathering real-world evidence in support of their safety and clinical effectiveness, including cost-effectiveness<sup>6</sup>.

## DRUG DEVELOPMENT AND CLINICAL TRIALS

The discovery of a drug with therapeutic potential is followed by extensive pre-clinical evaluation in cellbased and animal models, including pharmacology, toxicology and mutagenicity, before they are formulated for clinical development (e.g. tablets, injections). In the early phase (phase 1) study, healthy volunteers are usually involved in examining the pharmacokinetic profile, i.e. what the body does to the drug through absorption, distribution, metabolism and excretion (ADME). These properties are often evaluated in special patient groups, e.g., the elderly and those with impaired liver and kidney function, for dose adjustment. Once a drug level is achieved with an optimal regimen (i.e. dose and frequency), its effects on the body (pharmacodynamic), e.g. reducing blood pressure, will be examined in patient groups at different stages of the targeted disease in clinical trial settings (phase 2 - 4).

Complex diseases, such as NCD, are characterised by the clustering of risk factors and complications due to the perturbation of multiple biological pathways.

Both upstream (causes) and downstream (mediators or modifiers) factors can affect the clinical course. Thus, understanding the epidemiology of the disease (e.g. annual event rates) or natural variation of a disease marker (e.g. blood pressure and blood glucose), as well as the effect size of a drug and its variance, is essential for calculating the sample size of the trial aimed at reducing the event rate or improving the disease marker. Once these outcome measures and sample size are defined a priori, the hypothesis will be tested during the clinical trial in order to support their registration for a particular therapeutic claim. Approximately only 10% of drugs that were tested in phase 1 clinical trials successfully completed all phases of clinical trials and received regulatory approval. Reasons for withdrawing the drug from further evaluation include unacceptable side effects, lack of efficacy, poor pharmacokinetic properties, or commercial consideration.

Given the many factors that can influence the clinical course, adherence to a protocol with pre-defined inclusion and exclusion criteria, procedures and care processes, along with systematic documentation of concomitant medications, investigations and clinical events are essential in assessing the independent effects of a drug on a specific outcome. Since perception biases of both trial implementers (e.g. doctors and nurses) and participants (patients) may influence their behaviours (e.g. prescribing, counselling or adherence), which can affect clinical outcomes, these drugs are often compared against look-alike placebo without active ingredients.

Clinical trial participants usually receive the best of care in order to demonstrate the added values of these new drugs, which may also be compared against standard therapy to demonstrate its non-inferiority or superiority. To ensure the safety of the participants, timely reporting of any adverse events, notably serious adverse events including hospitalisation, major events and death, to the ethics board, regulatory agency and sponsors is essential. These adverse effects are regularly reviewed by a safety monitoring committee, which has the right

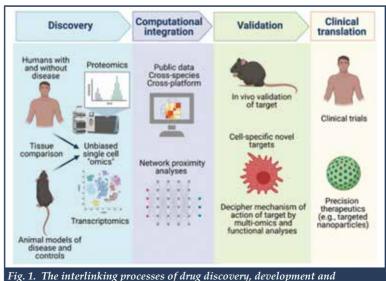


Fig. 1. The interlinking processes of drug discovery, development and distribution for clinical use (Adapted from reference 6).



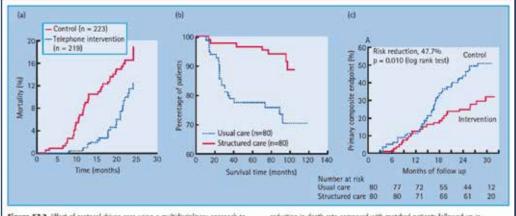


Figure 57.2 Effect of protocol-driven care using a multidisciplinary approach to reduce risk of complications in patients with chronic diseases including type 2 diabetes mellitus (T2DM) [82–84]. (a) Telephone counseling by a pharmacist between clinic visits reduced mortality rate by 50% in patients receiving five or more chronic medications. (b) Patients with T2DM without cardiorenal complications managed in a clinical trial setting was associated with a 70% risk

reduction in death rate compared with matched patients followed up in conventional care setting. (c) Patients with T2DM with chronic kidney disease managed by a pharmacist—doctor team had a 50% risk reduction in death and end-stage renal disease compared with patients managed in conventional care setting.

Fig. 2. The benefits of protocol-driven, team-based integrated care in reducing major clinical events (Adapted from reference 14).

to discontinue the study in the event of futility or clear benefits or harm. Finally, to increase the generalisability of these trial results, multi-centre randomised placebocontrolled trials are now the gold standard in the evaluation of an investigational new drug (IND).

#### GOOD CLINICAL PRACTICE (GCP) AND STANDARD OF OPERATIONS (SOP)

The 3R principle of clinical trial refers to the process of randomisation, which aims to balance both measured and unmeasured variables between the intervention and control/comparative group at baseline, the record of all relevant processes and data during the conduct of the trial for adjustment during analysis and retention of participants to avoid biased conclusion due to attrition with unknown status of the outcome measure.

Good clinical practice in a clinical trial setting refers to adherence to standards of operation (SOP) for maintaining ethical standards, data integrity and patient safety. To achieve these standards, a large multidisciplinary team, including but not limited to doctors, nurses, monitors, technologists and statisticians, governed by a scientific steering committee and an independent safety monitoring committee, is necessary. These RCTs are approved by institutional research ethics boards with the signing of written informed consent forms by trial participants to protect their safety and interest. Due to the large resource implications, it has been estimated that at least USD 1 -2 billion is required to develop a novel drug. The patent period for a novel drug lasts for 20 years, when 10 - 15 years are needed to gather sufficient safety and efficacy data for regulatory approval. Upon registration, the developer will need to use the remaining 5 -10 years to recuperate their investment, often including that for other drugs that have failed in other pre-clinical and clinical development programmes<sup>7</sup>.

## FROM CLINICAL TRIALS TO PROTOCOL-DRIVEN CARE

We have long observed that patients benefitted from participation in a clinical trial beyond effects related to the new drug intervention. The use of a clinical trial protocol delivered by a doctor-nurse team with regular monitoring to ensure treatment adherence, in part driven by a stable doctor-patient relationship in a trial setting, can independently reduce adverse clinical events. Our group first reported the benefits of protocol-driven care during a nifedipine versus enalapril trial in patients with type 2 diabetes and hypertension conducted in the early 1990s. During an 8-year period, compared to patients matched for age, sex and disease duration without hypertension managed in the usual care setting, the trial participants had 50 - 80 % risk reduction in major events and death rates<sup>8</sup>. In the RENAAL study which compared the renoprotective effects of losartan, an angiotensinreceptor blocker (ARB), versus placebo in patients with type 2 diabetes and chronic kidney disease, analysis of participants in Hong Kong revealed marked attenuation in the rate of decline of kidney function upon entry into the trial which was translated to a delay or mitigation of the need for renal replacement therapy<sup>9</sup>.

Subsequent quasi-experimental studies<sup>10</sup> and multicentre randomised controlled trials (RCT) confirmed the benefits of using a doctor-nurse or doctor-pharmacist team to treat patients with diabetic kidney disease to multiple treatment targets, including the use of organ protective drugs, notably statins and renin angiotensin system inhibitors, on reducing the risk of end stage kidney disease by 50 - 60 %<sup>11</sup>. In a meta-analysis on the effectiveness of quality improvement programmes aimed at reducing blood glucose, blood pressure and blood cholesterol in patients with type 2 diabetes, initiatives targeting the care system (e.g. task delegation and providing relay using assistants or technology to improve doctor-patient communication) and patients



ATTR-CM, a life-threatening and progressive disease that is widely and frequently underdiagnosed<sup>1,2</sup>

of adults aged 80 years or older were found to have significant myocardial TTR amyloid deposition at autopsy<sup>2</sup>

#### What is ATTR-CM?2

- · A type of cardiac amyloidosis
- · Can occur as either wild type or hereditary type
- · Progressive and life-threatening
- When the protein transthyretin misfolds, fibril deposits build up in the heart causing ATTR-CM

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warrant your immediate attention<sup>2-4</sup>:

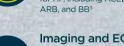
#### Cardiac:





#### HF therapy intolerance<sup>3</sup>

The standard therapies for HF, including ACEI, ARR and BR3



'Imaging finding of LVH and normal/low QRS voltage on ECG2

#### Non-cardiac:



Orthopaedic syndromes (e.g carpal tunnel syndrome. lumbar spinal stenosis and

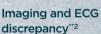
bicep tendon rupture)2



Polyneuropathy<sup>2</sup>









Family history of TTR amyloidosis<sup>4</sup>

Abbreviations: ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin-receptor blockers; ATTR-CM: Transthyretin amyloid cardiomyopathy; BB: Beta blockers; ECG: Electrocardiogram; Echo: Echocardiography; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; LVH: Left ventricular hypertrophy; TTR: Transthyretin References: 1. Rapezzi C et al. Nat Rev Cardiol. 2010;7(7):398-408. 2.Witteles RM et al. JACC Heart Fail. 2019;7(8):709-16. 3. Castano A et al. Heart Fail Rev. 2015;20(2):163-78. 4. Kittleson MM. Circulation. 2020;142(1):e7-e22.

References: 1. Rapezzi C et al. Nat Rev Cardiol. 2010;7(7):396-406. 2.vvitteles 1. Circulation. 2020;142(1):e7-e22.

YYNDAMAX ABBREVIATED PRESCRIBING INFORMATION
1. TRADE NAME: Vyndamax™ capsules (Tafamidis 61 mg) 2. PRESENTATION: 61mg soft capsules 3. INDICATIONS: Vyndamax is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM). 4. DOSAGE: The recommended dose is one capsule of Vyndamax 61 mg (tafamidis) orally once daily. 5. CONTRAINDICATIONS: Hypersensitivity to the active substances or to any of the excipients of the drug (Please refer to the full prescribing information for details). 6. WARNINGS & PRECAUTIONS: Women of childbearing potential should use appropriate contraception when taking tafamidis and continue to use appropriate contraception for 1-month after stopping treatment with tafamidis. Tafamidis should be discontinued to the standard of care for the treatment of patients with transthyretin amyloidosis. Physicians should monitor patients and continue to assess the need for other therapy, including the need for organ transplantation, a part of this standard of care. Tafamidis should be discontinued in patients who undergo organ transplantation. ThITERACTIONS: Substrates of efflux transporter SCP (breast cancer resistant protein; e.g., methotrexate, rosuvastatin, imatinib); substrates of uptake transporters OAT and OAT3 (organic anion transporters; e.g., non-steroidal anti-inflammatory drugs, burnetanide, furosemide, lamivudine, methotrexate, osetlamivir, tenofovir, ganciclovir, adefovir, cidofovir, zidovudine, zalcitabine), 8. PREGNANCY AND LACTATION: Tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception. Tafamidis should not be used during breast-feeding, 9. SIDE EFFECTS: Flatulence and liver function test increased. A causal relationship has not been established. Reference: Prescribing Information HK PI (Version Jul 2020) Date of preparation: Nov 2020 Identifier num





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- Over 40 years of experience
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- Team includes two registered doctors, a pharmacist and a registered nurse (ICU)

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(e.g. education and self-management) had the largest effect size<sup>12</sup>.

These studies emphasised the importance of integrating structured protocols, standard procedures, regular assessment, patient empowerment, treatment-to-target and monitoring of outcomes delivered by a trained team (e.g. nurse, pharmacist, healthcare assistant) led by an expert physician to implement evidence-based practice. This structured approach to care ensures that both care providers and patients are informed, aligned and engaged to achieve positive outcomes through self-management, timely intervention and appropriate use of drugs. The ultimate goal is to prevent hospitalisations, morbidities and premature mortality<sup>2, 13, 14</sup>.

Establishing a disease register is a core component of this data-driven integrated care model. Using diabetes as an example, in 1995, the Chinese University of Hong Kong Diabetes Research and Care Team first set up the Hong Kong Diabetes Register at the Prince of Wales Hospital as a data-driven quality improvement programme. In this initiative, we relocated the care setting from the busy clinic to a diabetes centre, improved the workflow, designed protocols and trained nurses and healthcare assistants to use structured procedures and simple equipment to perform blood, urine, eye and feet examination. These data were used to create a database for risk stratification and care triage. The data were also used to issue a personalised report to empower the patients regarding their own risk profiles for reinforcing self-management, while the doctors were given timely information to avoid therapeutic inertia. Given the reality that most patients are being followed up by different doctors in different settings, this structured assessment performed every 18 - 24 months provides quality assurance, patient empowerment and continuation of care, which has been proven to be lifeand cost-saving2, 15-17.

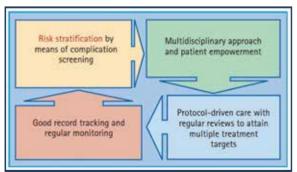


Fig. 3. Components for quality structured care inspired by principles adopted during the conduct of clinical trials (Adapted from reference 14).

In some settings like Hong Kong which has a universal health care system supplemented by a territory-wide electronic medical record (EMR), these registers can be used to create real-world evidence on the pattern of drug usage and their cost-effectiveness in real-world practice<sup>18-21</sup> to complement RCT efficacy data in a controlled setting. Importantly, these databases with structured data collection, e.g. the Hong Kong Diabetes Surveillance Database, curated from the Hospital Authority EMR<sup>22-25</sup>, have provided a rich resource for

ongoing epidemiological analysis on changing disease patterns and secular trends of outcomes to inform practice and policies. From a research perspective, these registers can potentially be used to identify patients who fulfil various inclusion and exclusion criteria for enrolment into RCTs for evaluation of novel drugs or patients with certain risk profiles (e.g. diabetic kidney disease) who may benefit from targeted intervention or additional support<sup>26-29</sup>.

#### NEW HORIZON FOR CLINICAL PHARMACOLOGY AND ENDOCRINOLOGY

In Hong Kong, some of these initiatives of using registers and protocol-driven care to improve the quality of pharmaceutical care have been initiated by clinical pharmacologists inspired by the conduct of clinical trials. In this light, clinical pharmacologists are also trained to minimise prescribing errors, deprescribing ineffective medications, promote adherence with prescriptions and minimize risk of adverse drug reactions. Apart from designing, coordinating, participating, analysing and reporting clinical trials, many of them also take on additional roles in formulating drug policies or regulation of new drug approval<sup>7,30</sup>.

Supported by the vision of the Hong Kong Government to develop biotechnology and value-based healthcare to increase the competitiveness of the city, there is an opportunity to revitalise specialities like clinical pharmacology and endocrinology, which share common goals of using quality pharmaceutical care to prevent multi-organ damage. Despite its silent nature, diabetes and NCD are the leading causes of premature death, morbidities and hospitalisations. To make our healthcare sustainable, there is an urgent need for practising physicians who stand between patients and technologies to take the lead and transform our practice environment and team structure to deliver data-driven, integrated, team-based care in order to prevent the preventable<sup>2</sup>.

For physicians who yearn for a better understanding of disease mechanisms and the development of new treatments, clinical pharmacology and endocrinology provide enormous opportunities for research and development of new therapeutics, treatment strategies and care models. In recent years, the Hong Kong Government has invested enormously in genomic medicine and data science to promote the discovery of biomarkers and drug targets with intellectual property. Some of these initiatives include the establishment of the Hong Kong Science and Technology Park, Phase 1 Clinical Trial Centres managed by multidisciplinary teams at the Chinese University of Hong Kong and Hong Kong University based at the Prince of Wales Hospital and Queen Mary Hospital, respectively and Hong Kong Genome Institute, the latter with a mandate to sequence 50,000 human genomes to uncover causes of rare and challenging diseases, such as young-onset diabetes.

#### CONCLUSION

The recent proposal of the Hong Kong Government to establish a Food and Drug Administration (FDA)-like unit at the Department of Health to expedite investigational new drug (IND) application and approval for registration of new drugs will further enhance the ecosystem necessary to turn Hong Kong into a hub of innovative medicine in the Greater Bay Area. In pursuit of these ambitious goals, developing career paths for clinical pharmacologists, endocrinologists and physician researchers interested in studying the impact of drugs on humans will accelerate the bedside-to-bench-to-bedside cycle, including drug discovery, evaluation and application to preserve health and prevent disease (Fig. 4).



Fig. 4. The inter-linking benefits of using cohorts, biobanks and databases to understand disease mechanisms, make discoveries and perform ongoing evaluation to inform practice and policies for promoting quality pharmaceutical care (created by JCN Chan)

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#### Novel Treatments of Obesity – 1G, 2G, or 3G?

#### Dr Paul CH LEE

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Dr Paul CH I FE

Obesity is a global health problem. The World Health Organization (WHO) recently set out plans to accelerate the prevention of obesity<sup>1</sup>. Indeed, over the past four decades, the age-standardised prevalence of obesity has tripled in men and doubled in women<sup>2</sup>. According to the World Obesity Federation, it is estimated that by 2035, almost 2 billion adults will be obese, as defined by body mass index (BMI)  $\geq 30 \text{ kg/m}^2$ , and over 4 billion individuals will have BMI  $\geq 25$  kg/m<sup>2</sup>, reaching epidemic proportions<sup>3</sup>. Obesity leads to increased risks of type 2 diabetes (T2D)<sup>4, 5</sup>, steatotic liver disease<sup>6</sup>, cardiovascular diseases (CVD)7, cancer8, as well as mortality. Both high BMI and fasting glucose have become the top five leading risks of all-cause mortality and disability-adjusted life-years9. Increased adiposity causes insulin resistance, which is the key metabolic defect underlying the pathogenesis of T2D, and hence, the majority of individuals with T2D are overweight or obese<sup>10</sup>. A previous study suggested that overweight  $(BMI \ge 25 - < 30 \text{ kg/m}^2)$  and obese  $(BMI \ge 30 \text{ kg/m}^2)$ individuals were at least 3 and 8 times more likely to develop incident T2D, respectively, regardless of their genetic predisposition<sup>11</sup>. Among T2D patients who are overweight and obese, it is increasingly recognised that body weight management is an equally important component of care as glycaemic control, cardiovascular risk factor management and cardio-renal risk protection<sup>12</sup>. Therefore, novel therapeutic strategies for individuals with obesity and/or diabesity are eagerly awaited, and recent studies suggested that we might soon be moving towards a "3G" era for the management of obesity and diabesity.

#### GLUCAGON-LIKE PEPTIDE 1 (GLP1) AND GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP)

The incretin effect describes the observation that oral glucose ingestion stimulates insulin response to a larger extent than following the infusion of iso-glycaemic intravenous glucose, which leads to similar glucose excursion<sup>13</sup>. In T2D patients, the incretin effect is reduced or absent. Glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP) are the two incretin hormones responsible for the incretin effect.

GLP1 is predominantly secreted from the enteroendocrine L cells located in the distal small bowel and colon, whereas GIP is secreted from the enteroendocrine K cells in the duodenum and jejunum<sup>13</sup>. Following meal ingestion, glucose, amino acids,

lipids and fatty acids can all stimulate the secretion of GLP1 and GIP with an increase in their circulating levels<sup>15</sup>. Both GLP1 and GIP are insulinotropic and stimulate insulin secretion from the beta ( $\beta$ ) cells of the pancreatic islets in a glucose-dependent manner. In contrast, their effects on glucagon secretion are different. GLP1 decreases whereas GIP increases glucagon secretion<sup>15</sup>.

#### GLUCAGON

Glucagon is a peptide hormone secreted from the alpha ( $\alpha$ ) cells of the pancreatic islets. Classically, its physiological actions in nutrient homeostasis are opposite to those of insulin. Glucagon binds to its receptors on hepatocytes, stimulates glycogenolysis and gluconeogenesis, and inhibits glycolysis and glycogenesis, collectively resulting in increased hepatic glucose production. Moreover, glucagon promotes hepatic amino acid metabolism and  $\beta$ -oxidation<sup>16</sup>. While hypoglycaemia is a potent stimulus for increased glucagon secretion, paradoxically, hyperglucagonaemia has been observed among obese individuals and T2D patients, which has been related to hepatic glucagon resistance and altered  $\alpha$ -cell to  $\beta$ -cell ratio, respectively<sup>16</sup>.

## 1G – GLP1 RECEPTOR AGONISTS (GLP1rA)

GLP1 receptors (GLP1R) are widely distributed in the central nervous system, including regions such as the hypothalamus that are highly involved in the regulation of food intake. Therefore, in addition to glucose lowering, administration of exogenous GLP1 causes anorectic effects, which lead to reduced food intake and contribute to weight loss. Moreover, exogenous GLP1 inhibits gastrointestinal motility, reduces gastric emptying and promotes satiety. As a result, pharmacological GLP1R agonism has been established not only as an important anti-diabetic agent for T2D patients<sup>17</sup>, but also as a popular treatment strategy for obesity.

Among the GLP1rA, both liraglutide 3.0 mg daily and semaglutide 2.4 mg weekly are currently approved by the United States Food and Drug Administration (FDA) as pharmacotherapy for obesity as an adjunct to lifestyle modification<sup>18</sup>. In the Satiety and Clinical Adiposity - Liraglutide Evidence (SCALE) Obesity and Prediabetes Study, a randomised-controlled trial involving 3,731 overweight or obese adults without diabetes (mean BMI 38.3 kg/m²; 61 % with prediabetes), treatment with liraglutide 3.0 mg daily for 56 weeks



reduced body weight by a mean of 8.0 % as compared to 2.6 % with placebo. There were significantly more participants achieving weight loss of  $\geq 5\%$ , > 10% and >15 % after liraglutide than with placebo (63.2 %, 33.1 % and 14.4 % vs 27.1 %, 10.6 % and 3.5 %, respectively)<sup>19</sup>. Following the success of liraglutide, in the Semaglutide Treatment Effect in People with Obesity (STEP) 1 Study, a randomised-controlled trial involving 1961 adults without diabetes (mean BMI 37.9 kg/m2; 43.7 % with prediabetes), treatment with semaglutide 2.4 mg once weekly for 68 weeks reduced body weight by a mean of 14.9 % as compared to 2.4 % with placebo. Similarly, a significantly higher proportion of participants achieved a weight loss of  $\geq 5\%$ ,  $\geq 10\%$  and  $\geq 15\%$  after semaglutide than with placebo (86.4 %, 69.1 % and 50.5 % vs 31.5 %, 12.0 % and 4.9 %, respectively)<sup>20</sup>. In both studies, treatment with GLP1rA was associated with improvement in various cardio-metabolic risk factors. Nausea was commonly reported among GLP1rA-treated participants, and around 4.5 - 6 % of them discontinued GLP1rA during the study due to gastrointestinal adverse events19, 20.

Orforglipron is an oral non-peptide GLP1rA currently in development for the treatment of obesity and T2D. In a recently published phase 2 randomised controlled trial involving 272 overweight or obese adults without diabetes (mean BMI 37.9 kg/m²), treatment with orforglipron 12 mg, 24 mg, 36 mg and 45 mg daily for 36 weeks reduced body weight by a mean of 9.4 %, 12.5 %, 13.5 % and 14.7 %, as compared to 2.3 % with placebo. A high proportion of orforglipron-treated participants achieved weight loss  $\geq$  5 %,  $\geq$  10 % and  $\geq$  15 % after 36 weeks (72 - 92 %, 47 - 75 % and 22 - 48 %, respectively)<sup>21</sup>.

## 2G - GIP/GLP1 RECEPTOR COAGONISTS

Despite both being incretin hormones, over the years, pharmacological development has been favoured towards agonism of GLP1R over GIP receptors (GIPR) due to several reasons. First, early reports demonstrated reduced insulinotropic effects of GIP in T2D patients<sup>13</sup>. Secondly, preclinical GIPR loss-of-function studies showed that blocking GIPR signalling was associated with protection against obesity induced by high fat diet<sup>22</sup>. Thirdly, GIP stimulates the secretion of glucagon, which theoretically could worsen hyperglycaemia in T2D<sup>22</sup>.

However, several recently published large-scale, multicentred, phase 2b and phase 3 randomised controlled trials of tirzepatide, a novel dual GIP and GLP1 receptor agonist administered subcutaneously, have rekindled interest in pharmacological GIPR agonism for the treatment of obesity and T2D. In the SURMOUNT-1 Study, which involved 2,539 overweight or obese adults without diabetes (mean BMI 38 kg/m<sup>2</sup>; 40.6 % with prediabetes), treatment with tirzepatide 5 mg, 10 mg and 15 mg once weekly for 72 weeks reduced body weight by a mean of 15.0 %, 19.5 % and 20.9 %, respectively, as compared to 3.1 % with placebo. Over 85 % of the tirzepatide-treated participants achieved ≥ 5 % weight loss, the general target required for clinical improvement in metabolic health. A higher proportion of participants treated with tirzepatide 15

mg weekly lost  $\geq 10$  %,  $\geq 15$  % and  $\geq 20$  % than those treated with 10 mg weekly (83.5 %, 70.6 % and 56.7 % vs 78.1 %, 66.6 % and 50.1 %, respectively), despite the similar incidence of gastrointestinal side effects<sup>23</sup>. In the SURMOUNT-2 Study, involving 1,514 overweight or obese adults with T2D (mean BMI 36.1 kg/m²; median glycated haemoglobin HbA1c 8.0 %), treatment with tirzepatide 10 mg and 15 mg once weekly for 72 weeks reduced body weight by a mean of 12.8 % and 14.7 %, respectively, as compared to 3.2 % with placebo. Moreover, the odds of achieving weight loss of  $\geq 5 \%$ ,  $\geq$ 10 %,  $\geq 15 \%$ ,  $\geq 20 \%$  were 8.3, 16.1, 25.2 and 25.6 times with tirzepatide 10 mg weekly, and 10.5, 19.4, 36.1, 42.2 times with tirzepatide 15 mg weekly as compared to placebo<sup>24</sup>. In the SURPASS-2 Study, an open-label trial comparing the different doses of tirzepatide (5 mg, 10 mg and 15 mg once weekly) against semaglutide 1mg once weekly in 1,879 adults with T2D (mean BMI 34.2 kg/m<sup>2</sup>; median HbA1c 8.3 %), treatment with tirzepatide at all doses were superior to semaglutide both in terms of glucose-lowering and body weight reduction. The incidence rates of gastrointestinal adverse events were similar between tirzepatide 5 mg weekly (40.0 %) and semaglutide 1mg weekly (41.2 %), but were higher for tirzepatide 10 mg (46.1 %) and 15 mg weekly (44.9 %)<sup>25</sup>. These findings were overall in keeping with those from a phase 2b trial comparing the different doses of tirzepatide with dulaglutide 1.5 mg once weekly in T2D patients, which demonstrated that tirzepatide 5 mg and 10 mg once weekly provided superior efficacy in glucose-lowering and body weight reductions than dulaglutide but with similar tolerability<sup>26</sup>. In all the above trials, tirzepatide treatment was associated with substantial reductions in serum triglyceride, very lowdensity lipoprotein (VLDL) and free fatty acid levels.

Tirzepatide is often described as an "imbalanced" agonist with stronger affinity and potency at the GIPR than the GLP1R. However, at the GLP1R, tirzepatide is biased towards engaging cyclic AMP signalling over β-arrestin recruitment, an overall effect that could reduce internalisation of GLP1R and prolong GLP1R agonism<sup>27</sup>. Although the extent to which this unique pharmacological property of tirzepatide has contributed to the promising clinical results remains to be elucidated, GIP has been shown to improve peripheral insulin sensitivity through enhancing the lipid-buffering capacity of white adipose tissue (WAT), which only expresses GIPR but not GLP1R<sup>28</sup>. GIP increases blood flow to the WAT, enhances insulinstimulated glucose uptake and lipoprotein lipase activity, promotes triglyceride storage and lowers circulating free fatty acid levels28. Moreover, GIPR is expressed in both neuronal and non-neuronal cells in the hypothalamus, as well as in cell populations with and without GLP1R co-expression. Therefore, it is possible that the addition of sustained pharmacological agonism of GIPR could provide synergistic anorectic effects than GLP1rA agonism alone<sup>29</sup>. Interestingly, in preclinical models, the addition of long-acting GIPR agonists also attenuated the aversive effects induced by GLP1rA co-administration<sup>30</sup>. Whether this would translate to a clinical advantage and improve tolerance, especially during dose escalation in humans, requires further investigation in clinical studies.



## 2G - GLUCAGON/GLP1 RECEPTOR CO-AGONISTS

While glucagon increases glucose levels, glucagon receptors (GCGR) are present in β cells and glucagon is a potent stimulator of insulin secretion<sup>16</sup>. Moreover, it is increasingly recognised that exogenous glucagon could contribute to weight loss by reducing food intake and gastrointestinal motility, promoting satiety, and increasing energy expenditure via its thermogenic effects<sup>16</sup>. Therefore, although counterintuitive at first sight, the combination of pharmacological agonism of GCGR and GLP1R becomes another potentially effective therapeutic strategy for obesity and diabesity. Cotadutide is a dual glucagon and GLP1 receptor agonist administered subcutaneously. In a phase 2b randomised controlled trial involving 834 adults with T2D on metformin monotherapy (mean BMI 35 kg/m<sup>2</sup>; median HbA1c 8.1 %), comparing cotadutide against liraglutide 1.8 mg once daily and placebo, treatment with cotadutide for 54 weeks significantly improved HbA1c as compared with placebo, but not liraglutide. Cotadutide at 100 ug, 200 ug and 300 ug daily also reduced body weight by a mean of 3.7 %, 3.2 % and 5.0 %, and the latter was significantly greater than the 3.3 % weight loss achieved with liraglutide 1.8mg once daily<sup>31</sup>.

## 3G - GIP/GLP1/GLUCAGON RECEPTOR TRI-AGONISTS

Finally, what if we engage all three receptors? Two recent phase 2 randomised controlled studies have evaluated the efficacy of retatrutide, a triple agonist of the GIPR, GLP1R and GCGR administered subcutaneously. In the Retatrutide Phase 2 Obesity Trial, which involved 338 overweight or obese adults without diabetes (mean BMI 37.3 kg/m<sup>2</sup>; 36 % with prediabetes), treatment with retatrutide 1 mg, 4 mg, 8 mg and 12 mg once weekly for 48 weeks reduced body weight by a mean of 8.7 %, 17.1 %, 22.8 % and 24.2 %, as compared to 2.1 % with placebo. All participants on retatrutide 8 mg and 12 mg once weekly, and 92 % of participants on retatrutide 4 mg achieved the target of  $\geq 5$  % weight loss. The majority of participants on retatrutide ≥ 4 mg once weekly had ≥ 15 % body weight reduction after 48 weeks. Strikingly, among participants treated with retatrutide 12 mg once weekly, 26 % of them even had  $\geq$  30 % body weight reduction<sup>32</sup>. In another phase 2 study comparing the different doses of retatrutide against dulaglutide 1.5 mg weekly and placebo in 281 T2D participants (mean BMI 35 kg/m²; median duration of diabetes of 8.1 years and HbA1c 8.3 %), treatment with retatrutide 4 mg once weekly for 36 weeks reduced HbA1c to a similar extent as dulaglutide. However, participants treated with retatrutide 8 mg and 12 mg once weekly experienced significantly greater glucose lowering than those treated with dulaglutide, with HbA1c reduction of up to 2.16 % in the retatrutide group after 36 weeks. Normoglycaemia, as defined by HbA1c < 5.7 %, was achieved after 36 weeks in over 15 % and 25 % of participants receiving retatrutide 8 mg and 12 mg once weekly, respectively. Among retatrutide-treated participants, dose-dependent body weight reductions of up to 16.9 % with retatrutide 12 mg once weekly were observed. Around 35 % of the retratrutide-treated participants experienced mild to

moderate gastrointestinal adverse events, but only 8 % discontinued treatment due to these effects<sup>33</sup>.

#### **CONCLUSION**

While these multi-receptor agonists demonstrated an unprecedented level of clinical efficacy in glucose lowering and body weight reduction, further studies are required to clarify their long-term safety and investigate their roles in obesity-related complications, including atherosclerotic CVD, heart failure, chronic kidney disease, obstructive sleep apnoea, as well as metabolicdysfunction steatohepatitis and liver fibrosis. Although most of these agents are still currently unavailable in Hong Kong, some of them are on course, and it is foreseeable that they will bring revolutionary changes in the management of obesity and/or diabesity in the next few years. That said, when they become available in clinical practice, all stakeholders should ensure stable stock supply to avoid drug shortage, which will pose an immense challenge to patients and their treating physicians.

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Important Notice: Breast-feeding is the best form of nutrition for babies and provides many benefits to babies and mothers. It is important that, in preparation for and during breast-feeding pregnant and lactating women eat a healthy, balanced diet, Combined breast and bottle-feeding in the first weeks of life may reduce the supply of their own breast-milk, and reversing the decision not to breast-feed is difficult. Always consult healthness professional for advice about feeding baby, If infant formula is used, mothers/ care givers should follow manufacturers instructions for use carefully faulure to follow the instructions may make baby II. The social and financial implications of using infant formula should be considered. Improper use

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#### **Dermatology Quiz**



### **Dermatology Quiz**

#### Dr CHONG Lai-yin

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Dr CHONG Lai-yin



Fig. 1: Confluent erythema over the trunk



Fig. 2: Scaling and erythema over the thighs

This 40-year-old man had rapidly progressive skin redness in past three months. The lesions spread downward from face and neck to the trunk (Fig. 1) and limbs (Fig. 2). He has mild itchiness, scaling and dryness. Apart from the skin lesions, his general condition was well. His past health was good. There was no significant family history.

#### **Ouestions**

- 1. What are your diagnosis and differential diagnoses?
- 2. How would you establish the diagnosis?
- 3. How do you treat this patient?
- 4. What is the prognosis of this disease?

(See P. 36 for answers)





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- Timmins P. Clin Pharmacokinet 2005:44:721-9

#### Abbreviated Prescribing Information

Contents: Metformin HCl Indications: Reduction in risk or delay onset of type 2 DM in adult, overweight patients with IGT and/or IFG, and/or increased HbA1C who are at high risk for developing overt type 2 DM and still progressing towards type 2 DM despite implement intensive lifestyle change for 3 - 6 months. Treatment of type 2 DM in adults as an adjunct to adequate diet & exercise. Monotherapy or in combination w/ other oral antidiabetic medicines or insulin. Dosage: Adult w/ normal renal function (GFR  $\geq$ 90 mL/min) Reduction in the risk or delay of the onset of type 2 DM Initially one 500-mg tab once daily w/ evening meal. After 10-15 days, adjust dose based on blood glucose measurements. Max: 2,000 mg once daily. Monotherapy in type 2 DM & combination w/ other oral antidiabetics agents Usual starting dose: One 500-mg tab once daily, or one 1,000-mg tab once daily. After 10-15 days, adjust dose based on blood glucose measurements. Max. recommended dose for 500 mg and 1g tab is 2g daily. Max. recommended dose for 750 mg tab is 1.5g daily. Combination with insulin Usual starting dose is one tablet XR 500 mg or XR 1 g once daily, while insulin dosage is adjusted on the basis of blood glucose measurements. For renal impairment patients A GFR should

be assessed before initiation of treatment and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g., every 3 - 6 months. Total max. daily dose of 2 g for GFR 60 - 89 mL/min, consider dose reduction for declining renal function. Total max, daily dose of  $2\,\mathrm{g}$  for GFR  $45\,$ -  $59\,\mathrm{mL/min}$ , review any increased risk of lactic acidosis before initiating metformin, whereas starting dose is at most half of max. dose. Total max. daily dose of 1 g for GFR 30 - 44 mL/min, review any increased risk of lactic acidosis before initiating metformin, whereas starting dose is at most half of max. dose. Pre- & Post-Prandial Advice: Swallow whole, do not chew/crush. Contraindications: Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis), severe renal failure (GFR < 30mL/min), hepatic insufficiency, infectious diseases, following an IV urography or angiography, heart failure, recent MI, resp. failure, shock, persistent or severe diarrhoea, recurrent vomiting, alcoholism. Lactation. Special Precautions: Regular renal & blood sugar monitoring. Risk of lactic acidosis, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Discontinue prior administration of iodinated contrast agents or surgery. May impair ability to drive or operate machinery in combination w/ other antidiabetic agents. Pregnancy. Elderly (for reduction of risk or delay of type 2 DM) Adverse Reactions: GI & taste disturbances. Interactions: Iodinated contrast agents, corticosteroids, NSAIDs, ACE inhibitors, diuretics, sympathomimetics, alcohol, COX II inhibitors, angiotensin II receptor antagonists, OCT1 and OCT2 inhibitor/ inducer Presentations: XR tab 500 mg x 60's. 750 mg x 30's. 1,000 mg x 60's. Date of version: JUN 2018

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## Drug-Induced Cardiac Arrhythmias: A Focused Update and Emerging Clinical Challenges

#### Dr Will YH CHAN

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Dr Will VH CHAN

#### **INTRODUCTION**

Drug-induced cardiac arrhythmias is a common medical condition encountered in daily clinical practice. While incidence rates and clinical manifestations vary by studies, a key underscoring principle is timely recognition and high levels of clinical vigilance given the appropriate clinical contexts. The American Heart Association released a scientific statement in 2020 that provided a comprehensive review of the overall framework and approach to drug-induced cardiac arrhythmias, and this can also serve as a quick reference to the lists of common drugs involved<sup>1</sup>.

The objective of this current article primarily focuses on updating the general clinicians on the recent clinical and research developments in this area, and highlighting drugs that are important but potentially less well recognised. A relevant and rapidly expanding clinical arena is that in cardio-oncology. Here, we will also succinctly cover the clinical pearls relating to cancer drug-induced cardiac arrhythmias.

#### DRUG-INDUCED BRADYARRHYTHMIAS

In general, drugs that precipitate bradyarrhythmias via direct actions either suppress the sinoatrial node or, alternatively, on the atrioventricular node and the His-Purkinje system (infra-nodal). Depending on the degree of suppression, the former can manifest as sinus bradycardia, or sinus pause with or without junctional escape rhythm. In comparison, drugs that inhibit atrioventricular conduction result in atrioventricular block. On top of these target-directed pharmacological actions, the potential influences an offending drug may impose on the balance between the autonomic tones are also important. For example, drugs such as cholinesterase inhibitors potentiate the parasympathetic nervous system, and may suppress the sinoatrial node automaticity, causing bradycardia.

Unsurprisingly, the most commonly encountered druginduced bradyarrhythmias in clinical practice are often a result of cardiovascular medication itself. The classical repertoire of heart rate-modulating agents, including beta-blockers, non-dihydropyridine calcium channel blockers (i.e. verapamil and diltiazem), and digoxin, has been well described. Perhaps less so familiarly recognised by general clinicians is ivabradine, a more recent addition to the armamentarium of heart rate control. Ivabradine is a specific funny current inhibitor that targets the hyperpolarisation-activated cyclic nucleotide-gated cation channels (HCN). It blocks the HCN in the sinoatrial node intra-cellularly and results in delayed diastolic depolarisation in a use-dependent manner. The "use-dependent" pharmacological property is usually favourable from a clinical use perspective, which means that the reduction in heart rate through HCN suppression is theoretically proportional to the absolute magnitude of the baseline heart rate. Thus, the greatest treatment benefits are derived in those with genuine tachycardia. Conversely, the risk of it causing profound bradycardia in patients with modest heart rates at the outset is generally low. Indeed, from prior large clinical trials, a good safety profile has been demonstrated, and the incidence of ivabradine-induced bradycardia ranged between 8 - 18 %, with the majority of them being asymptomatic. Ivabradine has been FDA-approved for reducing hospitalisation in patients with chronic heart failure with impaired left ventricular ejection fraction  $\leq 35$  % and heart rate  $\geq 70$  bpm, after maximally tolerated betablocker therapy. It is also indicated for patients with stable angina who did not respond to the first-line therapies (European Society of Cardiology class IIa recommendation)<sup>2</sup>.

Ticagrelor is another cardiovascular drug that has gained increasing clinical use and possesses bradyarrhythmic potential. Indicated for cardiovascular protection in acute coronary syndrome patients with or without coronary stenting, and those with a prior history of myocardial infarction, ticagrelor is an antiplatelet agent that reversibly antagonises the P2Y12 receptor. It has a faster onset of action and greater potency compared to clopidogrel. The mechanism of ticagrelor causing bradycardia is not entirely clear, but is believed to be mediated via increased levels of adenosine. In the DISPERSE-2 trial, which investigated the safety and initial efficacy of ticagrelor versus clopidogrel in patients with myocardial infarction, increased rates of ventricular pauses were observed in those who received ticagrelor. Correspondingly, patients at risk of bradyarrhythmia were subsequently excluded from the subsequent landmark phase 3 trials of ticagrelor (PLATO, and PEGASUS TIMI-54). Nevertheless, a greater proportion of patients was still observed to experience ventricular pause > 3 seconds during a holter monitoring subgroup analysis in PLATO. As such, in the Summary of Product Characteristics of Ticagrelor, there is a general caution for patients at risk for bradycardic events (e.g. sick sinus syndrome without a pacemaker implant, second- or third-degree atrioventricular block, or bradycardia-related syncope), as well as for the concomitant use of medicinal products known to induce bradycardia in conjunction with ticagrelor. In a systematic review and meta-analyses



that included 15 randomised controlled trials, the excess risks of bradyarrhythmia and severe bradyarrhythmia were respectively 15 % (95 % CI 1.05 to 1.26) and 29 % (95 % CI 1.02 to 1.65). Thus, while considering its derived clinical benefits, clinicians should also be cognizant of its potential bradycardic properties and avoid using it in patients with existing bradycardia or preponderance to heart block<sup>3</sup>.

With the potential implications of these specific cardiovascular drugs in mind, a significant clinical burden of bradyarrhythmias in the community setting still rests with various non-cardiovascular drugs that can cause bradycardia. These commonly include acetylcholinesterase inhibitors, anaesthetic agents, and antidepressants.

In the complete assessment of patients with suspected drug-induced bradyarrhythmias, a detailed medical history is essential. Electrolyte abnormalities, hypothyroidism, as well as alternative causes, including acute coronary syndrome, should be excluded. Acute clinical management principally involves cessation of the culprit agent, and supportive management, including advanced cardiovascular life support per indicated. Intravenous atropine may be used (0.6) mg every 3 - 5 minutes, up to a maximum dose of 3 mg). Other supportive therapies include intravenous infusion of isoproterenol, dopamine, dobutamine, or epinephrine. If responses remain refractory or the patient becomes hemodynamically unstable, temporary transcutaneous or transvenous pacing support should be promptly administered. Overt cases of drug overdoses involve specific management strategies, and these are to be detailed elsewhere.

It should be noted that amongst patients who had an atrioventricular block, presumably due to a culprit bradycardic agent, 56 % experienced subsequent recurrences of atrioventricular block<sup>4</sup>. As such, the "drug-induced" bradycardia episodes for these patients may represent an unmasking of underlying conduction system diseases or its predisposition. These patients may well warrant consideration for pacemaker implantation. If in doubt, a referral to a cardiologist for assessments should be made.

#### DRUG-INDUCED TACHYARRHYTHMIAS

#### **Torsades De Pointes and QT Prolongation**

In terms of drug-induced tachyarrhythmias, one of the most dreaded complications to recognise and prevent, is torsades de pointes (TdP). TdP is a rare, life-threatening form of polymorphic ventricular tachycardia associated with QT (referred to as QTc [corrected QT] in the subsequent text as appropriate) prolongation. When TdP degenerates into ventricular fibrillation, sudden cardiac death could result. Although congenital long QT syndrome can also present with a similar picture, drug-induced TdP is more frequently encountered. The true incidence of drug-induced TdP is unknown in the local Hong Kong population, but was reported to be 2.5 per million per year for males and 4 per million per year for females in a Western study<sup>5</sup>. As

an inconvenient truth, drugs with a propensity to cause TdP are implicated in broad ranges of common therapeutic areas. Other than cardiovascular drugs comprising mainly antiarrhythmics that possess proarrhythmic potentials themselves, the antimicrobials, antipsychotics and antidepressants are amongst the top categories implicated in the risk of TdP. Fluoroquinolones (levofloxacin, ciprofloxacin), macrolides (such as azithromycin, erythromycin, clarithromycin) (see illustrative Fig. 1), azole antifungal agents, and chloroquines are typical examples of such antimicrobials1. In terms of cellular mechanisms, TdP is indeed one of the most extensively studied adverse drug reactions, and thus the pharmacological basis has been rather well described. In brief, the primary mechanism by which offending drugs cause TdP is via blocking the IKr (commonly via blocking the hERG potassium channel), a major cardiac potassium current contributing to cardiac repolarisation, thus precipitating QT prolongation. Nevertheless, QT prolongation appears to be an important but not sufficient cause for TdP to occur. Risk factors for drug-induced TdP can be broadly classified into 3 categories<sup>6</sup>:

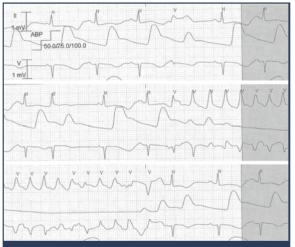


Fig. 1. ECG strip illustrating a patient developed polymorphic ventricular tachycardia secondary to azithromycin use and related QT prolongation during treatment of an episode of community-acquired pneumonia. Note that the initiation of ventricular tachycardia was preceded by an ectopic beat and a short-long-short coupling interval sequence.

#### **Patient-Specific Factors**

Firstly, these include demographic factors (advanced age > 65 years, female sex), existing heart diseases (acute myocardial infarction, heart failure with reduced ejection fraction, bradycardia), electrocardiographic factors (baseline QTc interval > 500 ms, post-dosing QTc interval increase by > = 60 to 70 ms when given an offending drug), electrolyte disturbances (hypokalemia, hypocalcemia, hypomagnesemia), use of diuretics, hypothermia, and renal impairment. Furthermore, a genetic element probably plays an impartial role. Such pre-determined "repolarisation reserve" is believed to confer an individual a defined intrinsic tendency of developing QTc prolongation and TdP when exposed to a given offending drug.



#### **Drug-Specific Factors**

The pharmacological properties of each drug to prolong the QTc interval and cause TdP to differ significantly. Knowledge of "classical" agents which may prolong the QTc interval allows clinicians to stay vigilant of the associated risk and to consider alternative agents if possible. And if treatment is started, electrocardiogram monitoring should be implemented after drug initiation. One example is arsenic trioxide, a drug used commonly for the treatment of acute promyelocytic leukaemia, in which case the proportion of patients having prolonged QTc was as high as 63 %<sup>7</sup>. Furthermore, although the QTc interval is a composite measure of assessing cardiac repolarisation and how a drug may affect it, its absolute value has limited applications. This is because different drugs may differentially affect cardiac repolarisation via exacerbating its transmural or spatial inhomogeneity in the heart (i.e. causing QT dispersion), which is important in causing TdP<sup>8</sup>. Above all and perhaps most relevant in clinical practice, rapid intravenous administration of an offending drug is a risk factor for causing TdP9.

#### **Scenario-Specific Factors**

Finally, these take account of the complex specific clinical factors for each individual case, including drugdrug interactions, altered excretion/metabolism of drugs resulting in increased drug exposures, as well as changes in medical conditions that may compromise individual patient's repolarisation reserve. Surely, the above three kinds of risk factors are interlinked rather than mutually exclusive.

Correspondingly, astute clinicians should preemptively identify patients who are prima facie evident for an increased risk of TdP, when considered for a specific therapy that might cause TdP. If possible, use of QTc-prolonging medications in patients with preexisting QTc interval > 450 ms should be avoided. Any reversible factors, in particular electrolyte disturbances and hypothyroidism should be duly corrected. Substitution with a suitable alternative drug, when available, should be considered. Appropriate renal adjustment should be performed when indicated. Rapid intravenous infusion of QTc-prolonging drugs should be avoided. Furthermore, using more than one concomitant QTc-prolonging drugs should be avoided. The attending clinician should also be proactive and look for any potential drug interactions high-risk for QTc-prolongation, especially those interfering with cytochrome P450 CYP 3A4 and CYP 2D6. In addition, QTc interval should be routinely monitored<sup>9</sup>.

As for general principles on the acute management of TdP, offending drugs should be stopped immediately. Hemodynamically unstable patients should promptly undergo defibrillation. Intravenous magnesium sulphate should be given, even without reference to patient's magnesium level. Any hypokalemia, hypocalcaemia or hypomagnesemia should be treated. If TdP remained refractory, overdriving cardiac pacing should be administered. Further specific managements follow those of the published guidelines.

Despite current knowledge, drug-induced TdP remains

a significant clinical challenge, both at the clinician and system levels. Given the diverse disease spectrums and therapeutic areas involved in the setting of an ageing population and polypharmacy, a multidisciplinary team approach with a strengthened role of the clinical pharmacists in upstream risk assessment will be valuable<sup>9</sup>. Further research and system improvements may help to drive further improvements in this area to mitigate the risks of avoidable deaths related to druginduced TdP worldwide.

#### Drug-Induced Atrial Fibrillation And Emerging Challenges From Cardio-Oncology

Atrial fibrillation (AF) is the most commonly encountered sustained cardiac arrhythmia in clinical practice. It is also probably the most common druginduced tachyarrhythmia. The more common culprit or exacerbating agents include alcohol, caffeine, adrenergic agonists, anticholinergics, psychotropic agents, antiarrhythmic agents, bisphosphonates, and abused substances such as cocaine and amphetamines.

Cardiotoxic including AF-inducing potentials of the earlier chemotherapeutic agents, such as the anthracyclines, have been well described. More recently, newer anticancer agents represent a rapidly expanding group of drugs that is gaining clinical importance<sup>10, 11</sup>. With therapeutic advances, the clinical course for many cancer patients has greatly transformed. Growing populations of patients with malignancies now have markedly improved clinical survival. At the same time, the rapidly growing number of options in the therapeutic armamentarium, particularly the small molecule oral kinase inhibitors and immunotherapies, pose clinical challenges with regard to potential cardiac complications, including AF.

Ibrutinib is a first-of-its-class Bruton Tyrosine Kinase (BTK) inhibitor, an oral therapy that is effective for the treatment of patients with B-cell haematological malignancies. BTK is a cytoplasmic tyrosine kinase that plays a key role in the downstream signal transduction pathway of the B-cell receptor, and is pivotal in modulating B-cell proliferation, differentiation and survival. Research showed that ibrutinib use was associated with significant cardiovascular adverse effects, particularly increased rates of hypertension, AF and bleeding. Increased bleeding risk and de novo AF in these patients may present a clinical conundrum in management. The risk of AF amongst patients receiving ibrutinib is increased up to 4-fold, with prevalence estimates observed at 3.5 to 25 % 12. Considering that hypertension is an important cause of AF, incident hypertension in patients treated with ibrutinib was up to 72 %<sup>13</sup>. Furthermore, new or worsened hypertension was associated with more than a doubling of major adverse cardiovascular events, including cardiac arrhythmias. Comparatively, the other two FDA approved newer-generation and more selective BTK inhibitors, namely acalabrutinib and zanubrutinib, are generally associated with lower risks of AF.

Experimental studies suggested that the mechanism of ibrutinib leading to AF is mediated via various

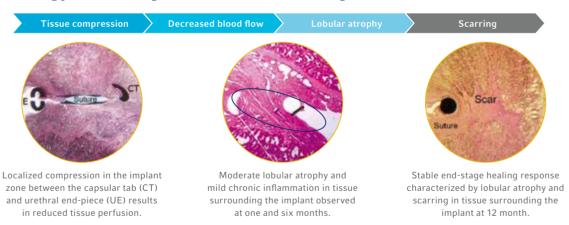




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"off-target" pathways, amongst which C-terminal Src Kinase (CSK) inhibition seemed the most promising<sup>14</sup>. Further research is needed in this area to elucidate the mechanisms of drug-induced AF in these novel cancer treatment modalities. These will allow us to select the most appropriate agents for our patients and formulate preventive strategies, ultimately maximising therapeutic efficacy at the minimised risk of cardiac complications.

The other novel cancer therapies of interest include immune checkpoint inhibitors and chimeric antigen receptor T cell (CAR-T) therapy, amongst others. However, data regarding their potential role in AF remained limited, and more prospective studies focusing on arrhythmic outcomes are needed.

The management principles of AF in cancer patients generally follow those of usual AF management. Aetiological assessments, including thyroid function tests, electrolytes and the exclusion of valvular/structural heart diseases, are essential. Rate, rhythm control, and stroke prevention with appropriate anticoagulation constitute the mainstay. Nevertheless, here, a structured review of the drugs is particularly pivotal. Cancer patients could be at increased vulnerability to drug-drug interactions in various ways. These principally occur via interfering with CYP3A4, CYP2D6, and P-glycoprotein. For example, verapamil and diltiazem are both CYP3A4 inhibitors and their use can potentially raise blood levels of various anticancer drugs. On the other hand, cancer therapies that are CYP3A4 or p-glycoprotein inhibitors (e.g. imatinib, ibrutinib, tamoxifen, and abiraterone) have the potential to increase serum level of direct oral anticoagulants. Such may potentially increase bleeding tendencies in cancer patients with AF. Conversely, cancer therapies that are enzyme inducers (such as dexamethasone and paclitaxel) may decrease serum levels of anticoagulants and precipitate an increased risk of stroke or thromboembolism. Other than thorough history taking and a meticulous risk assessment of drug-drug interactions, another possible answer to the clinical conundrum might be a direct measurement of anticoagulant activity in these patients on an individualised basis. However, overall evidence remains limited in this area, and further research is warranted11, 15.

#### CONCLUSIONS

With the increased complexity of therapeutic landscapes in the ageing population and the emergence of novel drugs, including cancer therapies, the clinical challenges of drug-induced cardiac arrhythmias are now greater than ever. Prompt recognition, high levels of clinical vigilance, and anticipatory risk mitigation with therapeutic monitoring in high-risk patients remain the key principles in clinical management. Treatment of specific cardiac arrhythmias follows the existing clinical guidelines. Risks and mechanisms of cancer therapyinduced AF, and the potential role of therapeutic monitoring of direct anticoagulants represent areas warranting further research in cancer patients with or at risk of AF. Reinforced systems approach in pharmacovigilance may further protect against the burden of drug-induced life-threatening arrhythmias, including TdP in the community.

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| Monday   | ay   | Tuesday   | Wednesday   | Thursday *In-person / Zoom Live  | Friday  | Saturday<br>*In-person   |
|--|--|---|---|--|---|--|
|  |  |   |   | HKMA-HKSTP CME Lecture A Novel Urinary DNA Isolation Method to Improve HPV Detection *Certificate Course in Ophthalmology 2023   | 3   | Seminar on Infectious Diseases 2023 Diseases 2023 Diseases 2023 Can You Be a Game Changer Too? Too? Too Seminary Care Seminary Care In Primary |
| *Toom Live horozent to solve the problems on Coerview and Updates on Management teatificate Course on Healthcare Mediation 2023 (Video Lectures)                           | * In-person / Zc<br>Hallux Valgus<br>Overview and<br>Ower Manageme<br>• Certificate Mo<br>Healthcare Mo<br>2023 (Video L                                   | oom Live s: An I Updates I Updates unst urse on ediation ectures) | * The Hong Kong Neurosurgical Society Monthly Academic Meeting - To be confirmed * In-person/Zoom Live HKMA-CUHK Medical Centre CME Programme 2023 (Rysical Lecture - Online) Women's Health - Topic: Common Breast Pathology * Certificate Course in Cardiology 2023 | *In-person Acute diarrhea Management in Pediatric Patients *Certificate Course in Ophthalmology 2023 - Module 2  | 10  | *In-person The HKMA District Health Network (YTM) Mental Health CME Seminar 1. No Health Without Mental Health - Destignatisation and Human Rights Advocacy 2. A Human Rights Approach to Psychosocial Disabilities  |
| *Zoom Live Individualised Management of Male Lower Urinary Tract Symptoms (LUTS) in Primary Care Setting *Certificate Course on Healthcare Mediation 2023 (Video Lectures) | *Zoom Live Individualised Management of Monagement of Lower Urinary Symptoms (Lt. Primary Care 9 *Certificate Cou Healthcare Mediation 2022 (Video Lecture | f Male<br>Tract<br>TTS) in<br>Setting<br>urse on                  | *Certificate Course in Cardiology 2023  | *Zoom Live Navigating the Management of Atopic Dematitis *Certificate Course in Ophthalmology 2023 - Module 2  | 17  | 18   |
| * In-person / Zoom Live HKMA-GHK CME Programme 2023 Topic: To-be-confirmed * Certificate Course on Healthcare Mediation 2023 (Video Lectures)                              | * In-person / Zoo<br>HKMA-GHK (<br>Programme 20<br>Topic: Το-be-α<br>* Certificate Cou<br>Healthcare Me<br>2023 (Video Le                                  | Dur Live CME 23 Onfirmed urse on diation ctures)                  | * Certificate Course in Cardiology 2023   | * In-person / Zoon Live HKAA-HKSIP CME Lecture HKAA-HKSIP CME Lecture Topic: DNA Methylation and IIs Role in Fletth and Diseases: Implications for Early Prediction, Prevention and Intervention Pophthalmology 2023 - Module 2 * FMSHK Executive Committee Meeting * FMSHK Council Meeting * FMSHK (Such Aumal General Meeting * FMSHK 59th Aumal General Meeting * HKSHK 59th Aumal General Meeting * HKSHK 59th Aumal | * In-person The HKMA District Health Network (Yau Tsim Mong) CME Lecture in Physical Attendance Mode - Osteoarthritis of Knees: Drugs? Injection? Others? | 25   |
| *Zoom Live The Role of Probiotics in the Treatment of NAFLD and Metabolic Disease  |  | 28  | * Zoom Live The HKMA District Health The HKMA District Health Network (Central, Western & Southern) CME Lecture - Diagnosis and Management of Common Skin Infections in Primary Care * Certificate Course in Cardiology 2023  | * In-person The HKMA District Health Network (Hong Kong East) CME Lecture in Physical Attendance Mode - Changing Paradigms in Hyperlipidemia Management What are the Available Evidence in CV Risk Reduction and Long Term Safety? * Certificate Course in Ophthalmology 2023 Ophthalmology 2023   |   |  |

For adult patients with CKD and T2D

## A different pathway leads to different possibilities

Delay CKD progression with Kerendia<sup>1</sup>

- The first and only non-steroidal MRA approved to treat CKD in T2D'14
- Proven to delay CKD progression and reduce the risk of CV events14
- Manageable impact on serum potassium<sup>1,4</sup>
- Included in 2022 ADA and KDIGO Guidelines with level A evidence<sup>25</sup>



\* As of 9 Jan 2023

ADA American Diabetes Association, OXD-chronic kidney disease; CV-cardiovascular, KD/GO-Kidney Disease Improving Global Outcomes; MRA-mineralocorticoid receptor antisponst; T2D-type

Seferences: 1. Kerendia 10 / 20 mg film-coated tablets Hong Kong prescribing information (Auly 2022). 2, Kidney Discase: Improving Global Outcomes (KDIGO) Diabetes Work Group. Ridney Ins. 2022;102(53):51-5127. 3. Drug Office, HTSAR, Available at: https://www.drugoffice.gov/ris/eps/drug/productDeta/ren/pharmaceutsial\_trade/140539. Accessed 9 Jan 2021. 4, Bakins GL, et al, N Engl. J Med. 2020;363:2219-2229. 5, American Diabetes Association Professional Practice Committee. Diabetes Care. 2022;45(5):ppd., 1):5175-5184.

#### Kerendia 10 / 20 mg tablets Abbreviated Prescribing Information

(Please refer to the full prescribing information before prescribing)

Composition: Active ingredient; finerenone, Excipients; crostamellose sodium, hypron Ittanium dio ode, ferric axide yellow (for 20 mg tablet), ferric oxide yellow (for 20 potassium is \$4.6 mmol/L; may be considered with additional serum monitoring within the First 4 weeks based on patient characteristics and serum potassium leves if serum potassium >5.0 mmol/L in in patients with eCFR <25 mL/min/1.73m². The starting dose is \$20 mg once daily if eCFR a66 mL/min/1.73m² \$10 mg once daily if eGFR 225 to 460 mL/min/1.73m\*. Continuation, Four weeks after initiation or re-start or up-titration, remeasure serum porassium and GFR. Thereafter, remeasure serum potassium periodically and as needed based on patient characteristics and serum potassium levels. Contraindications \*Taking concomitant medications, that are strong CYP344 inhibition \* With adversal insufficiency. Warnings and precadions: • Hyperkalanmia. • Avoid contemitant use with potassium sparing diversit, and other minerallocofficial receptor antagonats. Used with caution and monitor serum potassium when taken concentrating with potassium supplements. Intrethopinin, or trimethopinin-sulfamethoxazole. • Avoid in patients with severe hepatic impairment (Child Pugh C). Consider additional serum potassium monitoring in patients with moderate hepatic impairment (Child Pugh B). • Institution of Kerendia vith restricted in one trecommended in patients with effect of the Verbilland of the service of the vith moderate hepatic impairment (Child Pugh B). • Institution of Kerendia vith caution regarding serum potassium alreads in patients with each recommended in patients with each recommended in patients. recommended in paediatric patients. • Keneridia should not be used during pregnancy unless there has been careful consideration of the benefit for the mother and the risk to the foetus. If the patient becomes pregnant while taking Kerendia, the patient should be informed of potential risks to the foetus. Advise women of childbearing potential to use effective contraception and not to bree infeed. during treatment of Kirrendia.\* Monitor sumum potassium expertially during initiation of or changes to during of Kerendia or a moderate or weak CYP3A4 inhibitor. Avoid concomitant are with strong CYP3A4 inducers, incoordinate CYP3A4 inducers, or concomitant intake of grapefruit or grapefruit price. Undesirable effects: Very common (a10%), hyperkalaerina. Common (a1%) to <10%). hyponatrienia, hypotension, glamerular filtration rate decreased. For further defails, please refer to the full prescribing information (July 2022) (MA-M. FIN-HK-0074-1 Dec 2022).

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| Date | / Time                | Function   | Enquiry / Remarks   |
|------|-----------------------|--|---|
| 7    | 2:00 PM               | In-person / Zoom Live  | HKMA CME Dept   |
| 2    | <b>THU</b>            | HKMA-HKSTP CME Lecture A Novel Urinary DNA Isolation Method to Improve HPV Detection Organiser: The Hong Kong Medical Association and Hong Kong Science and Technology Park Speaker: Dr TAM Ching-ting Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong Certificate Course in Ophthalmology 2023 - Module 2  | Tel: 3108 2507<br>1 CME Point<br>Ms Vienna LAM  |
|      | 7.00 1 W              | Organiser: The Federation of Medical Societies of Hong Kong<br>Speaker: Dr Tommy Chung-yan CHAN, Dr Leslie Ka-lok CHENG  | Tel: 2527 8898  |
| 4    | <b>SAT</b> 2:00 PM    | In-person Seminar on Infectious Diseases 2023 1. Ending the AIDS Epidemic, Can You Be a Game Changer Too? 2. Management of Adults with Chronic Hepatitis B Infection in Primary Care 3. Vaccines and Immunization Updates Organiser: Hong Kong Medical Association and HK Society for Infectious Diseases Speaker: Dr Bonnie Chun-kwan WONG; Dr Loey Lung-yi MAK; Dr LAI Chun-yip Venue: Hospital Hall, 8th Floor, Block G, Princess Margaret Hospital | HKMA CME Dept<br>Tel: 3108 2507<br>3 CME Point  |
| 6    | 2:00 PM<br>MON        | Zoom Live<br>Innovative approach to solve the problems on LUTS<br>Organiser: The Hong Kong Medical Association<br>Speaker: Dr YU Cheong  | HKMA CME Dept<br>Tel: 2527 8452<br>1 CME Point  |
| 7    | 2:00 PM <b>TUE</b>    | Hallux Valgus: An Overview and Updates on Management Organiser: The Hong Kong Medical Association and Hong Kong Sanatorium & Hospital Speaker: Dr CHAN Wai-chung Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong  |   |
|      | 7:00 PM               | Certificate Course on Healthcare Mediation 2023 (Video Lectures) Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Ludwig Chun-hing TSOI   | Ms Vienna LAM<br>Tel: 2527 8898   |
| 8    | 7:30 AM <b>WED</b>    | Organizer: Hong Kong Neurosurgical Society Speaker(s): Dr XIAO Xiao Chairman: Dr Danny Tat-ming CHAN Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting   | CME Accreditation: 1.5 points<br>College of Surgeons of Hong Kong<br>Enquiry: Dr Calvin MAK<br>Tel: 2595 6456 Fax. No.: 2965 4061<br>HKMA CME Dept. |
|      |                       | HKMA-CUHK Medical Centre CME Programme 2023 (Physical Lecture + Online) Women's Health - Topic: Common Breast Pathology Organiser: The Hong Kong Medical Association and CUHK-Medical Centre Speaker: Dr IP Yiu-tung Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong  | Tel: 3108 2507<br>1 CME Point   |
|      | 7:30 PM               | Certificate Course in Cardiology 2023 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr CHENG Yuet-wong  | Ms Vienna LAM<br>Tel: 2527 8898   |
| 9    | 2:00 PM<br><b>THU</b> | In-person Acute diarrhea Management in Pediatric Patients Organiser: The HKMA District Health Network Speaker: Dr HUI Cheuk-man Venue: TBC   | HKMA CME Dept<br>Tel: 2527 8452<br>1 CME Point  |
|      | 7:00 PM               | Certificate Course in Ophthalmology 2023 - Module 2 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Michelle Ching-yim FAN, Dr Jasper Ka-wai WONG  | Ms Vienna LAM<br>Tel: 2527 8898   |
| 11   | 2:00 PM <b>SAT</b>    | In-person The HKMA District Health Network (YTM) Mental Health CME Seminar I. No Health Without Mental Health - Destigmatisation and Human Rights Advocacy 2. A Human Rights Approach to Psychosocial Disabilities Organiser: The HKMA District Health Network Speaker: Professor Michael Tak-hing WONG; Dr Simon Tat-ming NG Venue: Maggie, 2/F, Eaton Hotel, 380 Nathan Road, Kowloon, Hong Kong   | HKMA CME Dept<br>Tel: 2527 8452<br>2 CME Point  |
| 14   | + TUE 2:00 PM         | Zoom Live<br>Individualised Management of Male Lower Urinary Tract Symptoms (LUTS) in Primary<br>Care Setting<br>Organiser: The Hong Kong Medical Association<br>Speaker: Dr Vincent Tak-tsun LAW  | HKMA CME Dept<br>Tel: 2527 8452<br>1 CME Point  |
|      | 7:00 PM               | <u> </u>   | Ms Vienna LAM<br>Tel: 2527 8898   |
| 15   | 7:00 PM <b>WED</b>    | Certificate Course in Cardiology 2023 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Jason Kwok-chun KO   | Ms Vienna LAM<br>Tel: 2527 8898   |
| 16   | 2:00 PM<br>THU        | Navigating the Management of Atopic Dermatitis Organiser: The Hong Kong Medical Association Speaker: Dr WONG Hing-wing   | HKMA CME Dept.<br>Tel: 3108 2507<br>1 CME Point   |
|      | 7:00 PM               | Certificate Course in Ophthalmology 2023 - Module 2 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr HO Wing-lau  | Ms Vienna LAM<br>Tel: 2527 8898   |

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## JARDIANCE demonstrated 38% RRR in CV death<sup>1,2</sup>

Established HbA1c efficacy<sup>2</sup>

Demonstrated safety profile<sup>1,2</sup>

Convenient, once-daily oral dosing<sup>2</sup>

ADA & EASD recognize JARDIANCE as the SGLT2 inhibitor with stronger evidence of CV benefits<sup>3#</sup>

Jardiance (empagliflozin)

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

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

ASAPDIANCE demonstrate (a Property of the Control o

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

\* Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the ADA and EASD stated that among patients with established CVD, there is likely cardiovascular benefit, with the evidence of benefit modestly stronger for empagification than canagification.

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aroute adequate glycaemic control. Indicated in patients with type 2 diabetes meliture and established cardiovascular disease to reduce the risk of cardiovascular death. 10 mg: Jardiance is indicated in failure. Design and administration: Type 2 diabetes meliture: Do my once daily, in patients tolerating to my once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. Can be taken with or without food. No dose adjustment is required for patients with eCFR 2 on IM/min/1.73m<sup>-1</sup> or with hepatic impairment, or for citying patients. Mear 7 actions of the patients with or without 120M. 10 mg may be initiated or continued down to an expected or display the patients of the patients with or without 120M. 10 mg may be initiated or continued down to an expected or state of the patients with severe renal impairment (eCFR 40 mL/min/1.73m<sup>-1</sup>), end-stage renal disease and patients on dialysis, as glycaemic efficacy depends on renal function. Special warnings and precautions: Should not be used in patients with severe renal impairment (eCFR 40 mL/min/1.73m<sup>-1</sup>), end-stage renal disease and patients on dialysis, as glycaemic efficacy depends on renal function. Special warnings and precautions: Should not be used in patients with severe renal impairment efforts of the patients with a patient situation of the patients of the patients with a patient situation of the patients of the patients

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



| Date / Time            | Function   | Enquiry / Remarks   |
|------------------------|--|---|
| 21 TUE 2:00 PM 7:00 PM | In-person / Zoom Live HKMA-GHK CME Programme 2023 Topic: To-be-confirmed Organiser: The Hong Kong Medical Association and Gleneagles Hong Kong Hospital Speaker: To-be-confirmed Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong Certificate Course on Healthcare Mediation 2023 (Video Lectures) Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Sandy Kit-ying CHAN | HKMA CME Dept<br>Tel: 3108 2507<br>1 CME Point<br>Ms Vienna LAM<br>Tel: 2527 8898 |
| 22 WED 7:00 PM         | Certificate Course in Cardiology 2023 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr YUNG Chi-yui   | Ms Vienna LAM<br>Tel: 2527 8898   |
| 23 THU 2:00 PM 7:00 PM |  | HKMA CME Dept<br>Tel: 3108 2507<br>1 CME Point<br>Ms Vienna LAM                   |
| 7:00 PM<br>7:30 PM     | Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong   | Ms Nancy CHAN   |
| 8:30 PM<br>8:30 PM     | Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong <b>HKFMS Foundation 20<sup>th</sup> Auunal General Meeting</b> Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong   | Ms Nancy CHAN<br>Tel: 2527 8898   |
| <b>24</b> FRI 2:00 PM  | In-person The HKMA District Health Network (Yau Tsim Mong) CME Lecture in Physical Attendance Mode - Osteoarthritis of Knees: Drugs? Injection? Others? Organiser: The HKMA District Health Network Speaker: Dr HO Cham-on Venue: Maggie, 2/F, Eaton Hong Kong, 380 Nathan Road, Kowloon, Hong Kong  | Mr Peter HO<br>Tel: 3108 2514<br>1 CME Point                                      |
| 27 MON 2:00 PM         | Zoom Live The Role of Probiotics in the Treatment of NAFLD and Metabolic Disease Organiser: The Hong Kong Medical Association Speaker: Dr Norman Nor CHAN  | HKMA CME Dept<br>Tel: 3108 2507<br>1 CME Point                                    |
| 29 WED 2:00 PM         | Zoom Live The HKMA District Health Network (Central, Western & Southern) CME Lecture – Diagnosis and Management of Common Skin Infections in Primary Care Organiser: The HKMA District Health Network Speaker: Dr HO King-man  | Mr Peter Ho<br>Tel: 3108 2514<br>1 CME Point                                      |
| 7:00 PM                | Certificate Course in Cardiology 2023 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Harry George MONG  | Ms Vienna LAM<br>Tel: 2527 8898   |
| <b>30</b> THU          | In-person The HKMA District Health Network (Hong Kong East) CME Lecture in Physical Attendance Mode - Changing Paradigms in Hyperlipidemia Management: What are the Available Evidence in CV Risk Reduction and Long Term Safety? Organiser: The HKMA District Health Network Speaker: Dr CHEUNG Chi-yeung Venue: Wanchai Premises, 5/F, Duke of Windsor Social Building, 15 Hennessy Road, Wan Chai, Hong Kong  |   |
| 7:00 PM                | Certificate Course in Ophthalmology 2023 - Module 2 Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Frank Hiu-ping LAI, Dr Danny Siu-chun NG   | Ms Vienna LAM<br>Tel: 2527 8898   |

#### **Answers to Dermatology Quiz**

#### **Answers:**

1. The clinical picture is most compatible with Pityriasis rubra pilaris (PRP). Other differential diagnoses that must be excluded include Psoriasis vulgaris, Cutaneous T-Cell Lymphoma, Erythroderma (Exfoliative Dermatitis), and rarely Erythrokeratoderma variabilis progressiva.

Pityriasis rubra pilaris is a chronic papulo-squamous disease of unknown aetiology. The familial type (autosomal dominant inheritance) has a gradual onset, whereas the acquired form has an acute onset. Judging from the clinical features, this patient has Type I classic adult PRP, which is characterized by rapid onset of well demarcated reddish "orange tinted" scaly plaques, palmoplantar keratoderma with painful fissures and keratotic follicular papules commonly seen on the dorsal of proximal phalanges, wrists and elbows.

This is the most common form of PRP, accounting for over 50 % of all cases. The disease typically spreads in a craniocaudal direction. It may progress to Erythroderma with characteristic distinct areas of uninvolved skin, so called "Islands of sparing" (Fig.2). Nail and mucosal lesions may occur.

- Diagnosis is usually based on a correlation between clinical and histopathological findings. Skin biopsy, therefore, should be done. Though the histopathological findings are not diagnostic, they help to exclude other differential diagnoses.
- 3. Topical therapies often have limited effect in view of the extensiveness and refractoriness of PRP. Topical corticosteroids and emollients may relieve symptomatic but have little long-term therapeutic effect. Other agents like calcipotriol and tazarotene have equivocal effects. Phototherapy, in general, is unsatisfactory as compared to its use in Psoriasis, similar to the use of methotrexate. Oral retinoids such as acitretin might be useful when combined with phototherapy. In children, oral isotretinoin has been tried with good efficacy. In recent years, the use of biologics targeting tumour necrosis factor-alpha, interleukins 12 and 23, 17 and 23 had been reported, but so far, there is no formal approval for their use.
- 4. In general, the familial form of the disease may be persistent throughout life. The acquired form, however, may resolve spontaneously within 1 3 years. The Type I classic adult PRP has the best prognosis. It had been reported that 80 % of patients have remission in an average of 3 years.

#### Dr CHONG Lai-yin

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med) Specialist in Dermatology & Venereology

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# Joint Annual Scientific Meeting 2023

10 December 2023 • Sunday

**CME Accreditation in Progress** 

#### **Highlights**

- Using of Cryomodulation and Exosomes with RF Microneedling
- Personalized Treatment for Atopic Dermatitis
- Traditional Chinese Medicine for Psoriasis and Eczema
- Advances in Paediatric Dermatology
- Pearls in Dermatological Investigation and Practice

#### **Registration Fee**

HKCD, HKSPD, HKSDV member Waived

Non-member HK\$550

#### **Registration Deadline**

30 November 2023 (Thursday)

#### **Meeting Secretariat**

MIMS (Hong Kong) Limited

Tel: (852) 2155 8557 Fax: (852) 2559 6910

E-mail: mandy.choi@mims.com

Registration information

www.hkcderm.org/cme-calendar/



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T2DM patient typically achieved HbA1c target by 18 weeks on metformin monotherapy as demonstrated in the study<sup>2#</sup>



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Primary Endpoint: At week 18, mean change from baseline HbA1c was - 2.4% for sitagliptin/metformin FDC and - 1.8% for metformin monotherapy (p < 0.001).<sup>2</sup>

Study Design: This double-blind study (18-week Phase A and 26-week Phase B) randomized 1250 drug-nalve patients (defined as not on AHA therapy within the 4 months (or longer) preceding the screening visit) with T2DM [mean baseline hemoglobin A1c (HbA1c) 93%] to sitagliptin/metformin 50/1000 mg bid or metformin 500 mg bid or metformin 50/1000 mg bid or metformin 1000 bid). Results of the primary efficacy endpoint (mean HbA1c reductions from baseline was 9.9% Alexander of the study of the

Abbreviations: HbA1C-Haemogloin A1C, T2DM-Type 2 Diabetes Mellitus, FDC-Fixed-dose Combination, AHA-antityperglycameric agents, BID-twice a day. Reference: 1, American Diabetes Association Professional Practice Committee. 9, Pharmacologic approaches to give emic carbon to the control in patients with year carbon. Annual Practice Committee. 9, Pharmacologic approaches to give emic carbon to the process of the provided programs of the process of the proc







