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Important Safety Information: SHINGRIX is contraindicated in anyone with hypersensitivity to the active substances or to any of the excipients. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine. SHINGRIX should be given with caution to individuals with thrombocytopenia or any coagulopathy disorder since bleeding may occur following intramuscular administration to these subjects. Syncope (fainting) can be associated with the administration of injectable vaccines, including SHINGRIX. Procedures should be in place to avoid falling injury. In a post-marketing observational study in individuals aged 65 years or older, an increased risk of Guillain–Barre syndrome (estimated 3 excess cases per million doses administered) was observed during the 42 days following vaccination with SHINGRIX. Available information is insufficient to determine a causal relationship with SHINGRIX. In adults aged 50 years and above, the most frequently reported adverse reactions were pain at the injection site, myalgia, fatigue, and headache. Most of these reactions were not long-lasting (median duration of 2 to 3 days). Reactions reported as severe lasted 1 to 2 days. In adults aged 18 years of age who are immunodeficient or immunosuppressed due to disease or therapy (referred to as immunocompromised (IC)), the safety profile was consistent with that observed in adults ≥50 years of age. There are limited data in adults aged 18–49 years at increased risk of HZ who are not IC. Overall, there was a higher incidence of some adverse reactions in younger age groups. Studies in IC adults ≥18 years of age (pooled analysis): the incidence of pain at the injection site, fatigue, myalgia, headache, shivering, and fever was higher in adults aged 18–49 years compared to those aged 50 years and above. Studies in adults ≥50 years of age (pooled analysis): the incidence of myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms was higher in adults aged 50–69 years compared to those aged 70 years and above. There are no data from the use of SHINGRIX in pregnant women. As a precautionary measure, it is preferable to avoid the use of SHINGRIX during pregnancy. It is unknown whether SHINGRIX is excreted in human milk. As with any vaccine, a protective immune response may not be elicited in all vaccinees.

References: 1. GlaxoSmithKline, Shingrix Hong Kong Prescribing Information. GSKDA 2, MSD. Live attenuated Zoster Vaccine Prescribing Information.
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### The Cover Shot

In 1921, Frederick Banting and Charles Best, under the supervision of John Macleod, successfully prepared crude extracts from the canine pancreas, reinjected it into pancreatectomised dogs and led to the discovery of insulin. Two years ago, we celebrated the centenary of insulin discovery which has benefited mankind for over a century.

The cover shows two Shiba-Inu, a Japanese breed of small to medium-sized dogs. Their adorable fox-like face with dramatic expressions, coat colour and curly tails have made them one of the most popular companion dogs in Hong Kong. Originally used as hunting dogs, Shiba Inus are bold and curious, two good qualities essential in medical research, leading to transformative discoveries like insulin.

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**Dr Paul CH LEE**  
MBBS (HK), MD (HK), FHKCP, FHKAM (Medicine), FRCP (Edinburgh)  
Clinical Assistant Professor,  
Department of Medicine,  
School of Clinical Medicine,  
The University of Hong Kong
Treating Type 2 Diabetes - New Perspectives

Dr Paul CH LEE
MBBS (HK), MD (HK), FHKCP, FHKAM (Medicine), FRCP (Edinburgh)
Clinical Assistant Professor, Department of Medicine,
School of Clinical Medicine, The University of Hong Kong

Type 2 diabetes puts an individual in a lifelong challenge, which is partly related to the development of various complications and an increased risk of mortality. This issue of the Hong Kong Medical Diary is a collection of contemporary articles contributed by a group of specialists who aim to improve the overall standard of care for patients with type 2 diabetes in their respective areas of interest.

Over the years, despite the more liberal use of statins and renin-angiotensin-aldosterone system (RAAS) blockers, a significant proportion of patients with type 2 diabetes are still at risk of developing or dying of cardiovascular diseases (CVD), including heart failure. Moreover, the incidence of non-vascular complications such as diabetic kidney disease (DKD) remains high. The advent of sodium-glucose co-transporter 2 inhibitors (SGLT2i) and novel formulations of glucagon-like peptide-1 receptor agonist (GLP1rA) has declared a new chapter in managing type 2 diabetes. Furthermore, findings from several large-scale landmark randomised controlled trials of SGLT2i, GLP1rA, and non-steroidal mineralocorticoid receptor antagonists have also modified clinical guidelines for DKD and heart failure. Prof Syndey Tang and Dr Gary Chan, two nephrologists, and Dr Emmanuel Wong, a cardiologist, have provided us with a clinical overview of the changing treatment landscape in DKD and heart failure, respectively.

On the other hand, while we are hoping that patients with type 2 diabetes will live longer with an improved standard of diabetes care, it is time to put more focus and greater awareness on some emerging diabetic complications such as fatty liver and diabetic bone disease. It has been reported that over 70% of individuals with type 2 diabetes have fatty liver. Dr Loey Mak, a hepatologist, discussed the mutually detrimental relationship between fatty liver disease and type 2 diabetes, and the clinical care pathway in managing fatty liver disease in type 2 diabetes. Type 2 diabetes is also associated with an increased risk of frailty fractures, which is influenced by several diabetes-specific risk factors independent of the bone mineral density of affected individuals. Dr David Lui, an endocrinologist, shared with us practical tips for using these modern gadgets.

In recent years, along with the expanding armamentarium of pharmacological agents for treating diabetes and its complications, the more widespread application of diabetes technology, such as new glucose monitoring devices, has also enabled us to move towards a more personalised approach in diabetes care, so that diabetes treatment can be tailored to meet the needs of the individual patient. Dr Nicole Chau, an endocrinologist, enlightened us on the advances in the field and shared with us practical tips for using these modern gadgets.

The last decade marked a major breakthrough in the pharmacological management of type 2 diabetes. Along with the rising global prevalence of type 2 diabetes, there is a pressing and continuous need to optimise the current treatment strategies and identify new therapeutic targets. Prof Elaine Chow, an endocrinologist and an expert in clinical pharmacology, highlighted a few upcoming anti-diabetic agents and possible drugs in the pipeline.

There’s a saying, “The dog is a man’s best friend”. In the final Lifestyle article of this issue, Dr Eunice Leung and Dr Chariene Woo, two young endocrinologists and dog-lovers, shared their experience and stories of petting a dog in Hong Kong.

Finally, I would like to express my gratitude to all the contributing authors for their invaluable support, and I sincerely hope this issue will appeal to the readers of the Hong Kong Medical Diary. Enjoy!
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Pharmacological Therapy for Diabetic Kidney Disease in 2023

Dr Gary CW CHAN
B.Sc., MBBS, PhD, FHKCP, FHKAM(Medicine), FRCP(Lond, Edin)
Division of Nephrology, Department of Medicine, Queen Mary Hospital

Prof Sydney CW TANG
MBBS, MD, PhD, FHKCP, FHKAM(Medicine), FRCP(Lond, Edin, Glasg), FASN
The University of Hong Kong

INTRODUCTION

The burden of diabetes mellitus (DM) is rapidly rising, and current projections estimate the global prevalence of individuals with DM to reach 7.7% (439 million) by 2030.1 The main problem with this disease entity is its propensity to incur macro- and micro-vascular complications over time such that progressive kidney disease and cardiovascular (CV) morbidity and mortality is the common end-game for most.

It has been estimated that one-third of individuals with DM will develop diabetic kidney disease (DKD), which is the leading cause of end-stage kidney disease (ESKD) worldwide. DKD is, therefore, commonly encountered in clinical practice and awareness of the management strategies for this disease becomes essential. It is the aim of this article to broadly review the available pharmacological armamentaria for DKD, focusing more on the newer drugs that have changed the therapeutic landscape in recent years. It must not be forgotten, however, that a comprehensive strategy to retard kidney disease progression and abrogate CV complications over time such that progressive kidney disease and cardiovascular (CV) morbidity and mortality is the common end-game for most.

THE OLD GUARD

Glycaemic and Blood Pressure Control

For decades, our management of DKD has focused on glycaemic and blood pressure control. The trials and tribulations which have led to guidance on glycaemic targets and the common practice of renin-angiotensin system (RAS) blockade, using angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), have been well described.2

Current recommendations are to target HbA1c ranging from < 6.5% to < 8.0% in patients with diabetes and chronic kidney disease (CKD). Individualisation is important and must account for considerations such as the severity of CKD, presence and load of comorbidities as well as the patient’s remaining life expectancy. The benefits of rigorous diabetic control must be balanced against the risk of hypoglycaemia. Metformin remains the backbone oral hypoglycaemic agent for DKD individuals with an eGFR ≥ 30 ml/min/1.73 m2 when

the main concern is unsatisfactory glycaemic control, based on its effectiveness, availability, affordability, and evidence of CV benefit. It would be prudent to lower the total daily dose to 1g when eGFR drops below 45 ml/min/1.73 m2 to attenuate the risk of lactic acidosis.

A newer class of antidiabetic agents, which have hinted at renoprotective promise, are the glucagon-like peptide-1 (GLP-1) receptor agonists. These incretin-mimetics stimulate the release of glucose-dependent insulin, regulate post-prandial glucagon secretion and delay gastric emptying. GLP-1 receptor agonists have been demonstrated to substantially improve glycaemic control, without increasing the risk of hypoglycaemia, and reduce body weight. More importantly, this class of drugs has been shown to reduce major CV events in individuals with type 2 DM across a wide strata of estimated glomerular filtration rates (eGFR).3 These agents have also shown renal benefits in the form of albuminuria reduction, the precise mechanisms of which have not been elucidated. At present, GLP-1 receptor agonists have been advocated in patients with DKD who are not attaining glycaemic targets despite lifestyle modifications and the use of metformin and sodium-glucose co-transporter 2 (SGLT2) inhibitors.

Hypertension is a prevalent comorbidity in individuals with type 2 DM, and is an independent modifiable risk factor for the development and acceleration of micro- and macro-vascular complications. There is no doubt that the achievement of stringent blood pressure control, irrespective of the agent used, retards the onset and progression of DKD to confer a survival benefit. Inhibitors of RAS including ACE inhibitors and ARBs are widely employed to control the blood pressure of patients with DM. They are superior to other antihypertensive agents in DKD by virtue of their capacity to reduce intra-glomerular pressure and hence proteinuria by preferentially dilating the efferent arteriole.4 Attempts to achieve a more profound RAS blockade, by treating patients with DKD using a combination of ACE inhibitors with ARBs, however, did not produce a clear renal benefit. Instead, it was associated with an increased propensity for hyperkalaemia and acute kidney injury.5,6 Of note, the data for RAS blockade have been established only in secondary prevention trials. Henceforth, the clinical practice guidelines of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative have not enforced the implementation of ACE inhibitors or ARB.
for the primary prevention of DKD in normotensive individuals with normo-albuminuria.

**THE NEW ERA**

Two new classes of drugs holding the spotlight in the past eight years, with just as many landmark trials, have altered the prognostic landscape of patients with DKD. More importantly, the benefits appear to be above and beyond that offered by their glycaemic and blood pressure lowering properties. These two classes of drugs are the SGLT2 inhibitors and the nonsteroidal mineralocorticoid receptor antagonist (MRA).

**Sodium-Glucose Co-Transporter Inhibition**

Selective inhibitors of SGLT2 are able to harness the kidney’s ability to regulate glucose homeostasis by blocking the reabsorption of filtered glucose in the proximal convoluted tubules. This action concomitantly reduces tubular sodium reabsorption and increases sodium delivery to the macula densa. The result is afferent arteriolar vasoconstriction via tubuloglomerular feedback, which reduces intra-glomerular pressure to confer renoprotection.

The renal and CV benefits of SGLT2 inhibitors for individuals with DKD have been repeatedly demonstrated. These include major reductions in the risk of CKD progression, heart failure and CV death. Importantly, these benefits appear to be present regardless of eGFR or the severity of albuminuria. Moreover, this class of drugs is able to promote an attractive CKD portfolio, which includes blood pressure and body weight optimisation by way of its natriuretic properties and was first incorporated into the 2020 KDIGO guidelines, supported by both the American Diabetes Association and American College of Cardiology. These guidelines recommended starting an SGLT2 inhibitor in individuals with DM and CKD who have an eGFR ≥ 30 mL/min/1.73 m² on the basis of results from earlier investigations. Subsequently, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-Ckd) and the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trials included participants with an eGFR ≥ 25 mL/min/1.73 m². Most recently, the Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) enrolled an exclusive CKD population with an eGFR ≥ 25 mL/min/1.73 m² in association with macroalbuminuria or eGFR 25-59 mL/min/1.73 m² with microalbuminuria if diabetic retinopathy was present). FIGARO-DKD extended the inclusion criteria of FIDELIO-DKD and enrolled participants with milder CKD (eGFR 25-59 mL/min/1.73 m² with microalbuminuria irrespective of retinopathy status). Finerenone resulted in the composite outcome of ESKD, sustained eGFR decline of ≥ 40%, or death from kidney causes to be significantly lower in FIDELIO-DKD (HR: 0.82; 95% CI: 0.73-0.93; P = 0.001) and tended towards significance in FIGARO-DKD (HR: 0.87; 95% CI: 0.76-1.01). Reduced composite CV outcomes of CV death, non-fatal myocardial infarction or stroke, or hospitalisation for heart failure were also statistically significant in both trials, and these results were reiterated in the FIDELITY pooled analysis of these two trials (Renal HR: 0.77; 95% CI: 0.67-0.88; P = 0.0002 and CV HR: 0.86; 95% CI: 0.78-0.95; P = 0.0018).

Finerenone was well tolerated. FIDELIO-DKD and FIGARO-DKD enrolled participants on maximally tolerated RAS blockade. Investigator-reported hyperkalaemia occurred in 14% in the finerenone group versus 6.9% in the placebo group, which is reminiscent of the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial, in which combination therapy

SGLT2 inhibition has also been explored in ESKD patients who develop DM following renal transplantation. In a multicentre cohort of 2,083 kidney transplant recipients (KTR) with DM, SGLT2 inhibitors (n = 226 [10.8%]) prescribed for > 90 days reduced the composite risk of all-cause mortality, death censored graft failure and doubling of serum creatinine following multivariate and propensity score-matched analyses (adjusted HR: 0.43, 95% CI: 0.24-0.78; P = 0.006 and adjusted HR: 0.45, 95% CI: 0.24-0.85; P = 0.013). Further studies are required to fully delineate the use of SGLT2 inhibitors following renal transplantation, but careful selection of KTRs for this therapy is key. Favourable KTR characteristics for SGLT2 inhibition include i) > 6-12 months post-transplantation with stable graft function; ii) no recent episodes of rejection necessitating an increase in immunosuppression; iii) absence of recurrent urogenital infections and iv) absence of peripheral vascular disease.

**Nonsteroidal Mineralocorticoid Receptor Antagonism**

Finerenone is the latest addition to the current armamentaria for the management of DKD. It is a nonsteroidal MRA with no active metabolites and a greater potency and selectivity on MR when compared to its steroidal predecessors, spironolactone and eplerenone.

Two large pivotal randomised controlled trials examining the efficacy of finerenone have recently been published, Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO-DKD) and Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes (FIGARO-DKD). FIDELIO-DKD enrolled participants with a greater severity of CKD (eGFR 25 - 77 mL/min/1.73 m² in association with macroalbuminuria or eGFR 25-59 mL/min/1.73 m² with microalbuminuria if diabetic retinopathy was present). FIGARO-DKD extended the inclusion criteria of FIDELIO-DKD and enrolled participants with milder CKD (eGFR > 90 mL/min/1.73 m² in association with macroalbuminuria or eGFR 25-59 mL/min/1.73 m² with microalbuminuria if diabetic retinopathy was present). Finerenone resulted in the composite outcome of ESKD, sustained eGFR decline of ≥ 40%, or death from kidney causes to be significantly lower in FIDELIO-DKD (HR: 0.82; 95% CI: 0.73-0.93; P = 0.001) and tended towards significance in FIGARO-DKD (HR: 0.87; 95% CI: 0.76-1.01). Reduced composite CV outcomes of CV death, non-fatal myocardial infarction or stroke, or hospitalisation for heart failure were also statistically significant in both trials, and these results were reiterated in the FIDELITY pooled analysis of these two trials (Renal HR: 0.77; 95% CI: 0.67-0.88; P = 0.0002 and CV HR: 0.86; 95% CI: 0.78-0.95; P = 0.0018).

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using an ACE inhibitor and an ARB led to a heightened risk of hyperkalaemia when compared to single agent ARB (9.9% versus 4.4%).20 However, treatment discontinuation due to hyperkalaemia occurred in only 1.7% of the finerenone group versus 0.6% in the placebo group. Coupled with the excessive risk of acute kidney injury in VA NEPHRON-D, it would appear that the addition of finerenone to an ACE inhibitor or an ARB is a more favourable combination. Notably, FIDELITY showed that hospitalisation for hyperkalaemia was rare, and there were no hyperkalaemia related deaths.

At present, the position of finerenone with respect to SGLT2 inhibitors for the management of individuals with DKD is debatable. Whilst both agents have demonstrated renal and CV protective benefits, the breadth of data over time has positioned SGLT2 inhibitors as a first-line drug therapy for individuals with DKD, and is well reflected in the 2022 KDIGO guideline amendments. SGLT2 inhibitors were not the standard of care at the initiation of the FIDELIO-DKD and FIGARO-DKD trials, and the addition of finerenone to SGLT2 inhibition needs further investigation. It is however plausible that hyperkalaemia resulting from the use of ACE inhibitors or ARBs in combination with finerenone may be mitigated by SGLT2 inhibition.18

ON THE HORIZON

Selective Endothelin Antagonism

Endothelin (ET) exerts its effect via two receptor subtypes, namely ETA and ETB. Intra-renal ETA receptor antagonism has been postulated to be beneficial in DKD. The initial RCT testing avosentan in patients with type 2 DM was terminated early due to strong adverse CV signals, but did demonstrate albuminuria reduction.19 The CV complications were postulated to be due to ETA inhibition by avosentan at high doses. Using a highly selective ETA receptor antagonist, the Atrasentan and Renal Events in Patients with Type 2 Diabetes and Chronic Kidney Disease (SONAR) trial demonstrated a reduction in the composite renal outcome of serum creatinine doubling or ESKD (HR: 0.65; 95% CI: 0.49-0.88; P 0.0047).20 Subsequently, a post hoc analysis of SONAR revealed the efficacy of atrasentan in slowing renal deterioration was larger in study participants with a steeper pretrial eGFR decline.21 Although the data for selective ET antagonists are not yet mature, the available evidence appears to suggest a possible future role in the management of DKD.

CONCLUSION

Please read the article entitled “Pharmacological Therapy for Diabetic Kidney Disease in 2023” by Dr Gary CW CHAN and Prof Sydney CW TANG 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 April 2023. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

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

1. In patients with diabetic kidney disease, clinicians should target HbA1c to < 6.5% without addressing the increased risk of hypoglycaemia.
2. Metformin dose should be kept at a total daily dose of 2 g when eGFR drops below 45 ml/min/1.73 m².
3. Patients with diabetic kidney disease should be treated with a combination of ACE inhibitors and ARB to achieve a more profound RAS blockade.
4. With regard to the mechanisms of renoprotection, RAS blockers such as ACE inhibitors and ARBs are associated with preferential dilatation of the afferent arteriole, whereas SGLT2i restores tubuloglomerular feedback and reduces intraglomerular pressure through efferent arteriolar vasoconstriction.
5. In contrast to secondary prevention, the use of ACE inhibitors or ARB for primary prevention of diabetic kidney disease in normotensive individuals with normoalbuminuria has not been enforced by clinical guidelines.
6. The threshold for initiation of SGLT2 inhibitors has been lowered to an eGFR ≥20 ml/min/1.73 m² regardless of glycaemia in the updated 2022 KDIGO guidelines.
7. SGLT2 inhibitors, once started, can be continued as long as tolerated until the initiation of dialysis.
8. Ketoacidosis is an important adverse effect of SGLT2i, and caution should be exercised in individuals with risk factors for this event.
9. Although hyperkalaemia is a side effect of non-steroidal mineralocorticoid receptor antagonists, treatment discontinuation and hospitalisation due to hyperkalaemia are uncommon in clinical trials.
10. Optimisation of cardiovascular risk factors such as smoking cessation, stringent LDL control with statin therapy, as well as attention to symptoms of cardiovascular disease during the consultation process is equally important, as diabetic kidney disease is associated with heightened cardiovascular morbidity and mortality.

Pharmacological Therapy for Diabetic Kidney Disease in 2023

Dr Gary CW CHAN
B.Sc., MBBS, PhD, FHKCP, FHKAM(Medicine), FRCP(Lond, Edin)
Division of Nephrology, Department of Medicine, Queen Mary Hospital

Prof Sydney CW TANG
MBBS, MD, PhD, FHKCP, FHKAM(Medicine), FRCP(Lond, Edin, Glasg), FASN
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⁴ Baseline CKD stage ≥2, CKD with CV disease, baseline eGFR 30-60 mL/min/1.73 m², randomized to FORXIGA 10 mg or placebo.
⁵ Baseline eGFR >30 mL/min/1.73 m², randomized to FORXIGA 10 mg or placebo.
⁶ Baseline eGFR >60 mL/min/1.73 m², randomized to FORXIGA 10 mg or placebo.
⁷ Baseline eGFR >30 mL/min/1.73 m², randomized to FORXIGA 10 mg or placebo.
⁸ Baseline eGFR >30 mL/min/1.73 m², randomized to FORXIGA 10 mg or placebo.

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BRING PROTECTION TO LIFE
Coronary Microvascular Dysfunction in Patients with Diabetes

Dr WONG Chun-ka
MBBS, MRCP(UK), FHKCP, FHKAM
Clinical Assistant Professor, Department of Medicine, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR

INTRODUCTION

It has been well established that diabetes mellitus (DM) increases the risk of developing coronary artery disease (CAD). In the past, clinicians tended to equate CAD with the narrowing of the epicardial coronary arteries, primarily including the left main, left anterior descending, left circumflex, and right coronary arteries. In recent years, it has been increasingly recognised that coronary microvascular dysfunction (CMD) also contributes significantly to the development of myocardial ischaemia. It has been found that CMD is more prevalent among patients with types 1 and 2 diabetes, and CMD may lead to anginal symptoms and may vastly elevate the risk of major adverse cardiovascular events (MACE) among patients with diabetes.

CORONARY ANATOMY

The coronary vasculature consists of epicardial arteries, pre-arterioles, arterioles, and capillaries arranged in a proximal to distal fashion. Epicardial arteries are the most proximal blood vessels with the largest luminal diameter of 0.5 to 5 mm. Significant narrowing of these epicardial coronary arteries can be treated medically with the antiplatelet agents, cardiovascular risk factor control, and, if necessary, anti-anginal therapies. Alternatively, revascularisation can be achieved by performing percutaneous coronary intervention or coronary artery bypass graft surgery in patients with compelling indications. On the other hand, the coronary microcirculation, which consists of pre-arterioles, arterioles, and capillaries, is located more distally and has a smaller calibre with a diameter ranging from 100 to 500 micrometres in pre-arterioles, and to less than 100 micrometres in the capillary arteries. Together, they contribute to over 90% of the coronary vascular resistance. CMD is an all-encompassing term referring to both structural and functional dysfunction of the coronary microcirculation.

PATHOGENESIS

The pathogenetic mechanisms of microvascular dysfunction leading to reduced coronary blood flow are multifactorial. Various structural changes may lead to narrowing of the microvasculature, such as smooth muscle hyperplasia and fibrosis leading to thickening of the media and intima, as well as extrinsic compression of intramural microvasculature from the hypertrophic myocardium. In addition, metabolic alterations caused by DM may also lead to functional dysfunction and reduced coronary bed perfusion. It has been shown in experimental models that hyperglycaemia causes damage to endothelial cells via a wide variety of pathways, including accumulation of reactive oxygen species (ROS) and advanced glycation end products (AGEs), which in turn result in inflammation and apoptosis. DM is also associated with reduced nitric oxide (NO) bioavailability, the latter impairing the vasodilatory reaction of the coronary microcirculation. Hyperglycaemia also leads to increased NO getting quenched by AGEs and bound by ROS to form peroxynitrite.

CLINICAL MANIFESTATIONS

CMD may lead to symptomatic myocardial ischaemia in the absence of significant obstruction in epicardial coronary artery disease. Indeed, up to 46.1% of patients with angina but without significant epicardial coronary artery obstruction or inducible spasm had CMD on catheter-based coronary functional test. Furthermore, CMD is also implicated in myocardial infarction with non-obstructive coronary artery disease (MINOCA), where there is evidence of acute myocardial infarction but no significant obstruction of epicardial coronary arteries on coronary angiography. It is thought to be mediated by microcirculation thromboembolism or spasm. Furthermore, it has been postulated that CMD could have contributed to the development of diabetic cardiomyopathy. Small-scale studies suggested that reduced coronary flow reserve was associated with elevated left ventricular filling pressure among patients with diabetes. Nevertheless, there is generally a lack of clinical or experimental studies demonstrating the definitive causality between CMD and cardiomyopathy in heart failure patients.

DIAGNOSIS

The diagnosis of CMD in DM patients could be established using invasive and non-invasive approaches. The invasive catheter-based coronary functional test is currently the gold standard for diagnosing CMD. At the beginning of coronary catheterisation, coronary angiogram and fractional flow reserve (FFR) are performed to rule out obstructive epicardial coronary arteries. Subsequently, an assessment of the coronary microcirculation can be performed by placing a specialised pressure- and temperature-sensing wire in one of the epicardial coronary arteries. Typically the left anterior descending coronary artery is used for CMD assessment. Coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) are assessed...
by the bolus-thermodilution method. It is performed by injecting small boluses of saline into the coronary artery and measuring their mean transit time both at rest and during induced hyperaemia using adenosine. CFR can then be calculated using the ratio of mean transit time at rest and during hyperaemia, whereas IMR is calculated by multiplying the mean distal coronary artery pressure by the mean transit time at hyperaemia. CFR < 2.0 and IMR > 25 are considered abnormal. The endothelium-dependent coronary vasomotor function is assessed by escalating the rate of intracoronary acetylcholine, followed by a provocative test for epicardial coronary artery spasm using boluses of acetylcholine. Finally, non-endothelial vasodilator function is assessed using glyceryl trinitrate. Alternatively, non-invasive imaging can also be used to diagnose CMD. Rest and vasodilator stress perfusion cardiac magnetic resonance imaging (MRI), positron emission tomography (PET), or computed tomography (CT) can be performed for measurements of myocardial perfusion reserve (MPR), myocardial blood flow (MBF), myocardial perfusion reserve index (MPRI), and other indices.

**PHARMACOLOGICAL THERAPY**

A large number of randomised controlled trials (RCTs) have been completed that investigate the use of pharmacological therapies to improve coronary functional tests in patients with CMD with and without diabetes.

Non-dihydropyridine calcium channel blockers are among one of the earliest drug classes that have been explored owing to their theoretical benefit of improving microvascular vasomotor functions. In the EDT-CMD trial, 126 patients with CMD were randomised in a 1:1 ratio to receive diltiazem, a non-dihydropyridine calcium channel blocker, or a placebo. At six weeks, a smaller proportion of patients in the diltiazem group had epicardial coronary artery vasospasm when compared to the control group. Nonetheless, no significant difference in parameters of microvascular function between the two groups was observed.

In patients with DM, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) improved vascular function in experimental models and reduced MACE among patients with type 2 diabetes in landmark cardiovascular outcome trials. As a result, a number of RCTs were dedicated to investigating the effect of GLP-1 RAs on diabetic CMD. In a pilot study, 24 patients with DM and CMD were randomised to receive either liraglutide or usual care. At the end of the study, there was a small decrease in CFR following liraglutide therapy, but a statistically significant difference could not be reached between the two groups.

In another relatively small-scale study involving eight patients with type 2 DM, it was found that exenatide increased MBF on PET when compared to controls. However, as most of these RCTs consisted of a relatively small number of participants, larger scale multi-centre RCTs are required to definitely establish to the efficacy of GLP-1 RAs on diabetic CMD.

Sodium-glucose cotransporter two inhibitors (SGLT2is) have also been studied in the context of diabetic CMD. SGLT2is significantly reduced heart failure hospitalisation in patients with type 2 diabetes in several landmark cardiovascular outcome trials. More recently, a similar reduction in heart failure hospitalisation or cardiovascular death was observed even among non-diabetic populations across a wide range of left ventricular ejection fractions, including the EMPEROR-Preserved, EMPEROR-Reduced, DAPA-HF and DELIVER trials. Although SGLT2is were not associated with a reduction in vascular complications when compared to placebo in the aforementioned trials, it has been investigated for the treatment of diabetic CMD. As SGLT2is reduce left ventricular mass, theoretically, they may also alleviate myocardial impingement of the intramural coronary microvasculature and improve myocardial perfusion. In the SIMPLE trial, 90 patients with type 2 DM and high cardiovascular risk were randomised to receive either empagliflozin or a placebo. At 13 weeks, there was no significant difference in MFR quantified by PET between the two groups. Another smaller-scale RCT involving 13 patients with type 2 DM found that empagliflozin reduced resting MBF, but no stress MBF when compared to placebo. It is important to note that these studies did not require participants to have CMD diagnosed as an inclusion criterion. Future larger scale studies should focus on patients with diabetes and CMD confirmed using contemporary invasive or non-invasive approaches, as differences in coronary microcirculation structural and functional landscape may affect response to SGLT2is.

Over the years, a number of other pharmacological therapies, such as ranolazine, colchicine, ticagrelor, high-dose allopurinol, failed to demonstrate convincingly improved coronary microcirculation parameters in RCT settings. Currently, a number of ongoing RCTs continue to explore the role of including beta-adrenergic receptor blocker (NCT05294887) and proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) (NCT04338165) for CMD in patients with and without diabetes. Findings from these ongoing trials will provide us with the much needed information regarding the optimal treatment strategy for patients with diabetes and CMD.

**CONCLUSION**

CMD is increasingly recognised as a cause of myocardial ischaemia among patients with diabetes. Microvascular function tests can be performed using both invasive and non-invasive approaches. At the moment, no pharmacological therapy has been proven to improve the outcome of diabetic CMD. Ongoing trials will provide further insights regarding the optimal treatment strategy in the future.

**Declaration:** The author reports no conflict of interest.

**References**


SAMSCA® helps you manage HYPONATREMIA while you are treating your patient’s primary condition

SAMSCA® is effective at raising serum Na+ in HF patients over 30 days

Pooled analysis of SALT-1 and SALT-2, mean change from baseline vs. placebo (P<0.0001)*

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3.5 vs. 0.5 mEq/L

Day 30
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SAMSCA® has a significant effect on fluid balance in HF patients

Mean net fluid balance at day 1 in patients with baseline serum Na+ <135mEq/L (p=0.0027)*

3.5 vs. 0.5 mEq/L

SAMSCA® -1860mL vs. Placebo -787mL

Indication

SAMSCA® is indicated for the treatment of clinically significant hypervolemic and euvoicmic hyponatremia (serum sodium <135mEq/L) or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction, including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).

References:
2. SAMSCA® (Tolvaptan) Hong Kong Prescribing Information revised Mar 2019.

Abbreviated Prescribing Information

SAMSCA® (Tolvaptan) 15 mg & 30 mg oral tablets. INDICATION: treatment of: (1) clinically significant hypervolemic and euvoicmic hyponatremia (serum sodium <135 mEq/L), or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction, including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH). DOSAGE: Patients should be instructed to restrict fluid intake to maintain the dry weight and maintain serum sodium ≥130 mEq/L. The maximum daily dose is 30 mg once daily. ADVERSE REACTIONS: Headache, dry mouth, dystonia, tachycardia, nausea, vomiting, anorexia, hyperglycemia, hyperkalemia, pancreatitis, anasarca. DRUG INTERACTIONS: CYP 3A inhibitors, phenytoin, phenobarbital, carbamazepine.

HCP-SAM-200217-001

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*cv: cardiovascular; 1RRR: relative risk reduction; ADA: American Diabetes Association; EASD: European Association for the Study of Diabetes; CVD: cardiovascular disease; QALY: quality-adjusted life year; T2DM: type 2 diabetes mellitus*

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**References:**

4. Standard of care included CV medications and pharmacological agents given at the discretion of physicians.
5. Empagliflozin was not evaluated in the REWIND trial.
6. Management of hyperglycemia in type 2 diabetes. 2019. 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 mainly stronger for empagliflozin than canagliflozin.

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**JARDIANCE** 

Abbreviated Prescribing Information (API-JARD-02)

**Proved Effect:** JARDIANCE is indicated in the treatment of type 2 diabetes mellitus to improve glycemic control in adults 18 years or older when diet and exercise alone do not provide adequate glycemic control in patients with type 2 diabetes mellitus.

**Treatment of type 2 diabetes mellitus:** JARDIANCE is indicated in patients with type 2 diabetes mellitus to reduce the risk of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

**Contraindications:** Hypersensitivity to empagliflozin or any of the excipients. Use of JARDIANCE in patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m$^2$) or end-stage renal disease (dialysis or peritoneal dialysis) is contraindicated.

**Warnings and Precautions:**

- **Hyperglycemia:** Hypoglycemia has been reported in patients treated with JARDIANCE, especially when used in combination with insulin or incretins, or when used in patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m$^2$) or end-stage renal disease (dialysis or peritoneal dialysis).

- **Infections:** JARDIANCE may cause infections. Infections may be serious, including infections of the urinary tract, respiratory tract, and skin. The incidence of urinary tract infections was increased in patients treated with JARDIANCE compared to placebo in the clinical trial program.

- **Hypotension:** Hypotension is more common in patients treated with JARDIANCE compared to placebo. Hypotension may be more common in patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m$^2$) or end-stage renal disease (dialysis or peritoneal dialysis).

- **Renal Function:** Monitoring of renal function, including creatinine clearance and blood urea nitrogen, is recommended during treatment with JARDIANCE.

- **Hypoglycemia:** JARDIANCE is contraindicated in patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m$^2$) or end-stage renal disease (dialysis or peritoneal dialysis).

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**THE ONLY OAD WITH CV INDICATION**

Jardiance is indicated in T2DM patients and established cardiovascular disease to reduce the risk of cardiovascular death.
**Fatty Liver Disease in Diabetes**

**Dr Loey LY MAK**

MBBS (HK), MD (HK), MRCP (UK), PDipID (HK), FHKCP, FHKAM (Medicine)
Specialist in Gastroenterology & Hepatology
Clinical Assistant Professor, School of Clinical Medicine, The University of Hong Kong
Honorary Associate Consultant, Department of Medicine, Queen Mary Hospital

**INTRODUCTION**

Non-alcoholic fatty liver disease (NAFLD) is a condition characterised by excessive hepatic fat accumulation leading to steatosis in > 5% of hepatocytes, in the absence of secondary causes and excessive alcohol consumption. The term NAFLD encompasses a broad spectrum of clinical conditions ranging from non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), NASH cirrhosis and hepatocellular carcinoma (HCC). NAFL refers to pure hepatic steatosis without significant lobular inflammation or hepatocyte ballooning, and runs a relatively benign course. In contrast, NASH patients are bound to accelerated disease progression in terms of developing liver fibrosis, cirrhosis or HCC. It will take an average duration of 14.3 years for one stage of fibrosis progression in NAFL patients, compared to 7.1 years for patients with NASH. About 12 - 40% of patients with NAFL will develop NASH after 8 - 13 years. Once NASH is established, 15 - 25% of patients will develop cirrhosis, hepatic decompensation, HCC or death.

The global prevalence of NAFLD has increased over time and is estimated to be 25% and up to 42% in Southeast Asia. Specifically, the real prevalence of NASH is difficult to assess since it can only be confirmed by liver histology obtained via biopsy. Data from the post-mortem series showed that NASH was present in 5% of non-obese, 19% of obese and 50% of morbidly obese individuals. It has been projected that the prevalence of NASH will increase by up to 56% in the next decade in China, France, Germany, Italy, Japan, Spain, the United Kingdom and America, leading to a doubling of the liver-related morbidities and mortalities in year 2030. In fact, NAFLD-related liver transplantation has already surpassed many other indications and has become the second leading disease among waitlisted patients in the West. Locally, NAFLD affects 42% of the general population in Hong Kong. NAFLD is strongly associated with insulin resistance and is frequently regarded as a hepatic manifestation of the metabolic syndrome. Therefore, unsurprisingly, the prevalence of NAFLD is even higher in certain populations, including patients with type 2 diabetes mellitus (T2DM), obesity and other components of metabolic syndrome.

**IMPLICATIONS OF NAFLD IN DIABETES, AND VICE VERA**

The recent debate about reforming the nomenclature of NAFLD into metabolic dysfunction-associated fatty liver disease (MAFLD) highlights the central role of T2DM in NAFLD. The bidirectional association between NAFLD and T2DM has long been established. Subjects with NAFLD were found to have a more than 4-fold increase in the risk of incident T2DM in the subsequent five years, and improvement of NAFLD was associated with reduced incidence of T2DM. On the other hand, whether T2DM increases the risk of incident NAFLD is less clear. Nevertheless, the degree of glycaemic control is associated with the severity of NAFLD on histological assessment. In Chinese patients with T2DM, the prevalence of hepatic steatosis was found to be 72.8%, and advanced liver fibrosis was observed in 17.7% of subjects. This demonstrated the ubiquitous involvement of NAFLD among T2DM patients, and the heightened risk of progressive liver disease in this cohort.

The top three causes of mortality in NAFLD patients are cardiovascular complications, malignancies, and hepatic events. T2DM increases the risk of fibrosis progression, cirrhosis and mortality among NAFLD patients. Interestingly, the risk of HCC is reduced if adequate glycaemic control is achieved. Similarly, the natural history of T2DM patients without NAFLD differs greatly from those with concomitant NAFLD. The risk of cardiovascular events (myocardial infarction, ischaemic stroke, coronary revascularisation, or cardiovascular death) and microvascular complications, including retinopathy and chronic kidney disease, are increased by 1.8-fold in T2DM patients with NAFLD compared to those without. The diagnosis of NAFLD among T2DM also carries implications on the therapeutic options for both conditions (see below).

**DISEASE STRATIFICATION AND CLINICAL PATHWAY**

Clinicians should proactively screen for NAFLD in patients with T2DM. As NAFLD is largely asymptomatic, < 5% of subjects with NAFLD are aware of the disease. In addition, abnormal liver biochemistry, such as increased serum levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST), is not always present even for subjects with NASH. Non-invasive tests such as ultrasonography or vibration-controlled transient elastography (VCTE) are the more widely utilised screening modalities for hepatic steatosis.

Upon confirmation of excessive hepatic steatosis, a careful review of the clinical history is required to exclude secondary causes (such as chronic hepatitis C virus infection, hypothyroidism, alcohol use disorder...
Certificate Course on
Communication and Swallowing Problems in the Elderly Population 2023
(*Video Lectures*)

**Jointly organised by**
- The Federation of Medical Societies of Hong Kong
- The Hong Kong Association of Speech Therapists

**Objectives:**
Upon completion of the course, participants will be able to understand the communication and swallowing problems associated with common diseases in the elderly population. Speech therapists will share how these problems are identified and remediated. The course will feature solid theoretical background knowledge as well as day-to-day tips. Participants will be able to enhance their knowledge and confidence in handling individuals with communication and swallowing difficulties.

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<td>20 April 2023</td>
<td>Communication Disorders in Patients with Parkinson’s Disease</td>
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<td>27 April 2023</td>
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<td>4 May 2023</td>
<td>Neurogenic Communication Disorders – Aphasia and Related Cognitive Communication Disorders</td>
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<td>Hearing Ability and Problems in the Geriatric Population</td>
<td>Dr. Iris Hoi Yee NG, Assistant Professor, Department of Otolaryngology, Head and Neck Surgery, The Chinese University of Hong Kong</td>
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**Date:** 13, 20, 27 April & 4, 11, 18 May 2023 (Thursday)
**Duration of session:** 1.5 hours (6 sessions)
**Time:** 7:00 pm – 8:30 pm
**Course Feature:** Video lectures (with Q&A platform for participants to post the questions)
**Quiz for doctors:** DOCTORS are required to complete a quiz after the completion of each lecture
**Language Media:** Cantonese (Supplemented with English)
**Course Fee:** HK$1,000
**Certificate:** Awarded to participants with a minimum attendance of 70%
**Deadline:** 4 April 2023
**Enquiry:** The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898  Fax: 2865 0345  Email: vienna.iam@fmshk.org

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Once the diagnosis of NAFLD is established, the key clinical question would be whether the subject has low-risk NAFLD or intermediate-/high-risk NAFLD, where ‘risk’ refers to that of advanced liver fibrosis, as liver fibrosis is the main determinant of long-term prognosis (liver-specific mortality and overall mortality) in NAFLD. To risk-stratify NAFLD subjects, VCTE or serum-based indices or tests such as FIB-4 (consisting of age, platelet, ALT and AST) and Enhanced Liver Fibrosis (ELF) test can be used. Serum liver biochemistry should be checked if not already done. After the initial evaluation, patients with NAFLD should be referred to a hepatologist if there is persistently elevated ALT (>30 U/L) or if the patient belongs to the intermediate-risk group (FIB-4 1.3-2.67/ELF 7.7-9.8/liver stiffness 8-12 kPa) or high-risk group (FIB-4 >2.67/ ELF >9.8/liver stiffness >12kPa). The same approach should be applied to patients with clinically apparent advanced liver disease (such as the presence of ascites, oesophageal varices, and coagulopathy) due to NASH cirrhosis or HCC. Low-risk patients can be managed by the primary care team and endocrinologist for optimising glycaemic control, obesity management and cardiovascular disease prevention.

PHARMACOLOGIC ASPECTS

There are currently no approved pharmacologic therapies for NAFLD. The mainstay of management has relied heavily on achieving ≥10% weight loss by diet and exercise, obesity medications, or sometimes bariatric surgeries. In patients with both T2DM and NAFLD, guidelines recommend using glucagon-like peptide-1 receptor agonist or pioglitazone in biopsy-proven NASH; both have been shown to improve liver histological parameters. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), another class of anti-diabetic drugs, has been shown to reduce body fat and liver fat on imaging, and markers of hepatocyte injury such as ALT. Although there is currently no evidence of benefit for treating NASH with SGLT2i, this class of drugs should still be considered, as patients with T2DM with NAFLD are at heightened risk of cardiovascular disease.

WHEN TO ARRANGE A LIVER BIOPSY IN A PATIENT WITH TYPE 2 DIABETES AND CO-EXISTING NAFLD?

A liver biopsy is the only method to diagnose NASH in order to visualise the histological changes of hepatocyte ballooning and lobular inflammation. However, liver biopsy is an invasive procedure, and concerns regarding sampling error and inter-observer variability have limited its use in selected patients. Liver biopsy should only be performed when pharmacotherapy with pioglitazone, vitamin E, or novel compounds is being considered for NASH, where the histological findings are needed to establish a definitive diagnosis and a baseline for evaluation of drug efficacy. Another scenario where a liver biopsy can be performed is in subjects undergoing bariatric surgery, and a concurrent liver biopsy can be done intra-operatively under direct visualisation to minimise the risk of complications from the biopsy.

RESOURCES FROM THE PERSPECTIVE OF A EPATOLOGIST

Hepatologists play several essential roles in managing NAFLD patients. First, hepatologists (especially in tertiary hospital settings affiliated with an academic institution) accept the referral of intermediate-risk and high-risk NAFLD patients for monitoring and for consideration of recruiting them to participate in clinical trials. These trials could either be industry-initiated studies evaluating novel pharmaceutical compounds, or non-pharmacological interventions to assist in weight loss through lifestyle modifications. Secondly, patients with established cirrhosis from NASH need regular surveillance for liver-related complications. These include upper endoscopy for variceal screening, ultrasound scan of the liver for HCC detection, close monitoring of liver synthetic function, and consideration of liver transplantation for decompensated cases. Last but not least, hepatologists, like other healthcare team members, are responsible for educating the patients regarding the various clinical aspects of NAFLD. A very informative patient guideline focusing on NAFLD has recently been published and will be helpful to assist clinicians and their patients in understanding the condition and make informed decisions.

CONCLUSION

NAFLD affects the majority of patients with T2DM and demonstrates bidirectional association owing to their underlying shared pathophysiology of insulin resistance. Active case finding followed by risk stratification is essential to streamline clinical management. While there are still many knowledge gaps for this condition, joint efforts by multi-disciplinary team involvement will be indispensable to improve the disease outcomes for patients living with T2DM and NAFLD.

References

ATTR-CM, a life-threatening and progressive disease that is widely and frequently underdiagnosed

25% of adults aged 80 years or older were found to have significant myocardial TTR amyloid deposition at autopsy

What is ATTR-CM?
- 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

Please click the link below or scan the QR code to learn more about ATTR-CM and how you can save the lives of potential ATTR-CM patients
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The following Red Flags warrant your immediate attention:

Cardiac:
- HFpEF
- HF therapy intolerance
- Imaging and ECG discrepancy
- LVH on Echo

Non-cardiac:
- Polyneuropathy
- Orthopaedic syndromes (e.g. carpal tunnel syndrome, lumbar spinal stenosis and bicep tendon rupture)

Family history of TTR amyloidosis

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


Vyndamax ABBREVIATED PRESCRIBING INFORMATION
1. TRADE NAME: Vyndamax® capsules (Tafamidis 60mg).
2. PRESENTATION: 60mg 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 60 mg (tafamidis orally once daily).
5. CONTRAINDICATIONS: Hypersensitivity to the active substance 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 added 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, as part of this standard of care. Tafamidis should be discontinued in patients who undergo organ transplantation.
7. INTERACTIONS: Substrates of efflux transporter BCRP (breast cancer-resistant protein), e.g., methotrexate, rosuvastatin, mirtalib; substrates of uptake transporters OAT1 and OAT3 (organic anion transporters), e.g., non-steroidal anti-inflammatory drugs, bumetanide, furosemide, lamivudine, methotrexate, esetron, lenitofen, ganciclovir, adenosiv, clofazim, azidodeine, halobalaine.
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 breastfeeding.
9. SIDE EFFECTS: Palpitation 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 number: VYNX1120. FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.
23. Kuchay MS, Krishan S, Mishra SK, et al. Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial). Diabetes Care 2018;41:1801-1808.
Help your patients find **balance between HbA1c reduction and hypoglycemic risk**\(^1-7\)

- With a more stable 24-hour **glycemic profile**\(^1,8^*\)
- In a convenient† **insulin experience**\(^1,9,10\)
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- In steady-state PK/PD analyses in T1DM, Toujeo* showed a more stable and prolonged glucose lowering effect compared to insulin glargine 100 units/mL.1

* Toujeo* is available in easy-to-use pens,1,4,9 to be administered once daily at any time of the day, preferably at the same time every day.1 When needed, patients can administer Toujeo* up to 3 hours before or after their usual time of administration. Flexible dosing time was evaluated in two randomized, open-label clinical studies in patients with T2DM.1


Abbreviated prescribing information: Presentation Insulin glargine 300 IU/ml solution for injection. Indications Treatment of diabetes mellitus in adults, adolescents and children from the age of 6 years. Dosage Once daily (preferably at the same time every day) up to 3 hours before or after the usual time of administration), with adjusted individual dosage. Please refer to the full prescribing information for guidelines on switching between other insulin preparations. Administration Subcutaneous injection. Toujeo IS NOT INTENDED FOR INTRAVENOUS USE since it could result in severe hypoglycaemia. Toujeo must not be drawn from the cartridge of the SoloStar pre-filled pen into a syringe or severe overdose can result. Contraindications Hypersensitivity to insulin glargine or to any of the excipients. Precautions Toujeo has not been studied in children below 6 years of age. Elderly: Progressively deteriorating renal function may lead to a steady decrease in insulin requirements. Renal impairment: Insulin requirements may be diminished due to reduced insulin metabolism. Hepatic impairment: Insulin requirement may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism. Perform continuous rotation of injection site to reduce risk of lipodystrophy and cutaneous amyloidosis. Blood glucose monitoring is recommended after change in injection site. Hypoglycaemia. Intercurrent illness. Combination of Toujeo with pioglitazone. Medication errors prevention. Interactions Effects enhanced by oral antidiabetics, AGL, disopyramide, fribates, fluoxetine, MAOIs, pentoxifylline, propoxyphene, salicylates, sulfonamide antibiotics. Effects reduced by corticosteroids, danazol, diazoxide, diuretics, glucagons, isoniazid, oestrogens and progestogens, phenothiazine derivatives, somatropin, sympathomimetics, or thyroid hormones, atypical antipsychotics and protease inhibitors. Beta-blockers, clonidine, lithium or alcohol may either potentiate or weaken the effects of insulin. Pentamidine may cause hypoglycaemia, followed by hyperglycaemia. The signs of adrenergic counter-regulation may be reduced or absent under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine. Fertility, pregnancy and lactation Animal studies do not indicate direct harmful effects with respect to fertility and reproductive toxicity. The use of Toujeo may be considered during pregnancy if clinically needed. It is unknown whether insulin glargine is excreted in human milk. Overdose Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia. Mild episodes of hypoglycaemia can usually be treated withoral carbohydrates. More severe episodes with coma, seizure or neurologic impairment may be treated withglucagon (intramuscular or subcutaneous) or concentrated glucose solution (intravenous). Undesirable effects Hypoglycaemia, lipohypertrophy, injection site reactions. For common, uncommon, rare and very rare undesirable effects, please refer to the full prescribing information. Storage Before first use: Store in a refrigerator (2°C - 8°C). Do not freeze. Protect from light. After first use: Store below 30°C. Use within 42 days. Do not freeze. Preparation Toujeo 5 x 1.5 ml (450U) pre-filled pens. Legal classification Part 1 Poison Full prescribing information is available upon request. APi-HK-TOU-20.09
Diabetic Bone Disease

Dr David TW LUI

MBBS (Hons) (HK), MRCP (UK), FHKCP, FHKAM (Medicine)
Specialist in Endocrinology, Diabetes and Metabolism
Clinical Assistant Professor, Department of Medicine, School of Clinical Medicine,
Li Ka Shing Faculty of Medicine, The University of Hong Kong

INTRODUCTION

Both type 2 diabetes and osteoporosis are major global health problems. The prevalence of type 2 diabetes is estimated to be 10.5% in 2021 and is expected to rise to 12.2% by 2045. On the other hand, it is estimated that 1 in 3 postmenopausal women and 1 in 5 men aged 50 years or above will suffer from osteoporotic fractures, the dreaded complication of osteoporosis, in a lifetime. Hip and vertebral fractures are the hallmark complications carrying significant morbidities and mortality.

Diabetic bone disease (DBD) is a term which broadly describes osteoporosis due to diabetes. Individuals with type 1 and type 2 diabetes have an increased risk of fractures compared to individuals without diabetes. Interestingly, compared to individuals without diabetes, while bone mineral density (BMD) is lower among those with type 1 diabetes, the BMD is comparable to or even higher among those with type 2 diabetes. With an ageing population, type 2 diabetes and osteoporosis are becoming more prevalent, and so is the prevalence of DBD. This review focuses on bone fragility in type 2 diabetes.

EPIDEMIOLOGY OF FRACTURES IN TYPE 2 DIABETES

Incidence of Fractures in Type 2 Diabetes

A 2016 meta-analysis showed that individuals with type 2 diabetes had higher fracture risks than those without diabetes. The elevated risk was most consistently demonstrated for hip fractures with a relative risk of 1.4-1.7. Evidence also suggested an increased risk of fragility fractures at sites other than the hip in individuals with type 2 diabetes. Data suggested that DBD resulting in bone fragility is also present among Chinese individuals with type 2 diabetes, consistent with Caucasian studies. In Hong Kong, a retrospective longitudinal cohort of 5,469 Chinese individuals confirmed that those with type 2 diabetes had a higher incidence of hip fractures (3.01 per 1,000 person-years) than those without (1.36 per 1,000 person-years) upon a median follow-up of 7 years (age- and sex-adjusted p=0.017). Furthermore, a territory-wide cohort study (Hong Kong diabetes database) of 83,282 Chinese individuals with type 2 diabetes aged ≥ 60 years showed that hip fractures were common in type 2 diabetes, with an incidence of 5.44 per 1,000 person-years upon a median follow-up of 7 years.

Diabetes-specific Risk Factors

In addition to the conventional clinical risk factors of osteoporosis (age, sex, body mass index, history of fracture, parental history of hip fracture, current smoking status, alcohol consumption, rheumatoid arthritis and glucocorticoid use), epidemiological studies have identified several important diabetes-specific risk factors which explain the increased risk of fractures in type 2 diabetes.

Fracture risk in type 2 diabetes increases with the duration of diabetes. While fracture risk may not be elevated in individuals with recently diagnosed type 2 diabetes, diabetes duration of > 5 years is associated with an increased risk of fractures. When the duration of diabetes exceeds ten years, the elevated fracture risk relative to non-diabetes persists even in the fully adjusted model, which includes FRAX.

Glycaemic control is highly relevant to fracture risk in type 2 diabetes. Population-based studies have revealed that HbA1c ≥ 8.0% is associated with a 25% increase in the risk of hip fractures among older individuals with type 2 diabetes (aged ≥ 60 years), compared to the reference group with HbA1c < 7.0%, in Taiwan Diabetes Cohort Study and Hong Kong diabetes database from our group. Furthermore, a significant linear trend exists between HbA1c and the risk of hip fractures, such that the higher the HbA1c, the higher the excess risk of hip fractures. When HbA1c reaches > 9%, there is up to a 50% increase in the risk of hip fractures compared with individuals having good glycaemic control (HbA1c 6 - 7%).

Apart from achieving the HbA1c target, it is essential to maintain stable glycaemic control. Ample evidence shows that severe hypoglycaemia is associated with an increased risk of hip fractures. A positive correlation exists between the number of episodes of severe hypoglycaemia and fracture risk. The occurrence of falls likely represents one of the reasons for this association. Recently, HbA1c variability has been shown in the Hong Kong diabetes database to be an independent positive predictor of hip fractures in type 2 diabetes across varying degrees of glycaemic control. Indeed, the ‘glucocentric’ approach to diabetes management requires targeting three components of dysglycaemia, known as the ‘glycaemic triumvirate’: chronic hyperglycaemia, glycaemic variability, and hypoglycaemia.
Microvascular complications are associated with increased fracture risk in type 2 diabetes. In the Blue Mountains Eye Study, retinopathy is associated with an increased risk of fractures. In the Rochester Epidemiology Cohort, the presence of diabetic neuropathy is associated with an increased risk of fractures. These findings support the notion that DBD may be another manifestation of the microvascular disease of type 2 diabetes.\textsuperscript{12}

With the expansion of the armamentarium in managing type 2 diabetes, it is vital to understand the potential effects of various anti-diabetic agents on bone health. In the absence of prospective trials dedicated to evaluating bone fragility, insights are obtained from epidemiological studies and surveillance in clinical trials.\textsuperscript{11} Metformin and incretin-based therapies are associated with neutral or beneficial effects on fracture risk. Hence, they are the preferred anti-diabetic agents for individuals with type 2 diabetes when fracture risk is a concern.\textsuperscript{11} Thiazolidinediones should be used cautiously, as they are associated with more rapid bone loss and increased fracture risks, especially in women.\textsuperscript{13} Furthermore, one should consider the hypoglycaemic potentials of sulfonylurea and insulin when managing individuals with type 2 diabetes and high fracture risk, as hypoglycaemia is associated with an increased risk of fracture partly through increased fall risk.\textsuperscript{11} The choice of insulin may have an impact on fracture risk. For example, the use of basal insulin analogues may be associated with lower fracture risk than NPH insulin.\textsuperscript{11} As for sodium-glucose cotransporter 2 (SGLT2) inhibitors, there have been initial concerns about the increased risk of fractures. In the CANVAS trial, canagliflozin use was associated with a higher fracture risk than placebo. However, this has not been observed in subsequent randomised controlled trials and observational studies involving canagliflozin and other SGLT2 inhibitors (including dapagliflozin and empagliflozin). Recent real-world evidence from population-based observational studies, including a study in Hong Kong from our group, did not reveal increased fracture risks with SGLT2 inhibitor use across the spectrum of kidney function in individuals with diabetes.\textsuperscript{14} Nonetheless, given the signal of increased fracture risk with canagliflozin, careful considerations from the perspective of bone health are needed when prescribing canagliflozin.

**MECHANISMS OF BONE FRAGILITY IN TYPE 2 DIABETES**

The apparent paradox of higher fracture risk in type 2 diabetes despite comparable or even higher BMD illustrates that bone strength is determined not only by bone density, but also by bone quality. The impairment of bone quality may be due to alterations in bone microstructure. High-resolution peripheral quantitative computed tomography (HR-pQCT) has shown increased cortical porosity in individuals with type 2 diabetes compared to those without diabetes, particularly those who suffered from fractures or had microvascular complications. The increase in cortical porosity found in individuals with type 2 diabetes has been associated with impaired bone strength assessed by micro-finite element analysis.\textsuperscript{3}

The alterations to the intrinsic properties of the bone material also contribute to bone fragility in type 2 diabetes. Type I collagen is a major constituent of the bone, providing a structural framework that facilitates skeletal strength. The natural enzymatic cross-linking of type I collagen provides skeletal strength. However, non-enzymatic cross-linking may occur between the circulating glucose and the exposed amino acid residues, leading to post-translational modifications of the collagen and the formation of advanced glycation end-products (AGEs). In the presence of hyperglycaemia, the accumulation of AGEs leads to the more brittle bone, which is less able to deform before fracturing.\textsuperscript{15}

The quality of bone material is maintained through bone remodelling, comprising bone resorption through osteoclastic activities and bone formation through osteoblastic activities. A balance between bone resorption and formation is necessary to maintain bone mass. In contrast to postmenopausal osteoporosis due to excessive bone resorption, bone fragility in type 2 diabetes is characterised by attenuated bone remodelling. Studies have revealed lower levels of circulating biochemical markers of bone formation and bone resorption among individuals with type 2 diabetes.\textsuperscript{15}

**FRACTURE RISK ASSESSMENTS IN TYPE 2 DIABETES**

Multiple mechanisms and risk factors explain the increased fracture risk in type 2 diabetes. Therefore, while standard fracture risk assessment tools can still stratify fracture risk in type 2 diabetes, they may underestimate the fracture risk in type 2 diabetes due to their limitations in capturing the diabetes-specific fracture risk.

**BMD Measurements**

In type 2 diabetes, BMD can still stratify fracture risk, such that lower BMD is predictive of fractures in type 2 diabetes as in the general population. However, the excess fracture risk in type 2 diabetes is not captured by BMD since BMD in type 2 diabetes can be paradoxically higher. Schwartz et al. pooled data from three cohorts in the United States and showed that the BMD T-score underestimates fracture risk in type 2 diabetes.\textsuperscript{15} At the same risk of hip fracture, the BMD T-score of individuals with type 2 diabetes is approximately 0.5 units higher than the BMD T-score of those without diabetes.\textsuperscript{15}

**Trabecular Bone Score (TBS)**

DBD is characterised by impaired bone microarchitecture, which can be visualised on HR-pQCT. However, HR-pQCT is not available in routine clinical practice. TBS, derived from the lumbar spine image obtained in dual-energy x-ray absorptiometry (DXA), is an indirect index of bone microarchitecture. By evaluating the pixel grey-level variations in the lumbar spine image, TBS is obtained from the slope of the log-log transformation of variograms. Higher TBS values indicate denser bone microarchitecture, while lower TBS values indicate more porous bone.
Vertebral Fracture Assessment (VFA)

VFA can be performed in the same session of DXA, which captures the lateral image of the spine from T4 to L4. VFA can detect moderate to severe asymptomatic vertebral fractures. VFA holds advantage over routine vertebral x-ray since VFA is associated with a lower radiation exposure and is easier and quicker in image acquisition. In type 2 diabetes, individuals with an increased risk of vertebral fractures, VFA helps identify asymptomatic vertebral fractures, refining the fracture risk assessment in individuals with type 2 diabetes.

Fracture Prediction Tools

Several validated fracture prediction tools can assess fracture risk in the general population: FRAX, Garvan fracture risk calculator and QFracture score. FRAX has been validated internationally and is applicable to the Hong Kong population. In type 2 diabetes, although the risk factors included in the FRAX remain useful in predicting fracture risk, the absolute fracture risk is underestimated. In the absence of type 2 diabetes as an input variable in FRAX at the moment, several options for the adjustment of FRAX score for individuals with type 2 diabetes include (i) TBS adjustment, (ii) using 'rheumatoid arthritis' input as a proxy, or (iii) reducing the femoral neck BMD T-score by 0.5.17

A PRACTICAL APPROACH TO BONE FRACTILITY IN TYPE 2 DIABETES

Given the challenges in diagnosing and managing bone fragility in type 2 diabetes, the Bone and Diabetes Working Group of the International Osteoporosis Foundation (IOF) has proposed an algorithm for identifying and managing individuals with type 2 diabetes at increased fracture risk.17

Management According to Fracture Risk

- History of hip or vertebral fractures: Such history serves as an indication for anti-osteoporosis therapies.

- History of fractures other than over the hip and vertebra: DXA (which can be supplemented by VFA and TBS) is useful in assessing fracture risk. Anti-osteoporosis therapies are indicated in the presence of (i) morphometric vertebral fracture(s), (ii) BMD T-score lower than -2.0 (the cut-off is 0.5 units higher because of the potential underestimation of fracture risk by BMD T-score in type 2 diabetes), or (iii) FRAX score, after adjustment for type 2 diabetes, above the country-specific treatment threshold. Nonetheless, as mentioned above, the suggested adjustment and absolute cut-off are derived from data in the Western populations, which may require further validation in the Asian populations.

- No history of fracture: DXA should be considered especially if diabetes-specific clinical risk factors are present (refer to the section on 'Diabetes-specific risk factors').

Antiosteoporosis Therapies in Type 2 Diabetes

No randomised controlled trials have specifically evaluated the anti-fracture efficacy of anti-osteoporosis therapies in individuals with type 2 diabetes. Post-hoc analyses of randomised controlled trials suggest that bisphosphonates and most other antiresorptive drugs appear to have a similar efficacy in individuals with and without diabetes in terms of fracture risk reduction and BMD gain.19 Observational studies suggest that teriparatide is at least as effective in individuals with diabetes as in those without diabetes in reducing the risk of fractures. There are yet data regarding the safety and efficacy of romosozumab, specifically in individuals with type 2 diabetes.20

With the currently available evidence, for the treatment of bone fragility in type 2 diabetes, antiresorptive agents are the first-line anti-osteoporosis therapy. Osteoanabolic agents may be preferred for individuals at very high fracture risk.

For individuals not yet requiring anti-osteoporosis therapies, regular reassessment of clinical risk factors, FRAX and DXA may be appropriate.

Optimising Lifestyle Factors and Glycaemic Control

Lifestyle modifications are important adjuncts to achieving the best outcome for the bone health of individuals with type 2 diabetes. These include maintaining physical activity (including weight-bearing exercise), smoking cessation, limitation in alcohol intake, and ensuring sufficient vitamin D and calcium intake. Glycaemic control should be optimised. One should be cautious about the risk of hypoglycaemia in the elderly. From the perspective of bone health, metformin and incretin-based therapy are the preferred anti-diabetic agents, while thiazolidinediones, and possibly canagliflozin, should be avoided.17

CONCLUSION

Individuals with type 2 diabetes are at an increased risk of fragility fractures, which in turn are associated with significant morbidities and mortality. Since FRAX and BMD T-score underestimate the fracture risk in individuals with type 2 diabetes, strategies for adjustment (such as using TBS) to account for the
diabetes-specific fracture risk have been proposed. In addition to initiating anti-osteoporosis therapies for individuals indicated for treatment, optimising glycaemic control and appropriate choices of anti-diabetic agents can help bring about the best outcomes in managing DBD.

References
根據3項香港不同研究，
40%至75%曾感染
新冠病毒的患者受長新冠困擾

長新冠
症狀

美國疾病控制和預防中心 (CDC)
首次感染2019冠狀病毒後4周或更長時間內，出現
新發、復發或持續的健康問題，即患有新冠肺炎長期綜合
後遺症

世界衛生組織 (WHO)
通常在感染2019冠狀病毒後3個月內出現，並維持“至少
2個月”

2. WHO Director-General’s opening remarks at the media briefing on COVID-19 - 7 October 2021
Technologies in Managing Diabetes: Continuous Glucose Monitoring (CGM)

Dr CHAU Suet-ming
MBChB, MRCP(UK), FHKCP, FHKAM(Medicine)
Specialist in Endocrinology, Diabetes and Reproduction

In the management of diabetes, patient education and empowerment are two pivotal components in equipping patients to make well-informed decisions about their own treatment and care plans. Regular blood sugar monitoring therefore plays an important role in diabetes care at home.

Clinical guidelines have long adopted self-monitoring of blood glucose (SMBG) as a useful tool in helping patients with diabetes to maintain their glycaemic control. In the past three decades, modern technology has improved the performance, accuracy and utilisation of SMBG using glucometers. Buying a glucometer becomes a standard home monitoring tool for every newly diagnosed patient with diabetes. However, the major drawback of using a glucometer is pain. Patients had to endure the pain of finger prick for each measurement they obtained before they could use the glucose value for self-monitoring. Moreover, measuring glucose levels when the patient is not conscious, e.g. during sleep, is impossible.

The emergence of continuous glucose monitoring (CGM) has been a game-changer for SMBG since its introduction in the year 2000. CGM provides information unattainable by glucometers, as the former allows instantaneous real-time display of glucose levels, trends and variabilities with 24/7 coverage. Alerts and alarms can be set to inform patients about actual or impending hypo- and hyperglycaemia. Since then, the process of SMBG has become painless. The widespread use of smartphones has further popularised the use of CGM as an Internet-of-things (IoT) healthcare wearable among the diabetes population. Furthermore, the COVID-19 epidemic has accelerated the clinical use of CGM during inpatient glucose monitoring.

CONTINUOUS GLUCOSE MONITORING (CGM)

CGM is a device that continuously measures interstitial glucose levels. It consists of:

1. A sensor that is inserted into the subcutaneous tissue for interstitial glucose detection.
2. A transmitter that transfers sensor data to the monitor.
3. A monitor that allows the display of glucose levels with regular updates (e.g. 5-minute intervals).

In the past, there were three types of CGM: Retrospective, intermittent and real-time. For retrospective CGM, glucose values were blinded to both patients and doctors at the time of measurement, and a retrospective report was produced after the data download. Intermittent CGM requires the patient to regularly download the data using a reader. The use of these two types of CGM has gradually faded since the widespread use of a smartphone that advances the use of real-time CGM.

BENEFITS OF CGM

In February 2017, the Advanced Technologies & Treatments for Diabetes (ATTD) Congress put forward a recommendation for utilising, interpreting, and reporting CGM data in clinical care and research. CGM should be considered in conjunction with HbA1c for glycaemic status assessment and therapy adjustment in all patients with type 1 diabetes and patients with type 2 diabetes treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycaemia.

The major advantage of CGM over glucometers, besides doing away with painful finger pricks, is the visualisation of glucose excursion in a 24/7 manner. It helps patients to directly observe their glucose control over the wearing period, be it postprandial hyperglycaemia after a happy meal, or hypoglycaemia during sleep that results in hypoglycaemia unawareness. The patient can self-evaluate the effect of diabetes medication(s) at home, and the titration of insulin has never been that reachable and convenient. CGM has benefited especially pregnant ladies with gestational diabetes. Patients with type 1 diabetes even used the CGM data for endurance sports training and competition. As for parents having children with diabetes, the use of CGM allows remote glucose monitoring of their kids at school and supports school staff to help manage the sugar levels when the alarm rings. The overall effect is an improvement in glycaemic control and quality of life for both children and adults with diabetes, especially type 1 diabetes treated with either continuous subcutaneous insulin infusion or multiple daily insulin injection therapy.

STANDARDISATION OF CGM DATA PRESENTATION: AMBULATORY GLUCOSE PROFILE (AGP)

HbA1c is currently recognised as the key surrogate maker for the development of long-term diabetes complications in people with type 1 and type 2 diabetes.
It has been used as the primary end point in many CGM studies. As CGM can provide information about acute glycaemic excursions, glucose variability and the acute complications of hypo- and hyperglycaemia, a method to effectively use the CGM data to optimise clinical outcomes that require the user to interpret the collected data and act upon them appropriately is required. Therefore, common metrics for the assessment of CGM glycaemic status, graphical visualisation of glucose data and CGM daily profile, and clear clinical targets were developed.

In 2013, a panel of clinicians with expertise in CGM recommended the use of the Ambulatory Glucose Profile (AGP) as a template for data presentation and visualisation that was originally created by Mazze et al. in 1987. The standardised AGP report further incorporated core CGM metrics and targets along with a 14-day composite glucose profile that aids clinical decision-making. In 2019, the expert panel of the 2017 ATTD Congress international consensus group selected ten metrics that might be most useful in clinical practice (Table 1).

Moreover, to streamline data interpretation, “Time in ranges” is used as a metric of glycaemic control that provides more actionable information. The expert panel developed target percentages of time in the various glycaemic ranges to address the specific needs of special diabetes populations (e.g. pregnancy and high risks patients) to facilitate safe and effective therapeutic decision making within the parameters of the established glycaemic goals (Fig. 1 - 2).

**CASE SCENARIO: CGM USE IN GESTATIONAL DIABETES**

Ms W was a 30-year-old lady who had her 3rd pregnancy in 2022. She was on regular multiple daily doses of insulin and metformin after her 2nd pregnancy. Her HbA1c before pregnancy was 7% in April 2022. Metformin was stopped after she was pregnant in May 2022. She was CGM-naive before this pregnancy and had her first CGM inserted in June 2022. She used more CGM in the second half of the pregnancy as the glucose trends helped her monitor and titrate her insulin accordingly. However, she also noted some discrepancy between CGM and H’stix data (especially when below 4 mmol/L); therefore, she would also perform regular SMBG despite CGM use. Throughout the pregnancy, our diabetic nurses supported her with telemedicine through regular phone contact and virtual meetings.

The table below shows Ms W’s change in CGM performance throughout pregnancy. A major issue of her overall glycaemic control was her low sugar level. The reason was due to misconceptions about diet. Early into the pregnancy, she would reduce her food intake and increase her prandial insulin when she noted a high fasting glucose level, which resulted in subsequent pre-lunch hypoglycaemia. After counselling by diabetes educators with the aid of CGM, she increased her meal portion, and low glucose episodes were markedly reduced. Education on regular changes of injection site was also given. She was able to monitor her post-meal glucose levels and adjust her prandial insulin accordingly. Time in Range (TIR) and HbA1c were also much improved after using CGM. (Table 2 - 5)
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2020 AACE/ACE guidelines recommendation

ASCVD risk factor modification algorithm for patient who are under statin therapy, TG levels should be <1.7 mmol/L at every risk level.

*Study design: A total of 29,771 adults with metabolic syndrome (≥40 years) received statin treatment, of which 2,156 patients receiving combined treatment (statin plus LIPANTHYL™) were weighted based on propensity score in a 1:3 ratio with 8,598 participants using statin only treatment. The primary outcome was composite cardiovascular events including incident coronary heart disease, ischemic strokes, and death from cardiovascular causes.

**AACE—American Association of Clinical Endocrinologists; ACE—American College of Endocrinologists; ASCVD—atherosclerotic cardiovascular disease; CV—cardiovascular; ECLIPSE-REAL—Effectiveness of Fenofibrate Therapy in Reducing Cardiovascular Risk: Reduction in the Real World; HDL—high-density lipoprotein; HLC®—HCO-41LD cholesterol; LDL—low-density lipoprotein; TG—triglyceride.

Fig. 2 Graphical presentation of composite glucose profile 4

Table 2. Overall CGM performance of Ms W from June to December 2022.

![Graphical presentation of composite glucose profile](image)

![Table of CGM performance](image)
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are encouraged to improve adherence to CGM use and facilitate the appropriate use of glucose data that aid clinical decisions and adherence to diabetes therapies.

**THE WAY FORWARD**

It is foreseeable that the use of CGM will expand in chronic care management in patients with diabetes. In addition to being a convenient tool for providing immediate feedback on glucose levels and trends, it empowers patients with diabetes to take a greater initiative in controlling their own blood sugar levels and facilitates day-to-day treatment decision-making. In the era of big data, large-scale data analysis of CGM glucose data is underway. The next phase of CGM development may provide new insights and changes to our clinical practice in diabetes care in the years to come.

**References**

Upcoming Therapeutic Targets in Diabetes

Dr Elaine YK CHOW

MBChB, PhD, FHKAM (Medicine)
Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong
Phase 1 Clinical Trial Centre, Faculty of Medicine, The Chinese University of Hong Kong

INTRODUCTION

2022 marks the 100th anniversary of insulin and 50 years since the discovery of metformin. These traditional agents, alongside sulfonylureas, have been the cornerstone of glucose-lowering therapies for many years. In the past decade, the introduction of dipeptidyl-peptidase four inhibitors (DPP4i) and sodium-glucose transporter-2 inhibitors (SGLT2i) as well as glucagon-like peptide receptor one agonist (GLP1-ra) have further transformed the diabetes landscape. These newer agents show good glucose lowering efficacy while being devoid of the risks of hypoglycaemia. Moreover, SGLT2i and GLP1-ra additionally confer cardio-renal protective benefits. New therapeutic targets are emerging as we continue to seek glucose lowering drugs (GLDs) that can target fundamental pathophysiological deficits in beta-cell glucose sensing, insulin resistance and obesity with good safety and tolerability. A wider choice of agents will facilitate a personalised medicine approach as our understanding of the heterogeneity of diabetes continues to grow. In the following sections, I shall discuss several emerging drug classes that include twincretins and glucokinase activators in the management of type 2 diabetes (T2D).

The recent approval of teplizumab, a monoclonal antibody for high-risk individuals before the onset of frank hyperglycaemia, hails a major landmark in the quest for a cure for type 1 diabetes (T1D).

INCRETIN-BASED CO-AGONISTS

The incretin effect is mediated by glucagon-like peptide 1 (GLP1) and glucose-dependent insulintropic peptide (GIP), which are secreted by L cells and K cells, respectively, in the upper segment in the small intestine in response to nutrient provision. Tirzepatide is the first dual GLP1-ra semaglutide in 1,879 T2D patients sub-optimally controlled on metformin.4 At 40 weeks, mean HbA1c was reduced by -2.01%, -2.24% and -2.3% with tirzepatide 5 mg, 10 mg and 15 mg, respectively, versus -1.86% with semaglutide. With respect to body weight, there was a -7.6 kg, -9.3 kg and -11.2 kg dose-dependent decrease in body weight with tirzepatide 5 mg, 10 mg and 15 mg respectively versus -5.7 kg with semaglutide (P < 0.001). SURPASS-3 further investigated 1,444 patients treated with weekly tirzepatide 5 mg, 10 mg or 15 mg versus daily insulin degludec.5 At 52 weeks, between-treatment difference in HbA1c was -0.59% to 1.04%, P < 0.0001 for all tirzepatide doses. Severe hypoglycaemia at glucose < 3 mmol/l was lower (1 - 2%) in the tirzepatide group versus 7% in the insulin degludec group. Tirzepatide was well-tolerated with transient gastrointestinal side effects, mainly during the dose-escalation phase.

In summary, dual GIP and GLP1 agonism showed superiority in reducing HbA1c and body weight with similar gastrointestinal tolerability compared with GLP-ra, and low treatment discontinuation rates. Several other incretin-based tri-agonists are under development. LY3437943, a novel triple GIP, GLP-2 and glucagon receptor agonist, has been evaluated in a phase lb study in T2D. At 12 weeks, placebo-adjusted HbA1c decreased significantly by 1.4 - 1.6% at 3/6 mg dose, with a dose-dependent reduction in weight of up to -8.96 kg (90% CI -11.16 to -6.75).6 The safety and tolerability were similar to other incretin-based drugs. Cangrilintide, a long-acting amylin analogue, has been evaluated as an anti-obesity treatment.7 Phase 2 studies are underway as dual weight loss and glucose lowering agents when combined with semaglutide in T2D, holding much promise.

GLUCOKINASE ACTIVATORS

Glucokinase (GCK) catalyses the ATP-dependent phosphorylation of glucose to glucose-6-phosphate (G-6-P) and is the rate-limiting step of both glycolysis and glycogen synthesis.8 GCK is primarily expressed in the liver and the pancreas.9 GCK plays a role as a glucose sensor due to its unique allosteric properties.10 In the pancreatic beta-cell, GCK regulates glucose-stimulated insulin secretion and suppression of glucagon. In the liver, GCK enhances hepatic glucose uptake and glycogen synthesis.11 Dorzagliatin is a first-in-class, pancreatic and liver GKA which was approved for the treatment of T2D. In a phase I study in healthy volunteers, dorzagliatin exhibited dose-dependent decreases in fasting plasma
glucose (FPG) and postprandial glucose. In a phase II study among 258 T2D patients, dorzagliatin 75 mg twice daily led to HbA1c reduction of -1.12% (95% CI -1.39 to -0.86) daily versus a -0.35% (95% CI -0.60 to -0.10, p < 0.0001) in the placebo group. In the SEED phase 3 study, dorzagliatin monotherapy (75 mg twice daily) resulted in a placebo-subtracted HbA1c reduction of -0.57% (95% CI -0.79 to -0.36, p < 0.0001) compared with placebo alone in 463 drug naïve patients with T2D over a 24-week treatment period. Moreover, efficacy was maintained in the open-label 28-week extension period. Severe hypoglycaemia did not occur in either study arm, while clinically significant hypoglycaemia (< 3.0 mmol/l) occurred in 0.3% of the intervention group versus 0% in the control. Another phase 3 trial investigated the efficacy and safety of dorzagliatin add-on therapy to metformin in 767 T2D patients with suboptimal control metformin alone. After 24 weeks, patients in the dorzagliatin/metformin group achieved 1.02% (95% CI 0.93 - 1.11%) HbA1c reduction versus 0.36% (95% CI 0.26 - 0.45%) in the placebo/metformin group (P < 0.0001). Apart from dorzagliatin, TTP399, a liver-selective GKA being investigated as an adjunctive treatment in T1D patients. Dorzagliatin was also shown to increase beta-cell glucose sensitivity and restore glucose sensing in individuals who are heterozygous for GCK mutations, as an example of precision medicine.

TEPULIZIMAB

TID is a chronic auto-immune condition whereby autoantibodies directed against the islet cells lead to the destruction of beta-cells, even before the onset of frank hyperglycaemia in genetically-susceptible individuals. Tepulizumab is an Fc-receptor binding anti-CD3 monoclonal antibody, which acts upon CD8+ lymphocytes responsible for beta-cell destruction. In a randomised, phase 2, placebo-controlled trial of tepulizumab, 76 children and adults with stage 2 TID (positive islet autoantibodies but yet to develop hyperglycaemia) were randomised to receive a single 14-day course of tepulizumab or placebo. Diagnosis of TID was delayed by nearly two years in the intervention vs placebo group (48 vs 24 months) with a hazard ratio of 0.41 (95% CI, 0.22 to 0.78). Transient lymphopenia and rash occurred in some participants.

CONCLUSIONS

The latest American Diabetes Association and European Association of Study of Diabetes consensus now recognises glycaemic control, weight control, cardio-renoprotection and multifactorial risk factor control as of equal importance in the management of T2D. We expect the application of incretin-based co-agonists to continue to grow, given their multiple benefits on weight, glucose and cardio-protection. Similarly, it shall be seen whether immunotherapies, or other strategies towards beta-cell preservation, such as stem cell transplant, bring us closer to a "cure" or "remission" of TID. Amidst the excitement of emerging therapies, we should continue to make good use of existing drugs combined with patient education to optimise care for people with diabetes.
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<td>* Zoom Live &lt;br&gt;The rising importance of &lt;br&gt;Liver Protectant &amp; Latest &lt;br&gt;Guideline Updates</td>
<td>* Certificate Course on Medical Ultrasound 2023 (Video Lectures)</td>
<td>* The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed</td>
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<td>* In-person &lt;br&gt;Clinical Update of GLP1-RA on Obesity Management</td>
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<td>3 MON</td>
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<td>Zoom Live: The rising importance of Liver Protectant &amp; Latest Guideline Updates</td>
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<td>12 WED</td>
<td>7:30 AM</td>
<td>The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed</td>
<td>CME Accreditation College: 1.5 points College of Surgeons of Hong Kong Enquiry: Dr Calvin MAK Tel: 2955 6456 Fax.: 2965 4061</td>
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# Calendar of Events

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| **21 FRI** | 2:00 PM Zoom Live Management of Epistaxis  
Organiser: HKMA-KLN West Community Network  
Speaker: Dr Henry Chuen-kwong LAM | Mr. Peter HO  
Tel: 3108 2514  
1 CME Point |
| **25 TUE** | 7:00 PM Certificate Course on Medical Ultrasound 2023 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong  
Speaker: Dr Tina Pay-wing LAM | Ms Vienna LAM  
Tel: 2527 8998 |
| **26 WED** | 2:00 PM Zoom Live Approach to Shoulder Pain and Advance in Surgical Management  
Organiser: HKMA-Shatin Community Network  
Speaker: Dr Stephen Chor-yat CHUNG | Ms. Candice TONG  
Tel: 3108 2513  
1 CME Point |
| **27 THU** | 1:00 PM In-person / Zoom Live HKMA-HKSTP CME Lecture  
Topic: Contemporary Approach to High Risk Percutaneous Coronary Intervention and Heart Failure Management  
Organiser: The Hong Kong Medical Association and the Hong Kong Science Park  
Speaker: Dr Sunny Chun-fung TSANG  
Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central, Hong Kong | HKMA CME Dept  
Tel: 3108 2507  
1 CME Point |
|            | 7:00 PM Certificate Course on Communication and Swallowing Problems in the Elderly Population 2023 (Video Lectures)  
Organiser: The Federation of Medical Societies of Hong Kong  
Speaker: Dr Joshua LAI | Ms Vienna LAM  
Tel: 2527 8998 |
| **28 FRI** | 2:00 PM In-person Management of Treatment Resistant Depression  
Organiser: HKMA-KLN City Community Network  
Speaker: Dr LAM Chun  
Venue: President’s Room, Spotlight Recreation Club (博藝會), 4/F, Screen World, Site 8, Whampoa Garden, Hung hom, Kowloon | Ms. Candice TONG  
Tel: 3108 2513  
1 CME Point |

## Radiology Quiz

### Answers to Radiology Quiz

**Answers:**

1. Two roundish opacities are noted in the left middle zone associated with non-tapering tubular opacities. (Blue arrow) They are most likely pulmonary arteriovenous malformations with feeding arteries and draining veins.

2. The next step of investigation is to perform a contrast CT thorax to confirm the diagnosis.

3. The indications are (1) feeding artery of > 3 mm in diameter, (2) symptomatic/complications regardless of size (e.g., cerebral abscess or embolism, high output cardiac failure, cyanosis, polycythemia, or development of pulmonary arterial hypertension). The endovascular treatment option is endovascular coil embolisation.

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Dr John CY CHAN  
MBBS, FRCR
Life with Pets: From "Paediatrics" to "Geriatrics"

Dr Eunice KH LEUNG
MBBS (HK), MRCP (UK), FHKCP, FHKAM (Med)
Specialist in Endocrinology, Diabetes and Metabolism

Dr Chariene SL WOO
MBBS (HK), MRCP (UK), FHKCP, FHKAM (Med)
Resident in Endocrinology, Diabetes and Metabolism

Having a dog means you will always have a loyal friend and a good time, and yet at the same time, it also means you will experience ups-and-downs as well as inconveniences. Besides being in the same Endocrine team at Queen Mary Hospital, we both have a toy poodle. Here, we would like to share with readers our experience in being dog-owners in Hong Kong, and some of our favourite spots to spend time with our pets.

Eunice: Fafa is my 3-year-old poodle, and Elyse is my toddler, soon reaching ‘terrible two’. Fafa joined my family when he was barely 3 months old. I recalled having much trouble toilet training Fafa when he first came. I had to clean up his waste non-stop in the first couple of months. His waste could be found in the most unimaginable spots, including on top of and beneath sofas, beds, chairs, and on one occasion, even behind a door, which I discovered after opening the door unsuspectingly. To clean the dog’s waste could be challenging as it spread out evenly on the floor. Thankfully, a friend of mine, who is also a dog lover, was able to train Fafa; so Fafa was spot on thereafter.

While I was pregnant with my daughter Elyse, Fafa would not leave my side at all when I was home. I knew it was his way of protecting Elyse and me. My daughter Elyse has had the pleasure of growing up alongside Fafa since birth. Elyse has learnt to feed Fafa his favourite dog snacks. Fetching balls is their favourite pastime at home. Admittedly, it is also quite a handful when both Fafa and Elyse demand my attention, or when Fafa’s relentless barking wakes Elyse up from her naps. And to my horror, I caught Elyse pulling at Fafa’s tail or patting Fafa’s head very hard before I could talk any sense to Elyse. All in all, Fafa and Elyse are getting along well, and both are thriving harmoniously under my care.

Chariene: Belle is my 14-year-old blind poodle that is a bundle of joy and yet at the same time, a handful on occasion. The first time we saw Belle was at a pet shop in Happy Valley when I was sixteen years old. She was curious and playful, and our family (including my dog-phobic mother) immediately fell in love with her. We brought her home on Chinese New Year’s Eve and enjoyed our first family meal together. In the next morning, we found bilious vomitus on the floor with her lying feebly next to it. I still remember the panic and fear I experienced on the way to the vet on Yuan Dan morning. Instead of having turnip cakes and Niangao with our grandparents, I held onto her small fluffy paw and prayed she would make it through. To our family’s delight, she was a fighter, and after countless medications, transfusion (from a healthy Chow Chow) and months of rehabilitation (including steam room therapy for her persistent bronchitis), she recovered, and we could finally bring her home.
Unfortunately, she developed cataracts as well as retinal detachment after a few years, which has rendered her blind. Now she is home-bound and dependent and requires multitudes of eyedrops as well as oral medications up to four times a day. We thought her being blind meant that her other senses would be heightened; to our disappointment, this day never came, and she required all of our attention. Despite all of this, Belle is always happy. She has accompanied me while preparing for countless professional examinations and is always there for me. More importantly, Belle was there to fill the ‘empty nest’ for Mom after my brother left for university and I moved out of home. She has become inseparable from Mom. While we may have plenty of agendas on our plates, in the eyes of our pets, we are their entire world. I am not sure how many more years our feisty fighter will be around but we are eternally blessed to have her in our lives.

Fig. 3 Belle with an intravenous drip last year while being hospitalised for pancreatitis. (Personal collection)

Read on to learn about our recommendations on where to bring your pet in the coming weekend.

**PLAY**

Address: Lung Wo Road, Central, Hong Kong. Opening Hours: 24 hours.

This place offers you and your fluffy friend the best opportunity to let go of the leash and run freely. Central and Western District Promenade is a spacious area where you and your dog can play fetch and enjoy the view of the Victoria Harbour. Facilities: Turf area; garden benches; dog excreta collection bins; dog latrine; hand-washing facility.

Address: Bowen Road, Mid-levels, Hong Kong. Opening Hours: 24 hours.

Besides being a great fitness track for avid runners, Bowen Road at the Mid-levels is the place to go for a gentle stroll with your fluffy friend. With a flat path extending from Wanchai to Central with multiple entry and exit points along the way, it is a convenient location for a good workout for humans and dogs. If you are feeling adventurous with time to spare, you may even hike up from Wanchai Gap Road to the Peak and enjoy the views from Victoria Peak.
You can NOW PURCHASE Molnupiravir from us!

For more information, please contact MSD Professional sales representatives.


MOLNUPIRAVIR Selected Safety Information

**Authorized Use**

   - with positive results of direct SARS-CoV-2 viral testing, and
   - who are at high risk for progression to severe COVID-19, including hospitalization or death, and
   - for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate

2. Molnupiravir is not approved for any use, including the treatment of COVID-19, but is authorized for emergency use by the FDA under an Emergency Use Authorization (EUA).

3. The emergency use of molnupiravir is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic, under Section 564(b)(2) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bb-3(b)(2), unless the declaration is terminated or authorization revoked sooner.

**Limitations of Authorized Use**
4. Molnupiravir is not authorized:
   - for use in patients who are less than 18 years of age
   - for initiation of treatment in patients hospitalised due to COVID-19. Benefit of treatment with molnupiravir has been not been observed in subjects when treatment was initiated after hospitalization due to COVID-19
   - for use for longer than 5 consecutive days
   - for use in pregnant women, or post-exposure prophylaxis for prevention of COVID-19

5. Molnupiravir may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which molnupiravir belongs (i.e., anti-infectives).

**Contraindications**
6. No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under the EUA.

**Warnings and Precautions**
1. There are limited clinical data available for molnupiravir. Serious and unexpected adverse events may occur that have not been previously reported with molnupiravir use.

2. Molnupiravir is not recommended for use during pregnancy. Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

3. Molnupiravir is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and the potential risks of using molnupiravir during pregnancy were communicated to the pregnant individual.

10. Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently during treatment with molnupiravir and for 4 days after the final dose.

11. Prior to initiating treatment with molnupiravir, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated.

12. Hypersensitivity reactions, including anaphylaxis, have been reported with molnupiravir. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue molnupiravir and initiate appropriate medications and/or supportive care.

13. Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. The safety and efficacy of molnupiravir have not been established in pediatric patients.

**Adverse Reactions**
14. The most common adverse reactions occurring in ≥1% of subjects in the molnupiravir treatment group in the Phase 3 double-blind INFORM-2 trial were diarrhea (2% versus placebo at ≥3.1% nausea (1% versus placebo at ≥4%), and dizziness (1% versus placebo at ≥2.1%) all of which were Grade 1, mild or Grade 2 moderate.

15. Serious adverse events occurred in 7% of subjects receiving molnupiravir and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2% (1% of the subjects receiving molnupiravir and 12% 0% of subjects receiving placebo).

**Drug Interactions**
16. No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild to moderate COVID-19, have been conducted.

**Breastfeeding**
18. There are no data on the presence of molnupiravir or its metabolites in human milk. It is unknown whether molnupiravir has an effect on the breastfed infant or affects on milk production. Based on the potential for adverse reactions in the infant from molnupiravir, breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir.

**Mucosa of Reproductive Paratm**
17. Nonclinical studies to fully assess the potential for molnupiravir to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of molnupiravir. The risk beyond three months after the last dose of molnupiravir is unknown.

Before prescribing, please consult the full prescribing information.

MSD

ACHIEVE LASTING CHANGE

CONTINUOUS CONTROL

References:

~340,000 AD PATIENTS TREATED WITH DUPIXENT WORLDWIDE

*DUPIXENT is indicated to treat adults and adolescents ≥12 years with moderate-to-severe atopic dermatitis, and children aged 6 to 11 years with severe atopic dermatitis for systemic therapy.

Presentations: Dupilumab injection for injection in a pre-filled syringe with needle shield. Indications: Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy; severe atopic dermatitis in children 6-11 years old who are candidates for systemic therapy. Antihistamines and/or topical corticosteroids are added on maintenance treatment for severe atopic with type 2 inflammation characterised by elevated eosinophils and/or raised FeNO, which are inadequately controlled with high dose ICS plus oral systemic patient control. Chronic exacerbations with oral systemic patient control. Chronic exacerbations with oral systemic patient control. Chronic exacerbations with oral systemic patient control.

Sanoﬁ Hong Kong Limited
1/F & SECTION 212 on 2/F, AXA SOUTHIDE, 38 WONG CHUK HANG ROAD, WONG CHUK HANG, HONG KONG
Tel: (852) 2506 8333 Fax: (852) 2506 2537

**DUPIXENT is not an immunosuppressant

~85% patient satisfaction with DUPIXENT treatment at 1 year**

RAPID AND SUSTAINED CONTROL - CONSISTENT ACROSS ALL AGES

- Sustained improvement of itch, skin clearance, and QoL up to 52 weeks, with rapid control after first dose

UNIQUE LONG-TERM SAFETY PROFILE

- Only AD therapy:
  - With 4-years long-term safety data in adults
  - Approved in patients as young as 6 years old

START WITH EASE, STAY WITH CONFIDENCE

- DUPIXENT is the first-line systemic choice for achieving lasting change in patients as young as 6 years old with atopic dermatitis (AD)*