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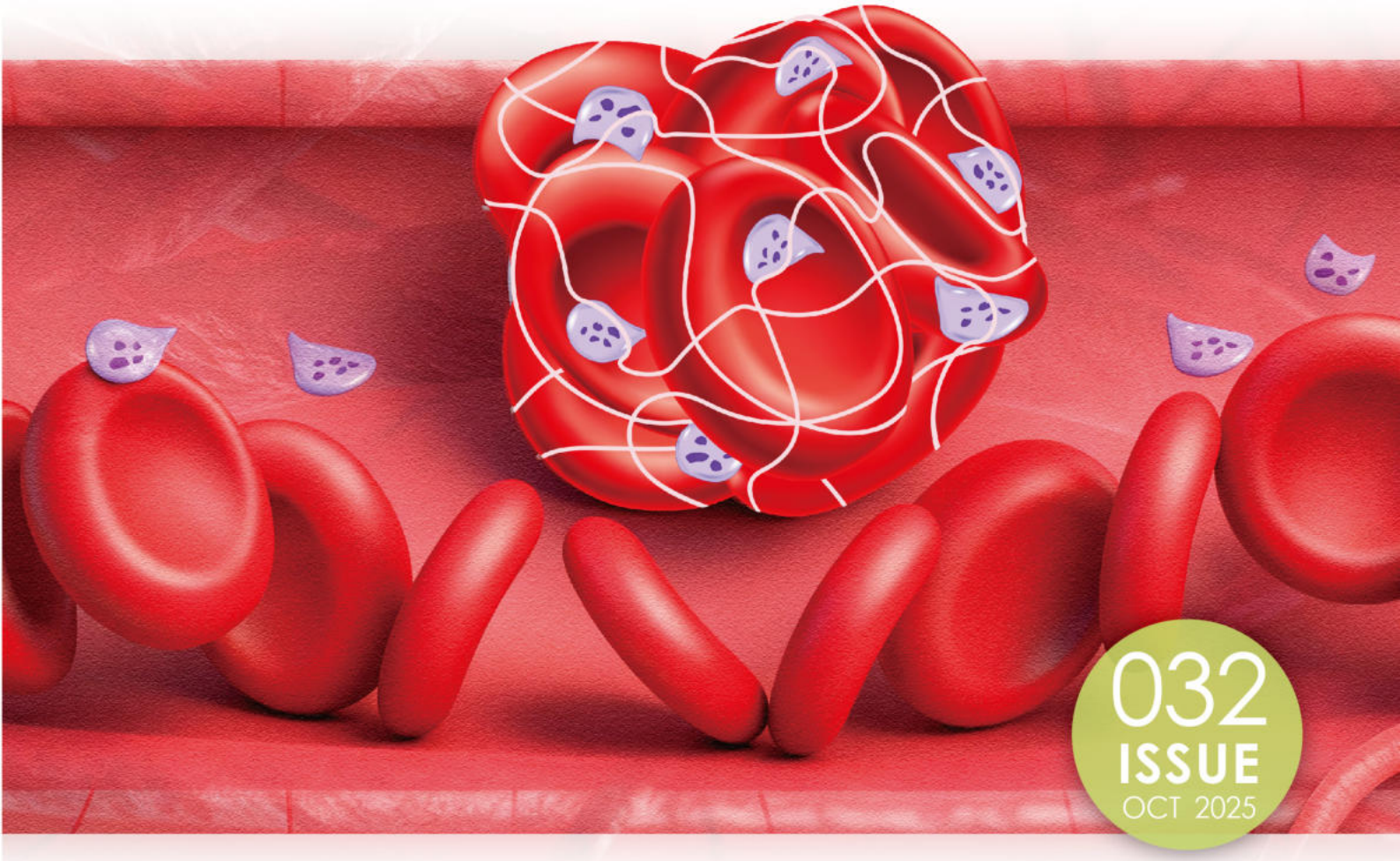
Achieving a Rebalance of the Teeter-Totter: Recent Advances in Hemophilia Treatment



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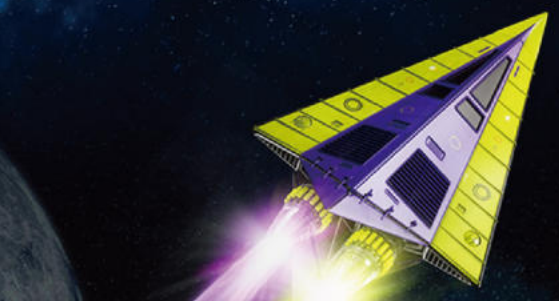
Atozet®
(ezetimibe and atorvastatin) tablets

POWERFUL LDL-C REDUCTION WITH ATOZET®

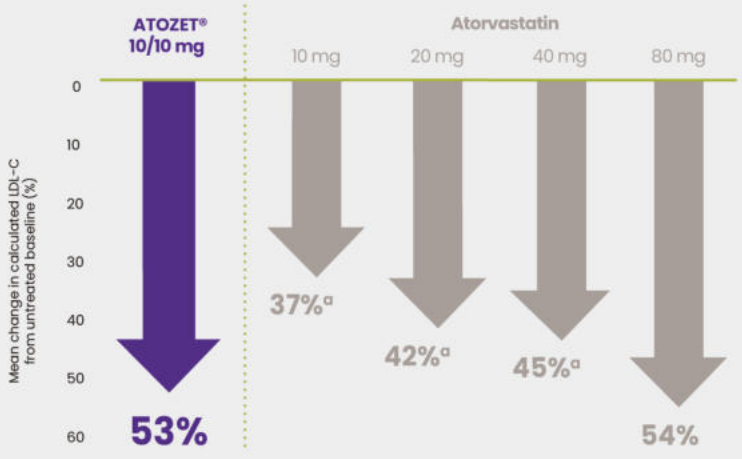
in high risk/very high risk patients with dyslipidemia[1]



In a clinical study of patients with hyperlipidemia and not on lipid-lowering therapy,

ATOZET® (Ezetimibe/ Atorvastatin) 10/10 mg powerfully lowered mean LDL-C by 53%[1]

Efficacy of the lowest dose of ATOZET® (10/10 mg) was similar to that the highest dose of Atorvastatin (80 mg)[1]



Mean pooled untreated baseline calculated LDL-C was 4.70 mmol/L (n=255) for the group receiving ATOZET® and 4.69 mmol/L (n=248) for the group receiving Atorvastatin. Mean reduction in calculated LDL-C from untreated baseline was 54% for ATOZET® 10/20 mg; 56% for ATOZET® 10/40 mg* and 61% for ATOZET® 10/80 mg*.[1]

* Strengths not available in some countries

[a] $p<0.01$ for combination therapy vs. corresponding dose of atorvastatin alone

Study design: In a prospective, randomized, double-blind study, 628 patients with baseline LDL-C 145 to 250 mg/dL and triglycerides ≤350 mg/dL were randomly assigned to receive 1 of the following for 12 weeks: ezetimibe (10 mg/d); atorvastatin (10, 20, 40, or 80 mg/d); ezetimibe (10 mg) plus atorvastatin (10, 20, 40, or 80 mg/d); or placebo. The primary efficacy end point was percentage reduction in LDL-C for pooled ezetimibe plus atorvastatin versus pooled atorvastatin treatment groups.

Reference

1. Ballantyne, C. M. et al. Effect of Ezetimibe Coadministered With Atorvastatin in 628 Patients With Primary Hypercholesterolemia - A Prospective, Randomized, Double-Blind Trial. Circulation. 107,2409–2415 (2003).

ATOZET® Selected Safety Information

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

Welcome to this issue, where we delve into the remarkable strides made in medicine throughout 2025 in the Feature Story. Rheumatology has seen a transformative year, with breakthroughs in biologic therapies, precision medicine, and AI-driven care reshaping the landscape for conditions like RA, SLE, and PsA. Highlights include the approval of innovative agents such as dapirolizumab pegol and sonelokimab, alongside smart drug delivery systems and digital health integration—ushering in a new era of personalized treatment.

In our Focus section, we trace the evolution of hemophilia treatment—from early transfusions to cutting-edge biologics and gene therapies—culminating in the recent approval of marstacimab, a novel non-factor therapy that redefines care standards.

Beyond these features, the Industry Update explores the neuroprotective potential of statin-based therapies and strategies for managing treatment-resistant bipolar and anxiety disorders. Meanwhile, the Epoch section offers a thought-provoking look at the possible neurocognitive effects of sweeteners.

We hope this issue informs and inspires. Enjoy the read!

Dr. Feng Xue
MPH, PhD
Chief Editor, V.Pulse

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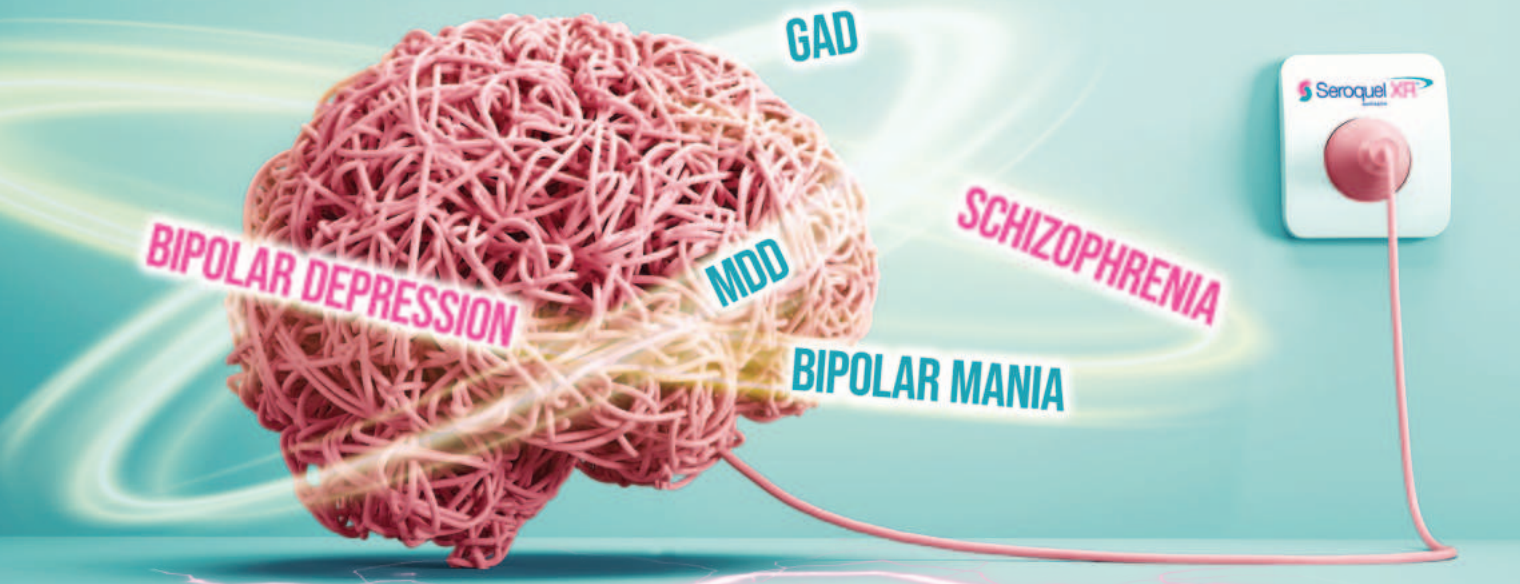
Major Mental Disorders



APPROVED INDICATIONS

- Bipolar Depression - 50-600mg/day*
- Major Depressive Disorder (MDD) - 50-300mg/day*
- Schizophrenia - 400-800mg/day*
- Bipolar Mania - 400-800mg/day*
- Generalised Anxiety Disorder (GAD) - 50-150mg/day*

* Dose range for acute treatment

Abbreviated Prescribing Information: Presentation: Quetiapine fumarate extended-release tablet. Indications: Bipolar Disorder: Maintenance treatment of bipolar I disorder; as monotherapy or in combination with lithium or sodium valproate, for prevention of relapse/recurrence of manic, depressive or mixed episodes; Treatment of depressive episodes associated with bipolar disorder; Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate. Schizophrenia: Treatment of schizophrenia, prevention of relapse and maintenance of clinical improvement during continuation therapy. Major Depressive Disorder (MDD): Treatment of recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies. Generalised Anxiety Disorder (GAD): Treatment of GAD. Dosage: Once daily, without food. Bipolar Disorder: Maintenance treatment: Use same dose as active treatment for prevention of manic, depressive or mixed episodes in bipolar disorder. Range 300-800 mg/day. Bipolar Depression: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4). Can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8. Acute Mania: 300 mg (Day 1), 600 mg (Day 2), up to 800 mg (after Day 2), alone or in combination with a mood stabilizer. Range 400-800 mg/day. Schizophrenia: 300 mg (Day 1), 600 mg (Day 2) and up to 800 mg after Day 2. Range 400-800 mg/day depending on response and tolerability. Same dosage for maintenance therapy. Recurrent MDD: Once daily in the evening. 50 mg (Day 1 & 2), increased to 150 mg on Day 3 & 4. Usual effective dosage: 150 mg. Range of 50-300 mg/day. Same dosage for maintenance therapy. GAD: 50 mg (Day 1 & 2), 150 mg (Day 3 & 4). Range 50-150 mg/day. Switching from Seroquel immediately release: Switch at equivalent total daily dose. Individual adjustments may be necessary. Elderly: 50 mg/day, increased in increments of 50 mg/day up to an effective dose depending on response and tolerability. Slower dose titration is recommended. Elderly MDD: 50 mg (Day 1-3), 100 mg (Day 4), 150 mg (Day 8), up to 300 mg depending on response and tolerability. Elderly GAD: 50 mg (Day 1-3), 100 mg (Day 4), 150 mg on Day 8. Patients with renal impairment: No dosage adjustment needed. Patients with hepatic impairment: 50 mg/day up to an effective dose. Contraindications: Hypersensitive to any components of this product. Precautions: Elderly patients with dementia-related psychosis or behavioural disorders; rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption; concomitant use with ADHD medication; conditions predisposing to hypotension; family history of QT prolongation, congenital long QT syndrome, heart failure, hypokalaemia or hypomagnesaemia, concomitant medicines known to prolong QTc interval; history of seizures, conditions that potentially lower seizure threshold; elevation in core body temperature; risk for aspiration pneumonia. Interactions: Centrally acting drugs: thioridazine; lorazepam; levodopa and dopamine agonists.CYP3A4 inhibitors: azole antifungals; macrolide antibiotics; protease inhibitors; grapefruit juice. Hepatic enzyme inducers: carbamazepine; phenytoin. Undesirable effects: Sedation; somnolence; insomnia; dizziness; syncope; headache; increased appetite; weight gain; dysphagia; dry mouth; nausea & vomiting; constipation; dyspepsia; tachycardia; palpitations; orthostatic hypotension; rhinitis; dyspnoea; blurred vision; abnormal dreams & nightmares; asthenia; dysarthria; fatigue; myalgia; peripheral edema; irritability; pyrexia; lipid changes; worsening of metabolic factors; elevations in serum transaminases (ALT, AST), γ-GT & serum prolactin; increases eosinophils: decreases in total T4, free T4 & total T3, and increases in TSH; leucopenia and/or neutropenia; mild asthenia; withdrawal symptoms after abrupt cessation. Full local prescribing information is available upon request.

Please read the complete prescribing information before prescribing.

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by Dr. Feng Xue

Rheumatology in 2025: *Breakthroughs, Technologies, and the Future of Care*

The field of rheumatology has undergone transformative changes in 2025, driven by innovations in biologic therapies, precision medicine, digital health, and neuroimmune modulation. This article explores the most significant advances in the diagnosis and treatment of rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriatic arthritis (PsA). Key developments include the approval of novel biologics such as dapirolizumab pegol (DZP) and sonelokimab, the emergence of smart drug delivery systems, and the integration of artificial intelligence (AI) in clinical decision-making. These breakthroughs promise improved patient outcomes, reduced side effects, and more personalized care. The article concludes with a discussion on the implications of these advances for clinical practice and future research directions.

Introduction

Rheumatology, the branch of medicine focused on autoimmune and inflammatory diseases affecting joints, muscles, and connective tissues, has seen a surge of innovation in 2025. With over 100 distinct conditions under its umbrella—including RA, SLE, and PsA—rheumatology has long been challenged by diagnostic complexity and treatment limitations.[1, 2] However, recent scientific and technological advances are reshaping the landscape, offering new hope to millions of patients worldwide.

This article reviews the most impactful developments in rheumatology in 2025, highlighting new therapies, diagnostic tools, and care models that are redefining the standard of care.

Biologic and Targeted Therapies: A New Generation

Dapirolizumab Pegol (DZP) in SLE

One of the most promising therapies in 2025 is DZP, a novel, polyethylene glycol (PEG)-conjugated antigen-binding fragment (Fab'), lacking an Fc domain. DZP binds CD40L, blocking CD40-CD40L interactions and CD40 activation, and has broad modulatory effects on SLE immunopathology.[3] The PHOENYCS GO phase 3 trial demonstrated that DZP resulted in significant improvement in disease activity at Week 48 vs placebo (40.9% vs 19.6%, nominal p<0.0001) and was generally well tolerated in patients with moderate-to-severe SLE (**Figure 1**).[3]

Sonelokimab: Nanobody Therapy for PsA

PsA is a progressive, multidomain and interleukin-17 (IL-17)-linked disease that results in substantially reduced quality-of-life. Sonelokimab is a novel nanobody that binds with a similarly high affinity to IL-17A and IL-17F, inhibiting all dimers. In a phase 2 randomized controlled trial, over 60% of patients treated with sonelokimab achieved minimal disease activity within 24 weeks, with significant improvements in joint and skin symptoms.[4] The small size of sonelokimab allows better tissue penetration compared with traditional monoclonal antibodies, making it a promising option for hard-to-treat inflammation.[5]

CPL'116: Dual JAK/ROCK Inhibitor for RA

Janus kinase (JAK) inhibitors are an effective treatment option in RA and other autoimmune diseases. However, the use of JAK inhibitors is associated with increased levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, and creatinine kinase, reducing the net clinical benefit of using them. Adding Rho-associated protein kinase (ROCK) inhibition to JAK inhibition might provide cardioprotection as ROCK inhibitors have been shown to reduce vascular inflammation, improve endothelial function, and prevent cardiac remodelling in preclinical models.[6]

CPL'116 represents a new class of dual inhibitors targeting both JAK and ROCK pathways. The findings of a phase 2 randomized trial suggest a dose-dependent response with CPL'116, with significant efficacy at the high dose of 240 mg twice daily in patients with RA unresponsive to methotrexate. CPL'116 was generally well tolerated and was not associated with lipid abnormalities or creatinine kinase increase. These findings warrant further investigation in larger studies and different clinical settings.[6]

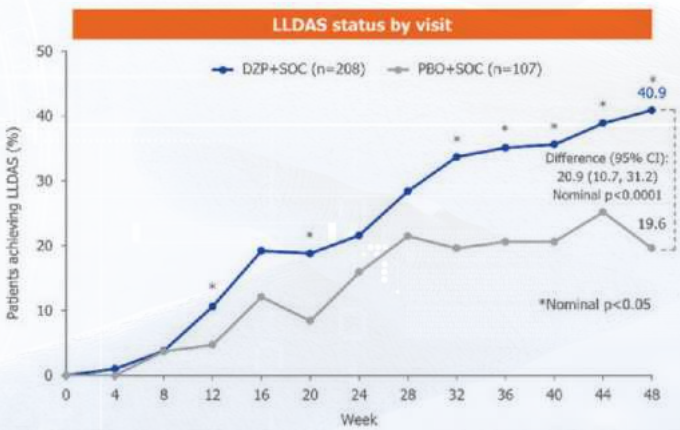
Smart Drug Delivery and Non-Immunosuppressive Therapies

Smart Gel Technology

A revolutionary pH-sensitive gel developed by Cambridge University responds to inflammation by releasing drugs only at affected sites. This smart material detects acidity changes caused by arthritis flare-ups and delivers pain relief precisely where needed, minimizing systemic exposure and side effects.[7]

Neuroimmune Modulation Devices

The Food and Drug Administration (FDA) has recently approved the SetPoint System, a neuroimmune modulation device, for the treatment of adults with moderately to severely active RA who have had an inadequate response, loss of response or intolerance to 1 or more biological or targeted synthetic disease-



CI=confidence interval; LLDAS=Lupus Low Disease Activity State; PBO=placebo; SOC=standard of care

Figure 1. *LLDAS status by visit*[3]

modifying anti-rheumatic drugs (b/tsDMARDs). In a phase 3 study, the SetPoint neuroimmune modulation device was found to be an effective treatment for patients with difficult-to-treat RA. The device is surgically placed under general anesthesia on the vagus nerve. By delivering electrical stimulation to the vagus nerve, the treatment is expected to reduce inflammation without immunosuppression and restore the immune pathways that are believed to be dysfunctional in RA patients.[8]

Role of Biomarkers in Precision Medicine

What makes the diagnosis of rheumatic disease particularly challenging is its very heterogeneous clinical presentations. The need for reliable, disease-specific biomarkers is more urgent than ever to make differential diagnosis easier and assess disease progression and severity over time.[9] Biomarkers play an essential role in advancing precision medicine, offering a strategic opportunity to improve health and lower healthcare costs.[10]

For example, the autoimmune mechanisms driving RA often start years before noticeable symptoms like joint pain and stiffness arise. Diagnostic biomarkers are essential tools for clinicians during this phase, as they enable the accurate identification of individuals at risk or in the preclinical stages of the disease, facilitating the use of this optimal period for intervention.[11] In addition to their diagnostic value, numerous RA biomarkers serve diverse functions across different stages of the disease, supporting risk assessment, monitoring disease activity, and informing treatment decisions (**Table 1**).[2]

Application of AI in Rheumatology

The integration of AI into rheumatology has revolutionized research and clinical practice, offering transformative advancements in diagnostics, biomarker discovery, genomics, digital health technologies, and personalized medicine. AI is being used to analyze imaging, lab results, and patient-reported outcomes to assist in early diagnosis and treatment optimization. AI tools are particularly useful in distinguishing between overlapping autoimmune conditions.[12, 13, 14]

Telehealth has become a cornerstone of rheumatology care. Using wearable health technologies, smart devices like smart watches and smartphone sensors can objectively and continuously monitor disease activity and patient function for conditions like RA. In 2025, virtual clinics are equipped with remote monitoring tools that track joint swelling, mobility, and fatigue in

Predictive	Monitoring	Prognostic	Diagnostic	Category of Biomarkers
				Inflammatory
	✓	✓	✓	ESR
	✓	✓	✓	CRP
	✓	✓		Calprotectin
				Antibody Biomarkers
Rituximab, Abatacept	✓	✓		ACPA
	✓	✓	✓	RF
	✓	✓		Anti-CarP
	✓	✓		Anti-MAA
	✓	✓		AAPA
	✓	✓		Serum-14-3-3η
Rituximab	✓	✓	✓	Anti-MCV
	✓	✓		Anti-PAD4
				Genetic Biomarkers
Abatacept	✓	✓	✓	HLA-DRB1 (Shared Epitope)
				Multi-Biomarker Panel
DMARD	✓	✓		MBDA Score
				Joint Damage Biomarkers
	✓	✓		MMP-3
Adlimumab	✓	✓		COMP

AAPA=anti-acetylated protein antibodies; ACPA=anti-citrullinated protein antibodies; anti-CarP=anti-carbamylated protein antibodies; anti-MAA=anti-malondialdehyde-acetaldehyde antibodies; anti-MCV=anti-mutated citrullinated vimentin; anti-PAD4=anti-peptidyl arginine deiminase 4; COMP=cartilage oligomeric matrix protein; CRP=C-reactive protein; DMARD—disease-modifying anti-rheumatic drug; ESR=erythrocyte sedimentation rate; HLA-DRB1=human leukocyte antigen DR beta 1; mBDA Score=multi-biomarker disease activity score; MMP-3=matrix metalloproteinase-3; RF=rheumatoid factor; Serum-14-3-3η=serum14-3-3 eta protein

Table 1. *Biomarkers in RA categorized according to their diagnostic, prognostic, monitoring, and predictive roles*[2]

real time. These data inform treatment adjustments and reduce the need for in-person visits. Apps using AI algorithms now help patients log symptoms and predict flare-ups, enabling proactive care and medication adjustments.[13]

Pediatric and Rare Disease Advances

Guselkumab for Pediatric Psoriasis and PsA

In 2005, the FDA expanded the use of guselkumab to children with plaque psoriasis (PsO) and PsA, offering a safer and more effective alternative to corticosteroids. The FDA's approval includes the treatment of pediatric patients 6 years and older weighing at least 40 kg with moderate to severe PsO, who are candidates for systemic therapy or phototherapy, and for the treatment of active PsA. Previously, these indications were only approved in adults. The approval for active PsA was supported by pharmacokinetic data extrapolated from prior PsO and PsA studies. Findings showed that the efficacy and safety data of guselkumab in pediatric patients with PsA was consistent with that from adults with PsO and PsA and children with moderate to severe PsO.[15]

Inebilizumab for IgG4-Related Disease

IgG4-related disease is a multiorgan, relapsing, fibroinflammatory, immune-mediated disorder with no approved therapy before 2025. Inebilizumab targets and depletes CD19+ B cells; and according to a phase 3 trial, inebilizumab reduced the risk of flares of IgG4-related disease and increased the likelihood of flare-free complete remission at 1 year.[16] In April 2025, inebilizumab became the first FDA-approved therapy for IgG4-related disease, addressing a major unmet need in this rare autoimmune condition. This approval offers a new therapeutic option for patients previously reliant on less targeted treatments.[17]

Challenges and Future Directions

Despite the remarkable progress in rheumatology in 2025, several challenges continue to shape the trajectory of care and research. Addressing these issues will be critical to ensuring that innovations translate into meaningful, equitable, and sustainable improvements for all patients.

• Access and Affordability

While biologics, nanobody therapies, and implantable devices offer transformative benefits, their high costs remain a barrier for many patients, particularly in low- and middle-income countries. Reimbursement policies, patent protections, and limited availability of biosimilars contribute to disparities in access. Expanding global manufacturing, streamlining regulatory pathways, and fostering public-private partnerships will be essential to make advanced therapies more affordable and widely available.

• Long-Term Safety and Real-World Evidence

Many of the newly approved treatments lack long-term safety data, especially in diverse populations and those with comorbidities. Post-marketing surveillance, patient registries, and real-world evidence studies must be prioritized to monitor adverse effects, treatment durability, and comparative effectiveness. These data will also help refine treatment guidelines and inform shared decision-making.

• Diagnostic Complexity and Disease Overlap

Autoimmune diseases often present with overlapping symptoms and comorbid conditions, complicating diagnosis and management. Although AI-driven tools and biomarker profiling are improving diagnostic accuracy, further refinement is needed to distinguish between similar conditions and predict disease progression. Investment in multi-omics research and integrative diagnostic platforms will be key to overcoming these challenges.

• Workforce and Training Gaps

The growing demand for rheumatologic care is outpacing the availability of trained specialists. In many regions, patients face long wait times and limited access to expert care. Expanding training programs, incorporating telemedicine into routine practice, and leveraging AI to support clinical decision-making can help bridge this gap and improve care delivery.

• Patient Engagement and Health Literacy

Empowering patients to actively participate in their care is vital for long-term disease management. However, disparities in digital literacy, language barriers, and limited access to technology can hinder engagement. Tailored education programs, culturally sensitive communication strategies, and inclusive digital tools must be developed to ensure that all patients benefit from the evolving landscape of rheumatology.

Looking ahead, to fully realize the potential of these advances, the rheumatology community must embrace a holistic and collaborative approach. Key priorities for the future include:

- Development of oral biologics and gene therapies to simplify treatment and improve adherence.[18, 19]
- Integration of AI and wearable technologies into routine care for early detection and personalized monitoring.

- Expansion of global research networks to foster innovation and share best practices across borders.
- Policy reform and advocacy to address systemic barriers to care and promote equitable access.

By confronting these challenges head-on and investing in inclusive, forward-thinking solutions, rheumatology can continue to evolve into a field that not only treats disease but transforms lives.

Conclusion

The year 2025 stands as a transformative milestone in rheumatology, marked by a convergence of scientific innovation, technological advancement, and patient-centered care. From nanobody therapies and smart drug delivery systems to AI-enhanced diagnostics and neuroimmune modulation devices, the field is rapidly evolving beyond traditional paradigms. These breakthroughs are not only enhancing disease control and reducing treatment burdens but are also reshaping how clinicians approach autoimmune and inflammatory conditions—with greater precision, personalization, and compassion.

Importantly, these innovations are empowering patients to take a more active role in their health journeys, supported by tools that offer real-time insights, remote monitoring, and tailored therapies. As the boundaries between disciplines continue to blur, collaboration among rheumatologists, immunologists, engineers, and data scientists will be essential to sustain this momentum.

Looking ahead, the challenge will be to ensure equitable access to these advances across diverse populations and healthcare systems. Continued investment in research, education, and global partnerships will be critical to translating these breakthroughs into meaningful, lasting improvements in quality of life for all individuals affected by rheumatic diseases.

In embracing this new era, the rheumatology community reaffirms its commitment to alleviating suffering, restoring function, and advancing care—guided by innovation, grounded in evidence, and inspired by the resilience of its patients.

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P=0.02 for superiority vs placebo

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Up to 86.1% of patients (Chinese population) achieved HbA_{1c} levels <7%[4]

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ARR = absolute risk reduction; CKD = chronic kidney disease; CV = cardiovascular; GLP-1 RA = glucagon-like peptide-1 receptor agonist; RRR = relative risk reduction; T2D = type 2 diabetes.
[a]Benefits include proven risk reduction in CV and kidney events. [b]Patients with T2D, T2D + CVD and T2D + CKD. [c]Ozempic® is indicated for the treatment of adults with insufficiently controlled T2D as an adjunct to diet and exercise, results apply to Ozempic® across SUSTAIN trials.

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Abbreviated prescribing information (Please consult the full prescribing information before prescribing)
Ozempic® (semaglutide). Ozempic® 0.25 mg solution for injection in pre-filled pen; Ozempic® 0.5 mg solution for injection in pre-filled pen; Ozempic® 1 mg solution for injection in pre-filled pen. **Presentation:** Ozempic® 0.25 mg & 0.5 mg solution for injection: Each pre-filled pen contains 2 mg semaglutide in 1.5 ml solution. Ozempic® 1 mg solution for injection: One pre-filled pen contains 4 mg semaglutide in 3 ml solution. **Indications:** Ozempic® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise as Monotherapy: when metformin is considered inappropriate due to intolerance or contraindications. Combination therapy: in addition to other medicinal products for the treatment of diabetes. For trial results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see the full prescribing information. **Dosage and Administration:** The starting dose is 0.25 mg Ozempic® once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. Ozempic® 0.25 mg is not a maintenance dose. Weekly doses higher than 1 mg are not recommended. Ozempic® is to be administered once weekly at any time of the day, with or without meals. Ozempic® is to be injected subcutaneously in the abdomen, thigh or upper arm. Ozempic® should not be administered intravenously or intramuscularly. When Ozempic® is added to existing metformin and/or thiazolidinedione therapy or to a sodium-glucose cotransporter 2 (SGLT2) inhibitor, the current dose of metformin and/or thiazolidinedione or SGLT2 inhibitor can be continued unchanged. When Ozempic® is added to existing therapy of sulfonylurea (SU) or insulin, a reduction in the dose of SU or insulin should be considered to reduce the risk of hypoglycaemia. Elderly: No dose adjustment is required. Therapeutic experience in patients age ≥75 is limited. Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience in patients with severe renal impairment is limited. Not recommended for use in patients with end-stage renal disease. Hepatic impairment: No dose adjustment is required for patients with hepatic impairment. Experience in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with Ozempic®. 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by Dr. Roy Lau

Beyond LDL-C Reduction – A Discussion on the Neuroprotective Effect of Statin-based Therapy

Dr. Li Ho Lun Terrance
Specialist in Neurology

Statins are the front-line therapeutic agents for preventing cardiovascular diseases (CVD) and atherosclerotic disorders related to hypercholesterolemia by lowering low-density lipoprotein cholesterol (LDL-C) levels[1]. In addition to this primary indication, there is emerging evidence suggesting the neuroprotective effects of statins against stroke and neural degenerative diseases, such as Alzheimer's disease (AD)[2]. To uncover the pathophysiological linkage between dyslipidaemia and neurological disorders, Dr. Li Ho Lun Terrance was invited to discuss the possible mechanisms of elevated LDL-C in contributing to the onset of neurological disorders. In particular, Dr. Li also shared his opinions on the neuroprotective roles of LDL-C lowering therapies.

When Dyslipidaemia Meets Neurological Disorders

"Dyslipidaemia is prevalent among patients with neurological disorders," Dr. Li expressed. Indeed, the correlations between dyslipidaemia and neurological disorders have been investigated extensively. For instance, a meta-analysis of 18 clinical studies by Zhao *et al*. (2024) revealed that patients with hyperlipidaemia had a 1.23-fold higher risk of cognitive impairment than those with normal lipid levels (odds ratio [OR]: 1.23, p=0.02)[3]. Additionally, a cross-sectional survey by Yi *et al*. (2020) revealed a significant correlation between dyslipidaemia and stroke (OR: 2.15, p<0.001)[4].

Dr. Li outlined that the pathological linkage between dyslipidaemia and neurological disorders can be explained in 3 aspects. The first aspect focuses on the pathogenesis of stroke. "As reported in previous literature, about 60% to 70% of stroke patients have high LDL-C," Dr. Li noted. In a recent cross-sectional study by Baral *et al*. (2022), the prevalence of dyslipidaemia among ischemic stroke patients even reached 80.0%[5].

The second aspect concerns dementia, with Alzheimer's disease (AD) being the most prevalent form. Dr. Li addressed that many patients with Alzheimer's disease (AD) exhibit hyperlipidaemia, which may be associated with the accumulation of β-amyloid. Essentially, Alzheimer's disease (AD) is characterised by the appearance of brain senile plaques composed of aggregated forms of β-amyloid, whereas elevated intracellular cholesterol levels might affect the processing of amyloid precursor protein, promoting the production of β-amyloid[1].

The third aspect is about neuroinflammatory disorders, such as multiple sclerosis (MS). MS is a chronic inflammatory disease of the CNS leading to demyelination and axonal degeneration. Existing literature suggested that higher LDL-C levels are associated with an increase in MS disease activity[6]. Accordingly, the reported prevalence of hyperlipidaemia among the population with MS ranged from 3.0% to 47.8%[7]. Dr. Li added that the possible mechanisms by which elevated LDL-C contributes to the onset of neurological disorders depend on the type of disorder. "Stroke is likely to be related to plaque formation, whereas other neurological disorders would be triggered by β-amyloid deposition or neuroinflammation," he described.

Briefing on the Pathophysiology of Stroke

While there is emerging evidence suggesting the association between dyslipidaemia and cognitive impairment, the increased risk of stroke attributed to dyslipidaemia has been well established. Hence, clinical guidelines generally advocate "the lower LDL-C the better" approach to mitigate the occurrence or recurrence of atherosclerotic ischemic stroke[8]. Nonetheless, the effectiveness of lipid-lowering medications on stroke prevention remains inconsistent. This variation likely arises from the heterogeneous aetiologies of stroke[9].

Dr. Li outlined that stroke can be classified into either haemorrhagic or ischemic stroke. According to a survey of stroke neurologists from 13 Asian regions, the median percentage of ischemic stroke is 75%, ranging from 59% in Vietnam to 90% in Hong Kong (**Figure 1**)[10]. Ischemic strokes occur when blood clots or other particles block the blood vessels to the brain. "Atherosclerosis or atherothrombotic diseases are the most common causes of ischemic strokes," Dr. Li highlighted. He further explained that a high LDL-C level would induce endothelial injury, leading to plaque formation and, subsequently, the blockage of blood vessels. Moreover, ischemic strokes can be cardioembolic, small-vessel disease, and other subtypes[11]. Essentially, LDL-C level is independently associated with the risk of ischemic stroke[12]. The extent to which lipid-lowering treatments affect stroke outcomes may vary depending on the stroke subtype. For instance, in case of large artery atherosclerosis, the optimal target level of LDL-C is relatively clear. However, when dealing with other stroke subtypes like small vessel occlusion or cardioembolism, the appropriate LDL-C target remains uncertain.[9]

In contrast, haemorrhagic strokes occur when an artery in the brain ruptures and the leaked blood increases intracranial pressure, resulting in damage to brain cells. Hypertension and aneurysms are the main conditions leading to haemorrhagic strokes[13]. Dr. Li addressed that high LDL-C levels are associated with amyloid angiopathy, especially among older patients, which increases the risk of haemorrhagic stroke. He further described that amyloid angiopathy occurs more in the cerebral cortex, whereas hypertension-related strokes often occur in deeper regions, such as the basal ganglia.

The Neuroprotective Roles of LDL-C Lowering Therapies

Dr. Li noted that reducing LDL-C would lower the risk of stroke by 20-30%. His comment aligned with the findings of a meta-analysis involving 312,175 participants from 49 trials by Silverman *et al*. (2016), which indicated that the relative risk (RR) was 0.77 ($p<0.001$) for major vascular events per 1 mmol/L reduction in LDL-C level (**Figure 2**)[14]. Remarkably, this reduction encompasses a 21% decrease in RR associated with ischemic stroke per 1 mmol/L decline in LDL-C, specifically through the use of statins[9].

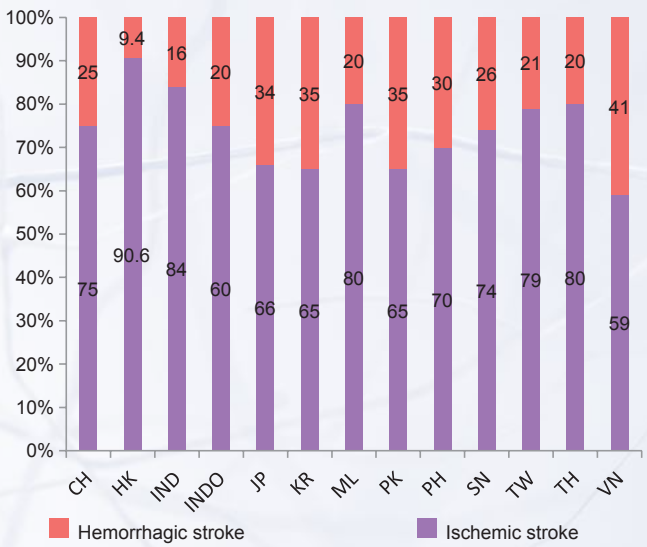

Figure 1: Proportion of ischemic and haemorrhagic stroke in each region[10]

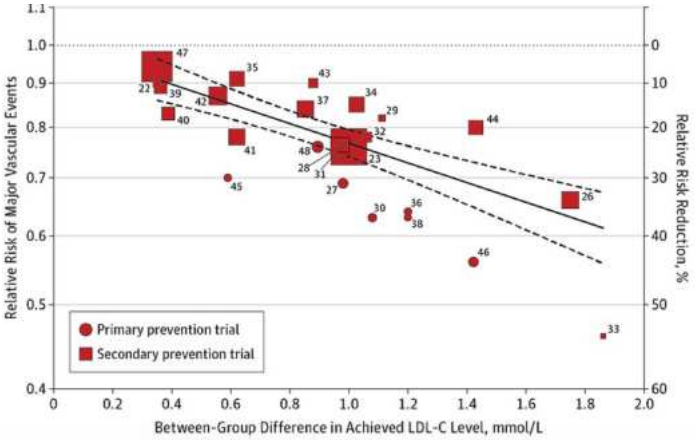

Figure 2: Association of Between-Group Difference in Achieved LDL-C Levels and Risk of Major Vascular Events[14]

Apart from reducing the risk of stroke, existing literature suggests that LDL-C lowering therapy, primarily with statins, is an effective strategy in reducing CVD risk and may have a positive effect on neurodegenerative diseases. For instance, in a former trial involving 98 patients with mild to moderate Alzheimer's disease (AD) by Sparks *et al*. (2005), atorvastatin reduced circulating cholesterol levels and yielded significant improvements in the Geriatric Depression Scale and the Alzheimer's Disease Assessment Scale-cognitive subscale compared to placebo at 6 months, whereas the benefit in Alzheimer's disease (AD) was sustained at 12 months[15].

Dr. Li added that reducing LDL-C can also reduce neuroinflammation and amyloid deposition. In this regard, he would prescribe LDL-C lowering therapy to patients with high LDL-C to prevent stroke and neurodegenerative diseases.

The Strategy for Managing Dyslipidaemia

To achieve the target LDL-C level, Dr. Li noted that statins are commonly used as the first-line treatment. Up-titration of statin dosage would be used if the response is inadequate, provided that the patient can tolerate the treatment. Practically, muscle pain is a common complaint among patients. Therefore, Dr. Li advised regularly monitoring the patient's creatine kinase (CK) level. "In cases where high-dose statin monotherapy cannot be tolerated, combined treatments should be considered," he recommended. Furthermore, in patients whose LDL-C levels remain uncontrolled despite combined therapies, treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be required.

The Synergy of Combined Statin and Ezetimibe in Controlling LDL-C

Regarding the clinical performance of combined statin and ezetimibe therapy in reducing LDL-C, Dr. Li commented that the efficacy of combined therapy is better than high-dose statin monotherapy. He noted that some patients tolerate lower-dose statins but may experience myopathy and cannot tolerate the high-dose statin monotherapy. Based on Dr. Li's clinical observations, there are fewer side effects associated with statin and ezetimibe combined therapy than high-dose statin monotherapy. "Gastrointestinal (GI) side effects are the more common types of side effects reported by patients, but they are generally mild and easily manageable," he remarked.

The LDL-C lowering and neuroprotective efficacy of combined statin and ezetimibe can be appreciated in the trial involving 148 coronary heart disease (CHD) patients with carotid atherosclerosis by Luo *et al*. (2016). In the trial, the patients were randomly allocated to receive a 12-month treatment of either atorvastatin monotherapy (n=74) or atorvastatin plus ezetimibe combined therapy (Ato/Eze, n=74). The results indicated that both treatments significantly ($p<0.05$) reduced serum LDL-C and carotid intima-media thickness (CIMT). Particularly, the LDL-C level (2.12±0.58 mmol/L vs 2.63±0.56 mmol/L, $p<0.01$) and CIMT (1.06±0.12 mm vs 1.13±0.11 mm, $p<0.01$) of patients received Ato/Eze was significantly lower than those who received atorvastatin monotherapy[16].

Essentially, an increased CIMT was reported to be related to myocardial infarction (MI) and stroke, and an independent risk factor for atherosclerosis[17]. The Cardiovascular Health Study (1999), which followed up 4,476 CHD patients, indicated that the risk for MI or stroke among patients in the highest quintile for CIMT was 3.15 times greater compared to those in the lowest quintile[18]. In this regard, further reduction in LDL-C and CIMT levels by Ato/Eze compared to atorvastatin monotherapy suggested that the combined therapy would be more effective in reducing the risks of CVD, MI, and stroke.

Early Use of Statin and Ezetimibe Combined Therapy for High-risk Patients

A recent trial involving 382 patients with acute ischemic cerebrovascular disease by Lv *et al*. (2024) demonstrated that, after 3 months of treatment, moderate-intensity statin with ezetimibe improved the achievement rate of LDL-C in the patients than high-intensity statin therapy (89.86% vs 70.77 %, $p=0.005$), with a higher reduction magnitude in LDL-C (-56.54% vs -47.995%, $p=0.001$)[19]. Based on the findings, moderate-intensity statin with ezetimibe can be considered as an initial treatment option for patients with acute ischemic cerebrovascular disease.

Coincidentally, Dr. Li opined that early use of statin and ezetimibe combined therapy is more likely in high-risk patients who have a low target LDL-C level. "In patients with known atherosclerosis, stroke, or acute coronary syndrome (ACS), their target LDL-C level is recommended at 1.4 mmol/L. As this treatment target is unlikely to be achieved with statin monotherapy, particularly those who have high baseline LDL-C, we would prescribe statin and ezetimibe combined therapy in the first instance," he highlighted. Besides, he added that in patients who reported side effects, such as mild pain or fatigue, with low-dose statin monotherapy, increasing the statin dosage is not advisable. Instead, statin and ezetimibe combined therapy should be considered.

Clinical Performance of Statin-based Combined Therapy in the Context of Neurology

Dr. Li illustrated the efficacy of statin-based combined therapy in local clinical settings using 2 case studies. In the first case, a patient in his 50s suffered an ischemic stroke, leading to weakness in the right side of his body. His initial LDL-C was about 4.3 mmol/L. By virtue of the high risk and high LDL-C level, the recommended LDL-C level for the patient was 1.4 mmol/L. However, the treatment target was unlikely to be achieved with statin monotherapy. Therefore, Dr. Li initiated Ato/Eze therapy directly. After 3 months of treatment, the LDL-C was reduced to 2.3 mmol/L. Then, Dr. Li added another statin to the regimen, which further reduced the LDL-C to 1.5 mmol/L after 5 months.

In the second case, a female patient in her 60s with a known stroke had a baseline LDL-C of 3.8 mmol/L. Statin monotherapy was prescribed initially and the LDL-C level was reduced to 2.2 mmol/L. Since the target LDL-C level was not achieved, the statin dose was increased. However, the patient complained of muscle pain and fatigue, which caused her to be unable to walk over long distances. Accordingly, instead of increasing the statin dose, Dr. Li prescribed Ato/Eze therapy. The treatment achieved the LDL-C target within 3 months.

Dr. Li noted that both patients remained on the combined therapy, and no safety issues were reported. He said that the dosage of the therapy would be maintained to ensure a low LDL-C, as a secondary prevention.

Final Remarks in Controlling LDL-C

In summary, Dr. Li reminded that it is crucial to monitor the LDL-C levels of patients, particularly those with a high risk. In cases where a dramatic reduction in LDL-C is required, he recommended the early use of combined therapy since it is more tolerable and has a more favourable side effect profile than the high-dose statin treatment. Last but not the least, he emphasised the need for closely monitoring patients' symptoms and the CK level throughout treatment.

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by Dr. Roy Lau

The Management of Treatment-resistant Bipolar Disorder and Generalised Anxiety Disorder— A Systematic Review

Prof. Malcolm Hopwood
Head, Professorial Psychiatry Unit, Department of Psychiatry, University of Melbourne Australia

The disease burden of mental disorders has become increasingly relevant as this causes a high degree of individual and social suffering, whereas mood and anxiety disorders are commonly involved. Previous pooled analysis suggested that the **lifetime prevalence of mood disorder reached 9.6%, and that of anxiety disorder was 12.9%**[1]. Practically, cognitive behavioural therapy (CBT) and pharmacological intervention are key treatments prescribed to manage mood and anxiety disorders. At the Annual Scientific Meeting of the Society for Advancement of Bipolar Affective Disorder (SABAD), which was held on 12/6/2025, Prof. Malcolm Hopwood discussed the pathophysiology of bipolar disorders and generalised anxiety disorder (GAD) and their clinical management.

A Closer Look at the Symptoms of Bipolar Disorders

A previous population-based survey (2003) indicated the 1-year prevalence of bipolar disorder in Australia to be about 1.0%, with a similar prevalence between males and females. The peak prevalence was observed in the age group between 18 and 24 years, accounting for 0.9%, and declined with increasing age, with the prevalence of 0.1% among adults aged >55 years[2].

Prof. Hopwood highlighted that the symptomatic structure of **bipolar disorder is primarily depressive rather than manic**. Notably, Judd *et al*. (2002) reported that patients with **bipolar disorder I (BP-I) experienced 3 times more depressive symptoms (31.9% of total follow-up weeks) than manic symptoms (9.3% of weeks)**[3]. In **bipolar disorder II (BP-II), depressive symptoms (50.3% of weeks) dominated the course over hypomanic (1.3% of weeks) and cycling/mixed (2.3% of weeks) symptoms** (**Figure 1**)[4]. Accordingly, a focus on the treatment for bipolar depression is needed.

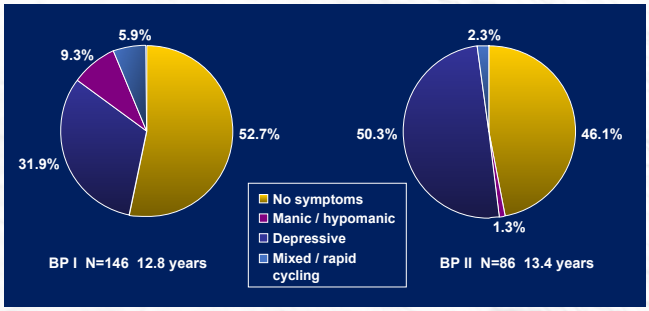

Figure 1. Symptomatic structure of bipolar disorder I and II[3,4]

Prof. Hopwood remarked that a **mixed state diagnosis** can be documented if a patient shows full criteria for one pole plus 3 of the symptoms of the opposing pole, according to the **DSM-5 criteria**. "Generally, the mixed state portrays a worse prognosis and lots of difficulties in treatment," he commented.

The Influence of Comorbid Anxious Distress with Mood Disorders

Given that the poles of bipolar disorder are overlapped, Prof. Hopwood noted that the boundary between unipolar depressive disorders, bipolar, and related disorders is sometimes based only on the symptoms exhibited by the patients. In DSM-5, a series of specifiers, such as severity, clinical features, onset status, etc., was applied to define mood disorders. For instance, a mood episode may be 'specified' as moderate, recurrent, late-onset, with mixed features and in partial remission[5]. Among the clinical features specifiers of

mood disorders, anxious distress is the most important feature after mixed features.

While **anxiety is a comorbidity of major depressive disorder (MDD), the specifier applies to bipolar disorder as well**. Essentially, patients with MDD who meet the criteria for the anxious specifier have significantly worse psychosocial functioning across a number of areas (**Figure 2**)[6]. **Prof. Hopwood added that persistent anxious distress is strongly predictive of treatment resistance and a higher risk of subsequent relapse**.

In bipolar disorders, a previous review of meta-analyses suggested that **at least half of those with bipolar disorder are likely to develop an anxiety disorder** in their lifetimes, and a third of them will manifest an anxiety disorder at any point in time, whereas comorbid anxiety disorders negatively impacted the presentation and course of bipolar disorder[7]. Hence, the findings suggested **a high risk of comorbid anxiety among patients with bipolar disorders, which may lead to suboptimal outcomes**.

Psychotherapies for Bipolar Disorder

Prof. Hopwood noted that the psychological interventions can also be applied to anxiety disorder. Lifestyle interventions, such as physical exercises and regular sleep cycles, are beneficial for patients with bipolar disorder.

Prof. Hopwood highlighted that the 2 best psychotherapies in terms of research base are CBT and **interpersonal and social rhythm therapy (IPSRT)**. CBT focuses on cognitive restructuring and includes self-monitoring, strategies to deal with dysfunctional thoughts, and behavioural techniques to promote social functioning. Clinical trials showed that CBT increased functioning and adherence and decreased relapses, mood fluctuations, need for medications, and hospitalisations in bipolar patients compared with standard treatments[8].

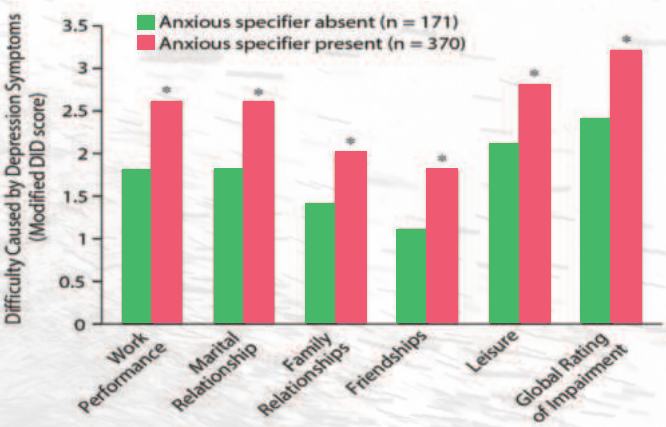

*Figure 2. Impact of the anxious distress specifier on psychosocial functioning in patients with MDD[6] , *p<0.001*

In contrast, IPSRT focuses on one of four problem areas, i.e. grief, interpersonal role transition, role dispute and interpersonal deficits, but extends into meticulous regulation of social and sleep rhythms[8]. Frank *et al*. (2005) reported that IPSRT led to a longer time to new affective episode, more regular social rhythms, and a reduced recurrence in patients with BP-I[9].

Pharmacological Management of Bipolar Disorders

In the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines 2018, recommended pharmacological treatments include acute mania, prevention of any mood episode, prevention of mania, prevention of depression, and acute depression[10]. Prof. Hopwood commented that the classification may not be helpful since a patient with bipolar disorder would need a choice covering all of the indications.

Prof. Hopwood presented the recommendations for bipolar depression of the Royal Australian and New Zealand College of Psychiatrists (**RANZCP**). Briefly, 6 options of monotherapy and 4 combination treatments are included (**Figure 3**)[5]. Prof. Hopwood emphasised that, provided **bipolar disorder is a lifelong condition**, the balance between efficacy and tolerability has to be considered in selecting treatment. He opined that although Olanzapine is effective in controlling bipolar depression, its side effects, such as weight gain, are a concern. According to the **RANZCP** guidelines, **Quetiapine is the most favoured second-generation antipsychotic (SGA) for bipolar depression in clinical practice, whereas lamotrigine is the preferred mood stabilising agent (MSA)**[5].

The Clinical Benefits of Quetiapine in Bipolar Disorder

Prof. Hopwood commented that the introduction of atypical antipsychotics into both bipolar depression management and maintenance has been one of the changes over the recent 2 decades. In particular,

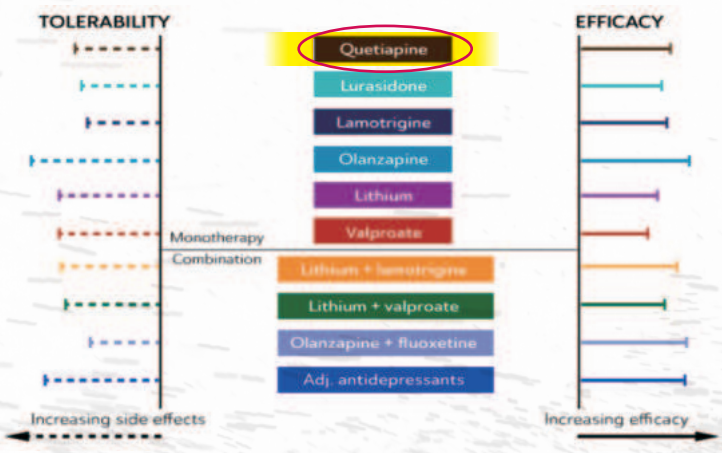

Figure 3. Effectiveness of medications used to treat bipolar depression in RANZCP [5]

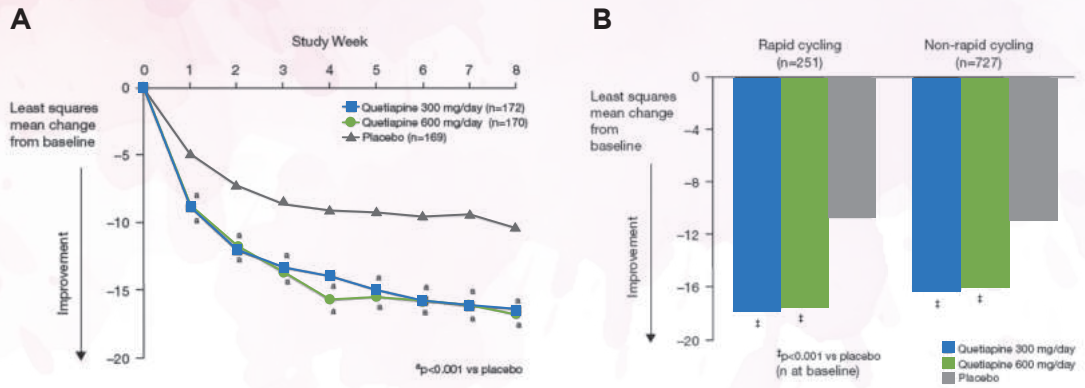

*Figure 4. Improvement in MADRS total score yielded in **A)** BOLDER I and **B)** BOLDER II trials*[11,13]

Quetiapine is the therapy with the largest amount of evidence support in bipolar depression.

The landmark trials demonstrating the efficacy of Quetiapine in managing bipolar depression are the **BOLDER I & II trials**. In the **BOLDER I trial**, patients meeting DSM-4 criteria for bipolar I (n=360) or bipolar II (n=182) depression were randomly assigned to 8 weeks of Quetiapine (600 or 300 mg/day) or placebo. **The results demonstrated that Quetiapine at either dose achieved significant improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) total scores compared with placebo from week 1 onward (Figure 4A)**[11]**. While bipolar with a rapid cycling course is a clinical challenge, an 8-week Quetiapine treatment, both 600 and 300 mg/day, was shown to significantly improve MADRS score in bipolar patients, regardless of rapid cycling courses, in the BOLDER II trial (Figure 4B)**[12,13].

Furthermore, the long-term efficacy of Quetiapine was demonstrated in the 52-week continuation phase study of the EMBOLDEN trial. Responders in the **EMBOLDEN I & II trials** (n=584) were randomised to the same Quetiapine dose or placebo for 26-52 weeks or until mood event recurrence. **The results indicated that the risk of recurrence of a mood event was significantly lower with Quetiapine than with placebo (hazard ratio [HR]: 0.51, p<0.001, Figure 5). Also, Quetiapine was associated with a lower risk for recurrence of depressive events** (HR: 0.43, p<0.001). Discontinuation rates due to adverse events were 4.3%, 4.0% and 1.7% for Quetiapine 300 mg/day, 600 mg/day and placebo, respectively[14].

Prof. Hopwood presented the findings of a meta-analysis conducted by his team (2018) **comparing the responder rates of Lurasidone, Quetiapine, and Cariprazine monotherapy with those of Olanzapine/Fluoxetine combination (OFC) therapy**. The MADRS responder rates for Lurasidone, Quetiapine, Cariprazinem and OFC were 52.0%, 59.7%, 46.3%, and 56.1%, respectively. Prof. Hopwood noted that the responder rates of the placebo group in the studies of Quetiapine (41.1%) were higher than those in other studies, which ranged from 30.2% to 35.9% (**Figure 6**). Thus, **Quetiapine yielded the best response among the therapies**.

The Key Burdens of GAD

Prof. Hopwood highlighted that **one of the most significant unmet needs in bipolar disorders is anxiety**. The combined lifetime prevalence of DSM-5 GAD among the general population was 3.7%, the 12-month prevalence was 1.8%, and the 30-day prevalence was 0.8%[15]. GAD also causes significant functional disabilities. For instance, an analysis of patient survey data in Europe by Toghanian *et al*. (2014), involving >3,500 patients with GAD, reported that when compared with matched controls, **patients with GAD were significantly more likely to visit healthcare providers, receive a higher number of total medications, and reduce work productivity**. Moreover, the direct and indirect healthcare costs associated with GAD were substantial[16].

Managing GAD with Quetiapine

Prof. Hopwood noted that there is very little clinical data about antipsychotics in GAD, but it does not imply the use of antipsychotics in the disease is uncommon. In the case of Quetiapine, a meta-analysis of 4 randomised controlled trials (RCTs) in 2010, involving 1,369 patients treated with Quetiapine, revealed that **Quetiapine monotherapy yielded a significantly higher response**

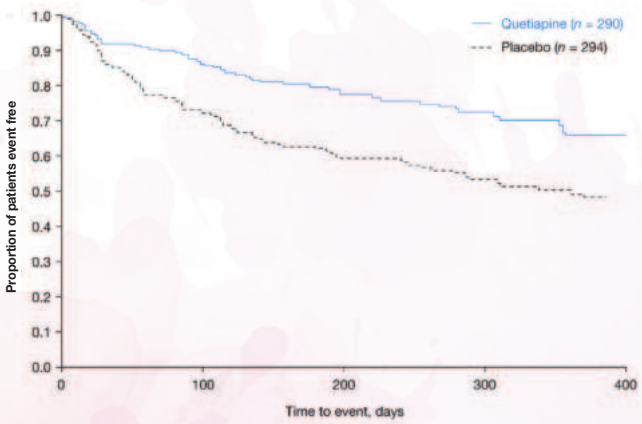

Figure 5. Time to recurrence of any mood event in the continuation phase[14]

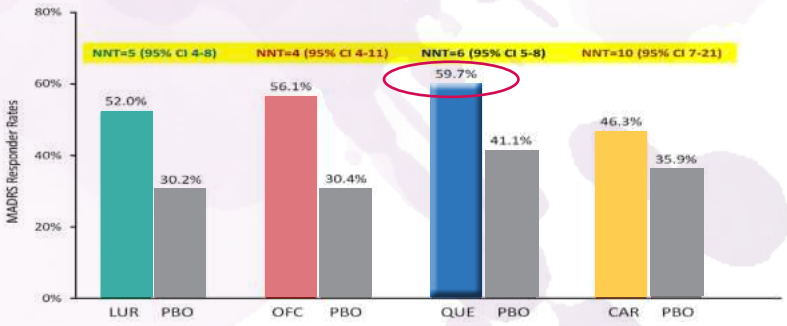

Figure 6. The MADRS responder rates of different therapies , LUR: Lurasidone, QUE: Quetiapine, CAR: Cariprazinem, PBO: placebo, NNT: number needed to treat, CI: confidence interval

than placebo (odds ratio [OR]: 2.21, p=0.03). Essentially, there was a significant difference in remission, as defined as a HAM-A total score of 7 or less, favouring Quetiapine monotherapy (OR: 1.83, p=0.03, **Figure 7**). Moreover, the study reported that the **risk of recurrence of anxiety symptoms was significantly higher in the placebo group as compared to Quetiapine group (OR: 0.18)**[17].

More recently, the World Federation of Societies of Biological Psychiatry (**WFSBP**) reported a guideline in **2023**, which included a review of all therapies with evidence in treating GAD. **Quetiapine was found effective as a monotherapy for GAD and post-traumatic stress disorder (PTSD)**. Particularly, the panel admitted that GAD is generally a chronic disorder and requires long-term treatment. Of importance, it was advocated that treatment should continue for at least several months after remission to prevent relapse. In this regard, **Quetiapine was one of the recommended therapies which was demonstrated to be more**

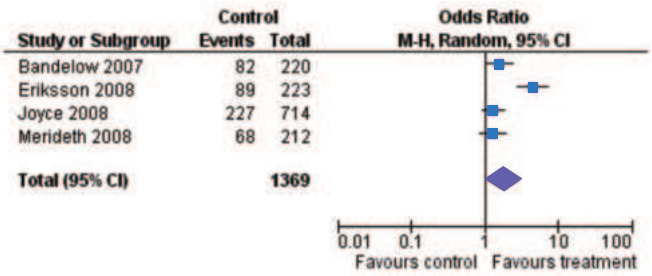

Figure 7. Forest plot of comparison between Quetiapine monotherapy and placebo in achieving remission in GAD[17]

effective than placebo in preventing relapse[18].

Although there are limited RCTs to evaluate treatment efficacy **in older patients, the WFSBP guideline found that Quetiapine was effective in older patients with GAD**. Given that Quetiapine monotherapy was confirmed to be efficacious in treating GAD, the **WFSBP concluded that Quetiapine should be included in the recommended treatments for GAD, whereas low doses (50-300mg/day)** would be suitable[18].

Final Remarks

Undoubtedly, bipolar disorder is a prevalent psychiatric disorder with a significant disease burden to patients, their families, and society, whereas the disease with comorbid anxiety is a more challenging clinical condition. Fortunately, based on the existing clinical data, various therapies have been demonstrated to be effective in managing the disease. Remarkably, **Quetiapine has been indicated as a preferable therapy in bipolar depression**, which balances efficacy and tolerability. **While the occurrence of GAD is an unmet need** in bipolar disorder, Prof. Hopwood suggested that **Quetiapine may be useful in that condition, either as monotherapy or in combination** with other agents by virtue of the established evidence.

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BP I=bipolar disorder I; BP II=bipolar disorder II; CANMAT=Canadian Network for Mood and Anxiety Treatments; CBT=cognitive behavioural therapy; DSM-5=Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; GAD=generalised anxiety disorder; HR=hazard ratio; IPSRT=interpersonal and social rhythm therapy; MDD=major depressive disorder; MSA=mood stabilising agent; OFC=olanzapine fluoxetine combination; OR=odds ratio; PTSD=post-traumatic stress disorder; RANZCP= Royal Australian and New Zealand College of Psychiatrists; RCT=randomised controlled trial; SABAD=Society for Advancement of Bipolar Affective Disorder; SGA=second-generation antipsychotics; WFSBP= World Federation of Societies of Biological Psychiatry

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INSURE Pooled Analysis Revealed: IRd is effective and safe for RRMM patients in routine clinical practice

by Michelle Lee

Multiple myeloma (MM) is one of the most common haematological malignancies with a global incidence ranging from 0.5 to 5 per 100,0001. MM contributes to 20% of mortality among haematological malignancies worldwide2. Relapsed/refractory multiple myeloma (RRMM) occurs in almost every patient with MM and has been a clinical challenge3. Ixazomib in combination with lenalidomide and dexamethasone (IRd) has been approved for the treatment of RRMM based on the results of the TOURMALINE-MM1 phase 3 study4,5. However, up to 72% of RRMM patients in routine practice would not meet eligibility criteria for randomised trials, underscoring the need for broader evidence6. The INSURE pooled analysis evaluated IRd in RRMM patients in global settings, showing that the effectiveness of IRd in routine clinical practice6.

INSURE Pooled Analysis Method[6,7]

Objective: To investigate the real-world effectiveness of IRd in RRMM in global settings.

INSIGHT MM - Global, prospective, non-interventional, observational study

- Enrolled 4307 MM patients from 15 countries over a period of 5 years

UVEA-IXA - European, retrospective/prospective, longitudinal cohort study

- Enrolled 309 RRMM patients receiving ixazomib-based treatment via an early access program in eight countries

REMIX - French, retrospective/prospective study

- Enrolled 197 RRMM patients receiving IRd via a compassionate use program in France

INSURE Study Population*:

(n=564)

564 adult RRMM patients who had received IRd as a ≥2nd line of therapy (LoT)

- INSIGHT MM (n=191); UVEA-IXA (n=195); REMIX (n=188)

Primary Outcomes:

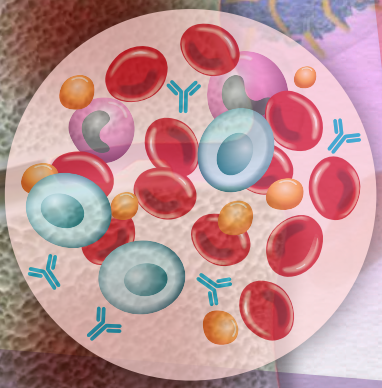
- **Time-to-next treatment (TTNT)**
- **Progression-free survival (PFS)**

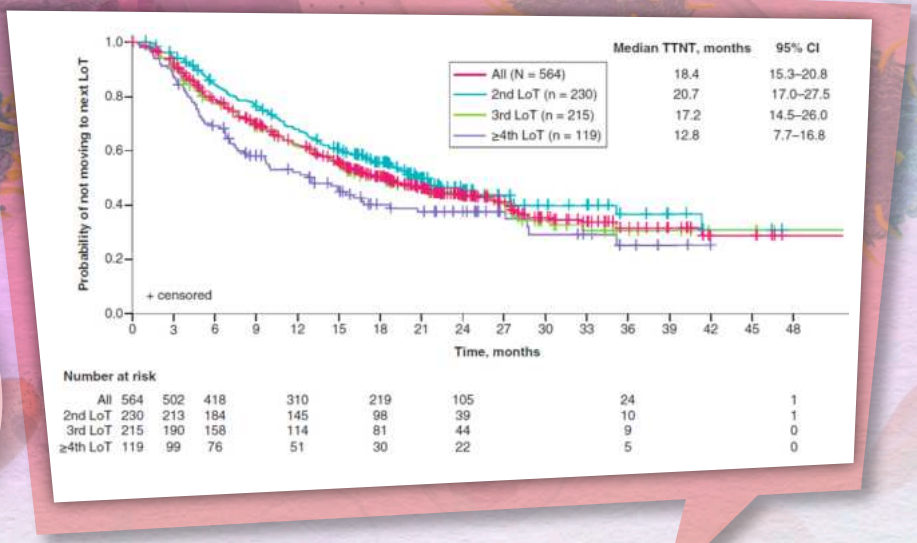
Key Secondary Outcomes:

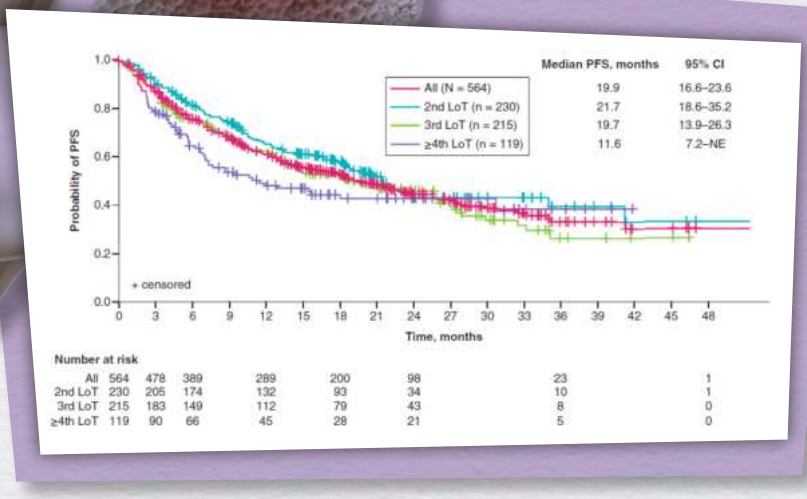
- Overall response rate (ORR)
- Rate of complete response (CR)
- Rate of very good partial response (VGPR)
- Duration of treatment (DOT)
- Overall survival (OS)
- Safety

*Adult patients (aged ≥18 years) with a diagnosis of MM were included if they had evidence of RRMM (defined as initiation of at least a 2nd LoT for MM after the diagnosis date) and had initiated a 2nd, 3rd, or later LoT with IRd in routine clinical practice. Only patients treated with the IRd triplet regimen were included; any patients who had received other ixazomib-based regimens were excluded. Assignment of LoT was physician-assessed. Patients were excluded from the analysis if IRd had been received during any prior LoT (including as maintenance or consolidation); IRd treatment had started >90 days prior to signing the informed consent form (INSIGHT MM only); they had been enrolled in a clinical trial at the time of receiving IRd; they had received a stem cell transplant in the same LoT as IRd; or if there was >2 months (≥60 days) difference in the start dates for ixazomib or lenalidomide.

Analysis results[6,7]







Median TTNT

18.4 Months

Median PFS

19.9 Months

Best ORR to IRd among all patients: 64.6%

ORR was 70.5, 63.1 and 52.8% among patients receiving IRd as 2nd, 3rd, and ≥4th LoT, with a median time to best response of 3.9, 5.2 and 3.5 months, respectively

Conclusion[6,7]

- **IRd's real-world effectiveness (median PFS 19.9 months, ORR 65%) aligned with the TOURMALINE-MM1 trial (median PFS 20.6 months, ORR 78%), with no new safety concerns.**
- **The treatment showed greater benefit when used in earlier lines of therapy, supporting previous findings.**
- **The study's robust methodology provided insights on frail patients and supports future real-world research.**

Abbreviations: CI, confidence interval; R, complete response; DOT, duration of treatment; IRd, Ixazomib in combination with lenalidomide and dexamethasone; LoT, line of therapy; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival, RRMM, relapsed/refractory multiple myeloma; TTNT, time-to-next treatment; VGPR, very good partial response;

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by Dr. Feng Xue

Achieving a Rebalance of the Teeter-Totter: Recent Advances in Hemophilia Treatment

The treatment of hemophilia has evolved dramatically over the past century, transitioning from rudimentary blood transfusions to sophisticated biologics and gene therapies. Blood transfusions are blood clotting products that replace the missing or deficient clotting proteins. Biologics, such as the factor mimetic emicizumab, work by replacing the function of factor VIII, offering less frequent, subcutaneous treatment options for hemophilia A; while gene therapy uses viral vectors to deliver the correct gene into liver cells, enabling them to make clotting factor IX or VIII.[1] Here is a brief overview of this evolution, culminating in the recent approval of marstacimab, a rebalancing agent, as a novel non-factor therapy.

Clotting Factor Products

In 1828, German physician Dr. Johann Lukas Schönlein and his student Friedrich Hopff coined the term "haemorrhaphilia" to describe the bleeding disorder, which was later shortened to "haemophilia" (British English) or "hemophilia" (American English). This term, derived from Greek words for "blood" and "love of" (haîma and philía), refers to the inherited genetic condition where the body's blood does not clot properly, leading to excessive bleeding.[2]

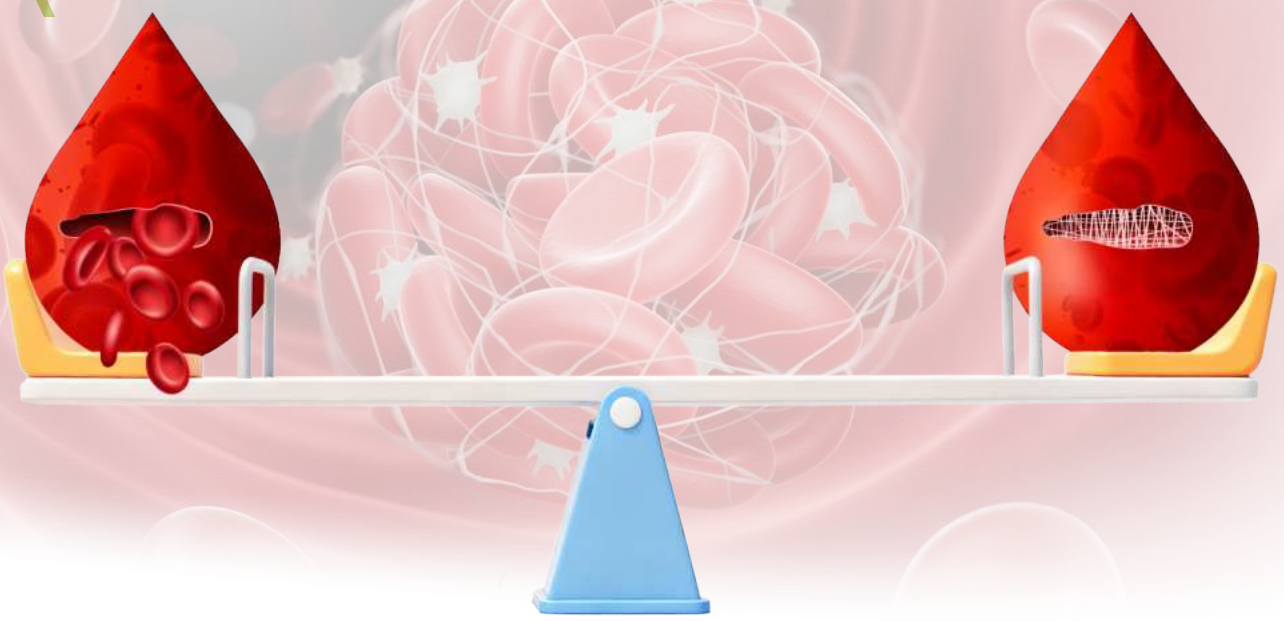
By the late 1950s and early 1960s, fresh frozen plasma was transfused in patients in the hospital. However, each bag of the plasma contained so little of the necessary clotting factor that huge volumes of it had to be administered. Many children experienced severe joint bleeds that were crippling. Intracranial hemorrhage could be fatal. By 1960, the life expectancy for a person with severe hemophilia was less than 20 years old.[2]

Not until the 1970s did freeze-dried powdered concentrates containing factor VIII and IX become available. Factor concentrates revolutionized hemophilia care because they could be stored at home, allowing patients to “self-infuse” factor products, alleviating trips to the hospital for treatment.[2] However, plasma-derived coagulation factor concentrates, prepared using traditional manufacturing processes, were found to transmit viral diseases, especially AIDS, hepatitis B and hepatitis C to patients.[3] Hemophilia patients in China were among the first in the country to be infected with HIV, contracting the virus in the mid-1980s from contaminated US-imported factor VIII concentrates. This led to a significant HIV epidemic within the hemophilia community in China; and the overwhelming impact was felt into the next few decades.[4]

Treatment for hemophilia advanced in the 1990s. Factor products became safer as tighter screening methods were implemented and advanced methods of viral inactivation were used.[2] Additionally, in 1992, the US Food and Drug Administration (FDA) approved the recombinant factor VIII concentrate, which is genetically engineered using DNA technology. Recombinant factor concentrates do not contain any plasma or albumin, and therefore, cannot spread any bloodborne viruses.[1] However, some patients develop inhibitors, or antibodies, to infused factor products. Inhibitors make it more difficult to stop a bleeding episode because they prevent the treatment from working. According to a 2021 meta-analysis, recombinant factor VIII is associated with a higher risk of overall and high-responding inhibitor development compared to plasma-derived FVIII in previously untreated patients with hemophilia A.[5] This calls for the development of a bypassing agent which may offer these patients an alternative option to help stop bleeds and joint damage.

Emicizumab: A Factor Mimetic

In 2017, approval of emicizumab, a bispecific monoclonal antibody mimicking factor VIII, revolutionized prophylaxis for hemophilia A. This agent is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A with factor VIII inhibitors.[6]



In hemophilia, the unmet needs regarding adherence to prophylaxis and lack of effective long-term prophylaxis regimens, especially in patients with inhibitors, led to the production of emicizumab, the first non-factor medicine.[7] Emicizumab restores the function of missing activated factor VIII (FVIIIa) by bridging activated factor IX and factor X, mimicking FVIIIa independently of factor VIII levels. Consequently, emicizumab promotes effective hemostasis in patients with hemophilia A.[8]

The promise of emicizumab as a convenient-to-administer, subcutaneous, non-factor FVIIIa mimetic with durable effectiveness was demonstrated in HAVEN 1 and 2 clinical trials.[9,10] The most concerning of the adverse events reported with emicizumab during clinical trials has been the occurrence of thromboembolic events and thrombotic microangiopathy. Critically, these complications were associated with concomitant replacement therapy with activated prothrombin complex concentrate (aPCC) at cumulative doses over 100 U/kg/day for more than 1 day.[7] Furthermore, emicizumab was also associated with the development of antidrug antibodies in 5.1% of patients (34/668) who participated in the HAVEN 1-4 clinical trials, which were presumed to be responsible for decreasing the plasma concentration of emicizumab and its subsequent loss of efficacy.[11]

Gene Therapy

As of 2022, 62 trials on gene therapy for hemophilia were underway.[12] On 29 June 2023, the FDA approved roctavian, the first gene therapy for adults with severe hemophilia A.[13] Gene therapy for hemophilia is based on the transfer of a non-pathogenic and non-replicating recombinant adeno-associated virus (AAV), the viral DNA of which has been replaced by a bioengineered gene cassette, with a tissue-specific promoter and other regulatory elements. Following intravenous infusion and subsequent cell transduction, endocytosis and import into the nucleus occurs, where the genetic material is released as episomal DNA. The therapeutic gene can then be expressed, thereby resulting in the production of the therapeutic protein, such as factor VIII or IX.[12]

Data from non-randomized phase 1 to phase 3 trials reveal an adequate expression of factors VIII and IX in patients with mostly severe hemophilia A or B. Even though they were no longer receiving prophylactic treatment, most patients experienced a considerable reduction, by 53% to 96%, in the number of bleedings compared to previous therapy. Persistently elevated factor levels have been described for up to six years in hemophilia A and up to eight years in hemophilia B.[14,15,16]

Disadvantages of AAV include pre-existing neutralizing antibodies to AAV, possible liver reactions, and a presumably non-permanent response; furthermore, due to the generation of neutralizing antibodies, the treatment can only be performed once. In contrast to other viral vectors, such as lentiviruses, AVV are largely not integrated in an individual's genetic information, explaining why hemophilia can still be passed on despite gene therapy.[12]

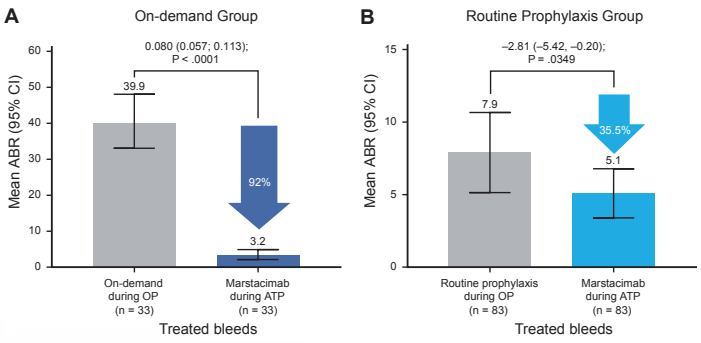
Marstacimab: A Novel Rebalancing Agent

On 11 October 2024, marstacimab was approved by FDA for patients ≥12 years with hemophilia A or B without inhibitors.[17] Although replacement treatment appears to be effective for hemophilia, the frequent venous infusions required for prophylaxis are burdensome to patients. Even with treatment, some patients still experience long-term joint damage from bleeds.[18]

The first non-factor prophylactic agent approved for hemophilia was emicizumab. It mimics the activity of factor VIII, so it is only indicated for hemophilia A and not hemophilia B. In contrast, the monoclonal antibody marstacimab inhibits the activity of tissue factor pathway inhibitor (TFPI), a naturally occurring

anticoagulation protein. As kind of a global hemostatic product, marstacimab increases the capacity to clot, independent of the level of any factor, rebalancing the hemophilia teeter-totter.[18]

In BASIS, a phase III, open-label, crossover trial, marstacimab was studied as a prophylactic treatment for severe hemophilia A and moderately severe to severe hemophilia B. In one cohort of the study, 116 patients without inhibitor antibodies were treated with weekly subcutaneous marstacimab in the active treatment phase of the study.[19] In the patients who had previously received on-demand clotting factors, the mean annualized bleeding rate (ABR) decreased from 39.9% to 3.2% with marstacimab treatment, corresponding to a reduction of 92%. In the group that had previously been receiving routine prophylaxis with replacement factors, the ABR decreased from 7.9% to 5.1%, corresponding to a decrease of 35.5% (**Figure 1**).[19] The BASIS trial also included patients with inhibitors to coagulation factors. These data have not been fully reported, but in June positive findings in this setting were also announced.[18]



ATP=active treatment phase; OP=observational phase

Figure 1. *Marstacimab prophylaxis reduced bleeding events compared with prior factor replacement therapy*[19]

Administered subcutaneously at a weekly fixed dose regardless of weight or age, marstacimab supports consistent thrombin generation and bleeding prevention in hemophilia A and B patients.[20] Although clearly an important innovation, especially for hemophilia B, more long-term data regarding efficacy and safety are needed to see how the therapy will fit with other treatment options.

Conclusion

The journey of hemophilia treatment reflects a remarkable trajectory from rudimentary transfusions to cutting-edge biologics and gene therapies. Early reliance on plasma products, though life-saving, carried significant risks. The advent of recombinant factor therapies in the 1990s marked a turning point in safety and efficacy, followed by innovations like factor mimetic therapies such as emicizumab. The recent approval of marstacimab represents a new frontier in hemophilia care. As a subcutaneous, non-factor therapy targeting TFPI, it offers a convenient and effective option for both hemophilia A and B patients without inhibitors. Its fixed dosing and weekly administration simplify treatment, potentially improving adherence and quality of life. Looking ahead, marstacimab complements a growing arsenal of therapies that aim not just to manage bleeding but to transform hemophilia into a condition with minimal daily burden. With gene therapy on the horizon and global access improving, the future of hemophilia care is more hopeful than ever.

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by Dr. Roy Lau

Screening and Detection of Cardiovascular-Kidney-Metabolic Syndrome Begins in the Community

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Cardiovascular-kidney-metabolic (CKM) syndrome is a health disorder attributable to the connections among cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic diseases, such as diabetes mellitus (DM) and obesity. Given that each of the 3 disorders can lead to or worsen one another, the management of CKM syndrome is clinically challenging[1]. Accordingly, screening for CKM risk factors and timely intervention are crucial for preventing CKM syndrome and hence optimising patient outcomes. As CKM syndrome involves multiple organ systems, interdisciplinary cooperation among various specialties is essential. In particular, the primary care provided by general practitioners (GPs) plays a pivotal role in managing CKM syndrome. In the recent lecture series jointly organised by the Hong Kong Society of Nephrology (HKSN), the Hong Kong Kidney Foundation (HKKF), and the Hong Kong Association of Renal Nurses (HKARN), a panel of 6 local nephrologists was invited to discuss the pathophysiology of CKM and share their opinions to tackle this disorder.

The Interplay among CVD, CKD, and Metabolic Diseases

CKM syndrome is a novel construct emphasising the pathophysiological interplay of CVD, CKD, and metabolic derangements, including those at risk for CVD and those with existing CVD. In addition to highlighting the risk of comorbid conditions, addressing the CKM concept enables the implementation of a holistic framework that incorporates screening, staging, and management for the early identification of potential CKM-related events[2]. The overarching principle of CKM care is to adopt a multidisciplinary approach which seeks to prevent fragmented care.

Although the public awareness of CKM syndrome is low, CKM-related events are very common. The serial cross-sectional cohort study (2023) of 11,607 adults in the United States (US) suggested that >1 in 4 participants aged ≥65 years had ≥1 cardiac, renal, and metabolic condition, whereas cardiac, renal, and metabolic multimorbidity was observed in 8% of participants (**Figure 1**). Remarkably, a significant increase in prevalence was observed from 5.3% in 1999-2000 to 8.0% in 2017-2020[3].

A nationwide cohort study involving 877,537 participants by Kim *et al*. (2025) indicated that 15.3% of the participants experienced CKM stage progression. Compared to individuals who maintained the same stage of CKM, those with progression of CKM stages had a higher risk of composite outcome of all-cause death, heart failure (HF), stroke, and myocardial infarction (MI)[4]. Provided the increased risk of mortality and comorbidities, CKM conditions are expected to escalate healthcare costs.

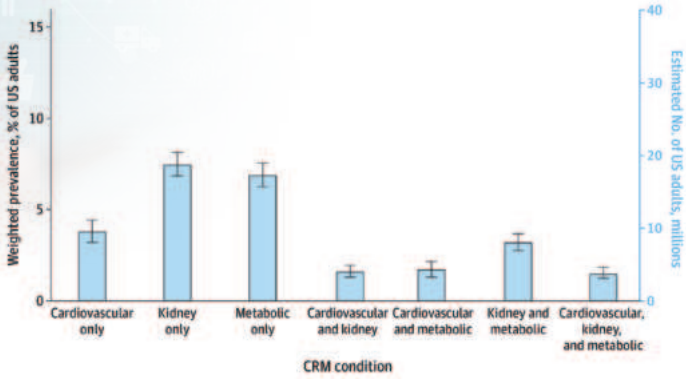

Figure 1: *Prevalence and overlap of CKM conditions in US adults*[3]

The Staging of CKM Syndrome

It has been generally recognised that CKM syndrome is a progressive condition. Accordingly, the American Heart Association (AHA) addressed the CKM staging to highlight the stepwise increase in absolute CVD risk. Essentially, the staging model underscores the importance of early detection of CKM-related changes and guides intensified therapies for each CKM stage. At stage 0, no CKM risk factor is observed. Stage 1 indicates excess or dysfunctional adiposity but no evidence of subclinical or clinical CKD or CVD. Stage 2 refers to the occurrence of established metabolic risk factors or CKD, whereas stage 3 suggests a subclinical CVD in CKM syndrome and a very high risk of CKD. At stage 4, clinical CVD occurs without (stage 4a) or with (stage 4b) kidney failure (**Figure 2**)[5]. The panel emphasised that implementing effective preventive measures, particularly at stages 0 to 2, helps reduce, or even avoid, disease progression to later CKM stages.

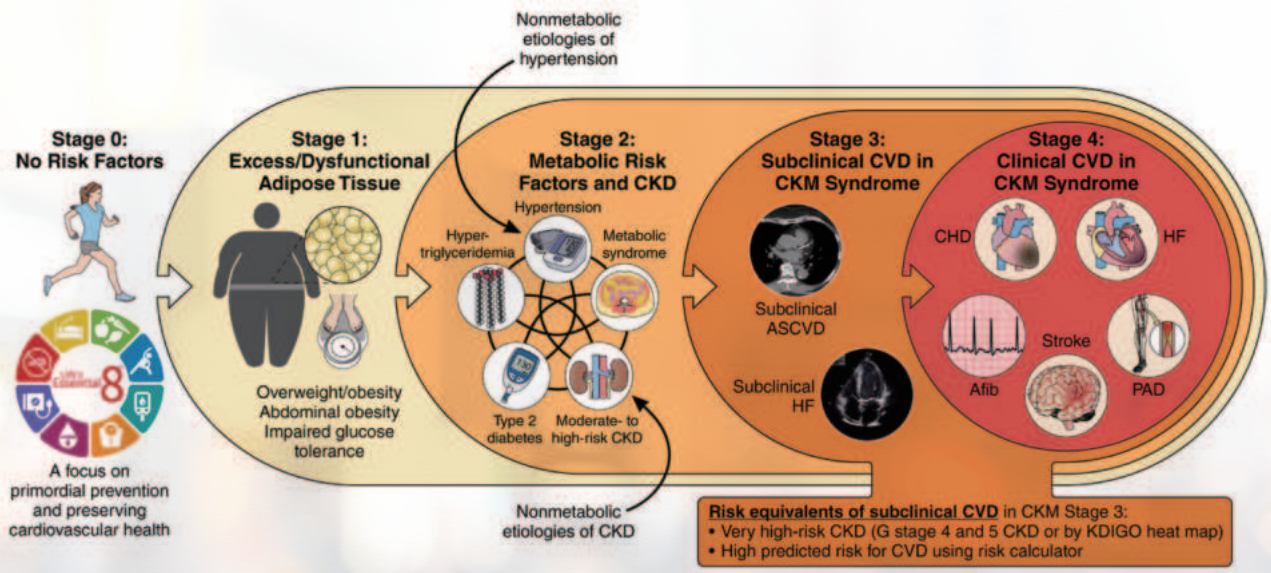

Figure 2: *Stages of CKM syndrome*[5]

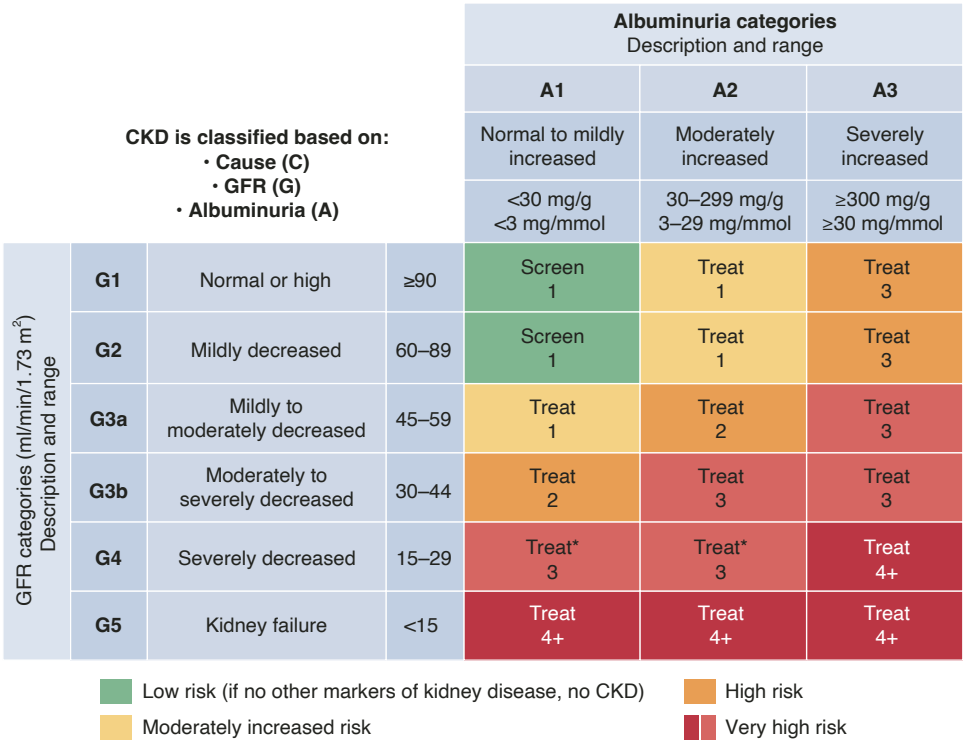

Figure 3: Albuminuria and GFR grid reflect the risk of CKD progression[7]

Risk Assessment for CKM Syndrome

The CKM health framework prioritises identifying and treating CKM risk factors during the preclinical phase to prevent CV complications and kidney failure. In this regard, absolute risk assessment based on an individual's risk factors and clinical signs is crucial for reflecting one's risk of disease events. For instance, the PREVENT equations proposed by the AHA (2023), which consider factors along the 3 axes of CKM syndrome, such as estimated glomerular filtration rate (eGFR), as predictors, enable the estimation of 10- and 30-year risk for total CVD[6].

In the context of CKD, the Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Guidelines recommended that the risk of CKD should be estimated based on both eGFR and albuminuria (**Figure 3**). For instance, an eGFR 45-59ml/min/1.73 m^2 indicates mildly to moderately decreased kidney function and corresponds to stage 3a CKD, whereas a moderately increased albuminuria is indicated by the level of 30-299 mg/g. The co-existence of moderately decreased kidney function and moderately increased albuminuria suggests a high risk of disease progression, and monitoring twice a year is recommended[7]. Notably, the panel reminded that the diagnosis of CKD is documented based on 2 separate measurements, at least 3 months apart.

CKM Screening – The Roles of Primary Care

The essence of CKM screening is to identify individuals at risk for suboptimal CKM health, facilitating timely intervention and preventing complications. Given that most individuals are asymptomatic at early CKM stages, primary care doctors play a central role in identifying these cases and ensuring regular follow-up. For patients exhibiting CKD risk factors, including hypertension, DM, and CVD, the measurements of eGFR and albuminuria are recommended for early diagnosis of CKD.

To facilitate the early identification of CKM cases, the panel advocates for a universal approach to CKM screening for all asymptomatic adults, which includes the annual measurement of BMI (body mass index), waist circumference, blood pressure, lipid levels, glycaemic status, urinalysis, and eGFR. Besides, the stage-dependent approach, which specifies screening intervals, is recommended as well (**Table 1**).

Table 1. Screening interval as per the stage-dependent approach

CKM Stage	Clinical Presentations	Screening Interval
Stage 0	Healthy	Every 3-5 years
Stage 1	Overweight/obese or prediabetes	Every 2-3 years
Stage 2	DM, hypertension, or hypertriglyceridemia	Annually

The Management of CKM Syndrome

The management of CKM syndrome is initiated at stage 0, even though no CKM risk factors are observed. The interventions at CKM stages 0 and 1 focus on lifestyle modification and weight management, with the goal of preventing metabolic risk factors and CKD[5]. At stage CKM stage 2, the CKM risk factors are established. In addition to more intensive lifestyle intervention targeting multifactorial risk control, pharmacotherapies for comprehensive control of residually uncontrolled metabolic syndrome components are recommended[5].

Remarkably, the first consensus recommendation on the management of CKD in Hong Kong has been published recently. In addition to CKD, the consensus has taken the components of CKM syndrome into account. Particularly, the consensus recommended that persons with hypertension, DM, or CVD should be screened for CKD. Besides, the consensus recommended to monitor the eGFR and albuminuria of patients with early CKD stages at least twice annually and more often in those with a higher risk of progression[8].

The Local Consensus Recommendations on Pharmacotherapies

According to the local consensus on CKD management, first-line treatment with the maximum tolerated dose of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEi/ARB) should be initiated for patients with DM and hypertension or albuminuria for renal protection and blood pressure control. Besides, ACEi/ARB is also recommended in non-diabetic CKD patients with hypertension and a urine albumin-creatinine ratio of ≥200 mg/g for blood pressure control and renal protection[8].

In patients with type 2 DM and CKD (eGFR≥20ml/min/1.73m^2), a sodium-glucose cotransporter-2 inhibitor (SGLT2i) can be initiated as first-line therapy for glycaemic control, renal and cardiovascular protection. Moreover, SGLT2i can also be used in non-diabetic CKD patients with an eGFR of ≥20 mL/min/1.73 m2 and a urine albumin-creatinine ratio of ≥200 mg/g for renal and cardiovascular protection[8].

The 4 Pillars of Pharmacotherapies in CKM

Renin-angiotensin system (RAS) blockade, SGLT2i, non-steroidal mineralocorticoid receptor antagonists (ns-MRA), and glucagon-like receptor 1 receptor agonists (GLP-1RAs) are the 4 pillars of pharmacotherapies in CKM management. In addition to pharmacotherapies, the panel emphasised that lifestyle modifications, lipid control, as well as blood pressure and glycaemic control also play vital roles in controlling CKM syndrome.

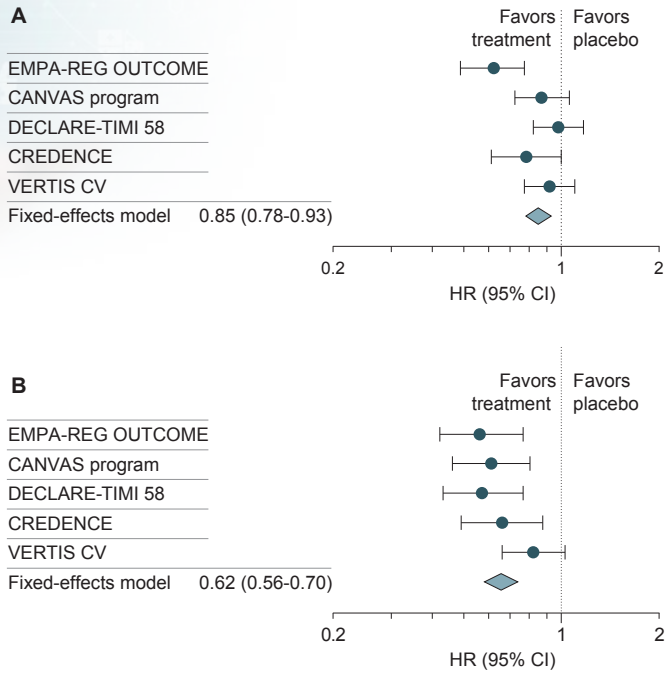

Figure 4: *Effects of SGLT2i on A) overall cardiovascular death, and B) overall kidney outcomes*[12]

RAS Blockade

Apart from controlling blood pressure, the inhibition of RAS by ACEi/ARB has been proven to be effective in reducing intraglomerular pressure by preferentially dilating the efferent arteriole[9]. For instance, the network meta-analysis by Palmer *et al*. (2015) suggested that ACEi/ARB were the most effective strategies to reduce the risk of end-stage kidney disease (ESKD) among patients with type 2 DM and CKD compared to other blood pressure-lowering agents[10].

Regarding the issue of hyperkalaemia upon ACEi/ARB treatment, the panel opined that there should not be a simple cut-off for discontinuing treatment at 5.0 mmol/L. Instead, monitoring serum creatinine and potassium within 2-4 weeks after starting or changing the dose of ACEi/ARB is recommended to confirm the occurrence of hyperkalaemia. In cases where hyperkalaemia occurs, optimising the patient's diet to reduce potassium intake and considering medications, such as diuretics and sodium bicarbonate, are advisable. Reducing the dose or stopping ACEi/ARB may be considered if mitigation strategies are ineffective[7].

In the case of advanced CKD, Bhandari *et al*. (2022) reported that discontinuation of RAS inhibitors was not associated with a significant difference in the long-term rate of decrease in the eGFR[11]. Nevertheless, there were numerically greater number of CV events in patients who discontinued SGLT2i. Therefore, the panel recommended continuation of RAS inhibitors

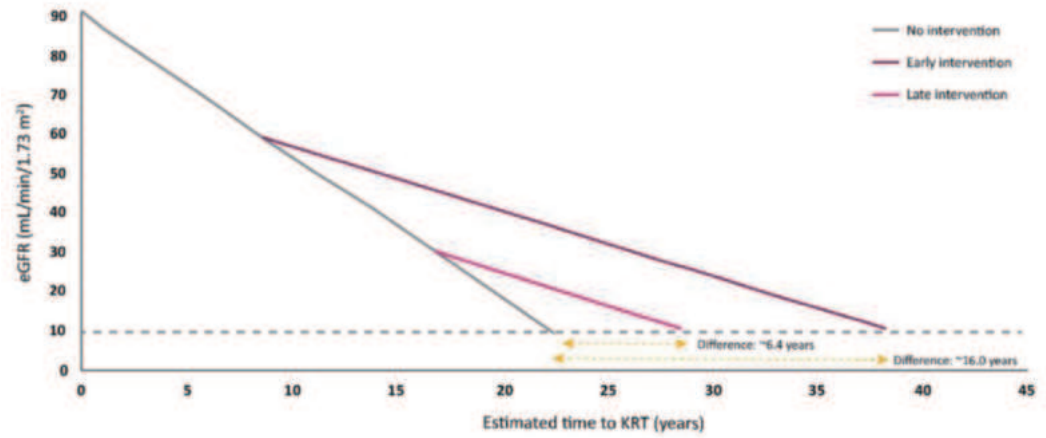

Figure 5: *Estimated delay of KRT by early prescription of SGLT2i*

for patients even in advanced CKD (eGFR <30ml/min/1.73m^2) to reduce the risks of CV complications.

SGLT2i

As per the KDIGO 2024 Guidelines, an individualised HbA1c target ranging from <6.5% to <8.0% is recommended in patients with DM and CKD not treated with dialysis[7]. Of note, SGLT2i facilitates glycaemic control by increasing urinary glucose excretion. Furthermore, SGLT2i also reduces intraglomerular pressure and appears to attenuate the inflammatory and fibrotic responses of human proximal tubular epithelial cells to high glucose[9].

The cardiorenal protective effects of SGLT2i have been well established. For instance, a meta-analysis by McGuire *et al*. (2021) indicated that SGLT2i was associated with a reduced risk of major adverse cardiovascular events, hospitalisation for heart failure, or cardiovascular death (**Figure 4A**), and kidney outcomes (**Figure 4B**)[12].

Given the clinical benefits of SGLT2i in patients with eGFR≥20ml/min/1.73m^2 are widely accepted, the panel advised that SGLT2i should be continued when eGFR drops below 20ml/min/1.73m^2. Interestingly, an estimate of up to 16 years delay to kidney replacement therapy (KRT) could be achieved for commencing SGLT2i treatment when eGFR=60ml/min/1.73m^2, whereas a delay of only 6.4 years would be yielded for commencing SGLT2i when eGFR=30ml/min/1.73m^2 (**Figure 5**). Essentially, the delay to KRT implies the saving of time and expenses associated with haemodialysis, while preserving the patient's quality of life.

ns-MRA

Mineralocorticoid receptor (MR) activation is closely related to the development of inflammation and fibrosis in the heart, kidneys, and vasculature. Thus, inhibiting MR with ns-MRA offers a promising approach to control the progression of CKD and improve cardiovascular morbidity and mortality[13]. According to the FIDELITY study, finerenone, an ns-MRA, was associated with reduced risks of composite cardiovascular outcomes (hazard ratio [HR]: 0.86, p=0.0018) and kidney disease progression (HR: 0.77, p=0.0002, **Figure 6**), when compared to placebo among patients with diabetic kidney disease (DKD) across a range of GFR[14].

Of note, hyperkalaemia is a clinical concern associated with finerenone. Nonetheless, the pooled results of the FIDELITY study revealed that <2.0% of patients who received finerenone discontinued the treatment due to hyperkalaemia, and there was no fatal case reported[14]. Hence, the panel recommended the use of the maximum tolerated dose of finerenone if the serum potassium is ≤4.8mmol/L, while suspending finerenone is needed if the serum potassium level rises above 5.5mmol/L. Notably, the panel suggested that finerenone can be resumed if serum potassium level is reduced to ≤5.0mmol/L.

GLP1-RA

GLP-1RAs stimulate insulin release in response to glucose load through incretin release. By delaying gastric emptying and effects on the satiety centre in the brain, GLP-1RAs provoke weight loss[15]. Additionally, GLP-1RAs have been reported to provide cardiovascular and renal benefits. A meta-analysis by Sattar *et al*. (2021) revealed that GLP-1RAs reduced all-cause mortality (HR: 0.88, p=0.0001), hospital admission for heart failure (HHF, HR: 0.89, p=0.013), and composite kidney outcome (HR: 0.79, p<0.0001) than placebo, with no increase in risk of severe hypoglycaemia, retinopathy, or pancreatic adverse effects, among DM patients[16]. By virtue of the promising clinical benefits demonstrated

in previous clinical trials, SGLT2is were included in the treatment recommendations of the US Food and Drug Administration (US FDA).

The Signs for Referring to Nephrologists

The panel recommended considering referral to nephrologists if persistent proteinuria (>1g/day) is observed despite optimisation of medications. Additionally, the involvement of nephrologists is advisable in the occurrence of nephrotic and nephritic symptoms, such as proteinuria and microscopic haematuria, as well as any unexplained impaired renal function.

Effective CKM Management – The Nephrologists' Perspectives

Clinical guidelines generally advocate lifestyle interventions as a core component in managing CKM syndrome at all stages. For first-line therapy, metformin and SGLT2i were recommended by the panel. Moreover, GLP-1RAs are prescribed if an individualised glycaemic target needs to be achieved. In cases where hypertension occurs, ACEi/ARB should be used. If the albumin-creatinine ratio (ACR) is ≥30mg/g and serum potassium is normal, ns-MRA should be considered for cardiovascular protection. Besides, statins would be needed to control hypercholesterolaemia.

To conclude, the panel emphasised that early recognition and treatment are key to better outcomes in managing CKM syndrome. Provided the asymptomatic nature of early CKM stages, screening for CKD and other CKM risk factors is of paramount importance. Collaborative community efforts by colleagues in primary care in screening and education are essential for identifying individuals at high risk for CKM syndrome and enhancing public awareness of the disease.

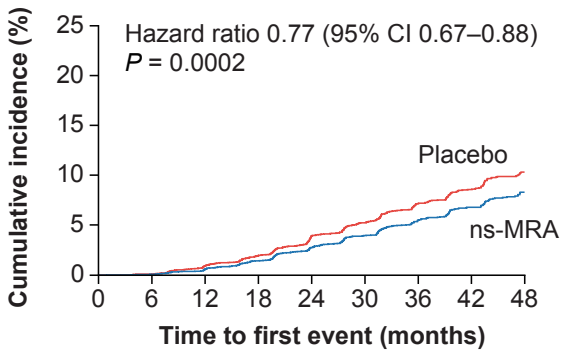

Figure 6: *Composite kidney outcomes on patients treated with ns-MRA or placebo*[14]

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by Jasmine Lai

Have Sweet Things Been On Your Mind?

The Potential Neurocognitive Consequences of Sweeteners

Sweeteners arrived to the market as the silver-bullet alternative to the rising health risks of sugar. Companies proactively innovated and reformulated their products to offer a diet-friendly option for the health-conscious, and low and no-calorie sweeteners (LNCSs) became a cornerstone in healthy diets, weight and diabetes management, and oral care.[1,2] Yet as the spotlight continues to sharpen on the adverse health effects of ultra-processed foods, the long-term health impacts of LNCSs are also being questioned.[3]

A New Longitudinal Study Links Sweeteners to Cognitive Decline

The adverse effects of LNCSs have been controversial. Some studies note associations with type 2 diabetes, cancer, cardiovascular disease and depression.[3] LNCSs have also been linked with a higher risk of dementia, decreased memory performance and executive function. These studies did not explore what intake levels had harmful cognitive effects, which prompted Gonçalves *et al*. (2025) to investigate further.[3]

Using data from The Brazilian Longitudinal Study of Adult Health (ELSA-Brazil), the group conducted an observational study spanning eight years, making it the largest and longest prospective study to date on LNCS consumption and cognitive decline. The study looked at 12,772 dementia-free civil servants aged between 35-74, excluding those with incomplete data, and those who had unusually high caloric intake, Parkinson's disease, passed away or were lost to follow-up. At baseline, participants completed a validated Food Frequency Questionnaire to calculate LNCS consumption. They were also assessed using six cognitive tests in three waves across the study period.[3] The results presented were analysed using linear mixed-effects models adjusting for age, sex, race/ethnicity, education, income, physical activity, body mass index, hypertension, diabetes, cardiovascular disease, depressive symptoms, alcohol consumption, smoking, total calories, and MIND diet.[3]

Consumption Patterns and Cognitive Effects of Combined and Individual LNCSs

From the questionnaire, participants were grouped into tertiles that corresponded to normal (0.02–37.2 mg; mean 19.9 mg, SD 9.7 mg), intermediate (37.3–102.3 mg; mean 65.6 mg, SD 16.7 mg), and high (102.4–856.5 mg; mean 192.0 mg, SD 91.2 mg) combined LNCS consumption. They identified seven LNCSs (aspartame, saccharin, acesulfame K, erythritol, xylitol, sorbitol, and tagatose); sorbitol was the most consumed LNCS in all three groups. Those with the highest consumption were more likely to be older, women, White, more educated, with higher incomes and more physically active, but also exhibited a higher frequency of hypertension and uncontrolled diabetes.[3]

Participants with moderate and high consumption had the greatest global cognition and verbal fluency declines (both $p<0.001$ compared to the first tertile) (**Figure 1**). Assuming that the cognitive decline trajectory of participants in the first tertile represented normal cognitive aging, this corresponded to 1.3 and 1.6 years of

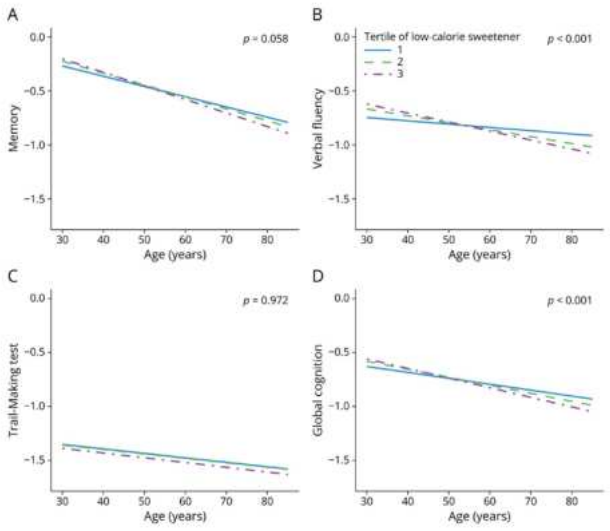

Figure 1: Association of combined LCNS consumption tertiles with cognitive function trajectories from baseline to median 8 years of follow-up in the whole sample.[3]

cognitive ageing, respectively. A different categorisation based on intake frequency found that only daily LNCS intake was associated with accelerated decline in memory (p<0.05), verbal fluency (p<0.001) and global cognition (p = 0.001). However, more conservative calculations did not show the same relationships between LNCS consumption tertiles and cognitive decline.[3] Tagotose, the only natural option studied, was the only sweetener not linked with cognitive decline. The rest varied in association with memory, verbal fluency, and global cognitive decline, but not the Trail-Making test. (**Figure 2**).[3]

LNCS Consumption May Confer Riskier Cognitive Consequences at Middle Age

When the results were stratified, age was revealed to be a modifier of the relationship (p<0.001), as faster verbal fluency and global cognition declines with high LNCS consumption was only found in participants under 60 years old. High sorbitol consumption was associated with poorer memory, whereas high tagatose consumption seemed to show slower rates of memory and global cognition decline. Again, this relationship was only in participants below aged below 60, further supporting natural sweeteners as the preferred choice.[3]

Magnified Cognitive Effects with Diabetes

A diabetes diagnosis also modified the relationship (p = 0.016), but the picture was less straightforward. Both diabetics and non-diabetics in the two highest tertiles were associated with global cognition decline, but only diabetics had declines in memory, whereas non-diabetics had declining verbal fluency. The effects of a high consumption of individual sweeteners varied in diabetics and non-diabetics (**Figure 3**), but all seven sweeteners negatively affected cognition in participants with diabetics. Nevertheless, the magnitude of the association of combined LNCS intake with cognitive decline was larger in participants with diabetes than in participants without diabetes, potentially given their already inflammatory state. Stratification by obesity and diet were also tested, but these factors did not modify the relationship.[3]

The Potential Mechanisms Behind Sweeteners and Cognitive Vulnerability

Various animal and clinical studies revealed that sweeteners release neurotoxic metabolites and may induce microbiota changes and glycemic responses, affecting blood-brain barrier integrity and synaptic functions.[3] Sweeteners may also affect dopamine and addiction responses, satisfaction and food choices. However, such responses vary greatly from person to person, and a clearer understanding awaits as research on the gut-brain axis matures.[4-6]

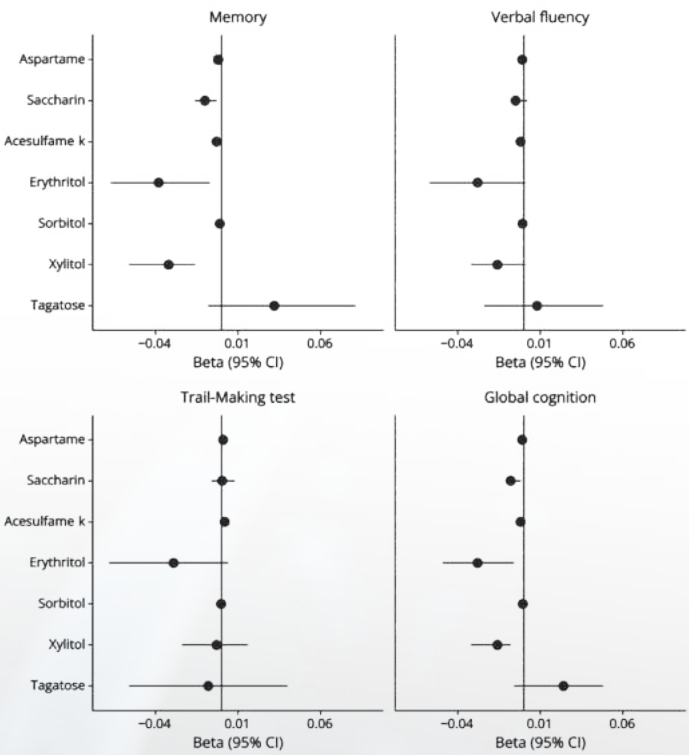

Figure 2: Association of individual LCNS consumption with cognitive function trajectories from baseline to median 8 years of follow-up in the whole sample.[3]

Current Guidelines Over Sweetener Consumption are Also Unclear

LNCSs have been approved by regulatory agencies globally for consumption within Acceptable Daily Intake levels and are at times suggested as a strategy for weight and diabetes management, such as by Diabetes UK.[1,7] Moreover, previous concerns associating LNCS with possible carcinogenicity and metabolic effects have not sparked regulatory reform.[8] But the stance of the Hong Kong Centre for Food Safety takes a more conservative approach in line with recommendations from the WHO, which advocates to reduce overall sweetness in diets and consider other ways of weight control other than sweeteners.[9]

Sweeteners may affect cognitive decline, but the results of the reported study are challenged by the correlations and confounding inherent to observational studies, especially in nutrition, the potential inaccuracies of self-reported questionnaires, and the natural possibility of social desirability bias. Moreover, dietary habits may have changed since participants were first given the Food Frequency Questionnaire at the beginning of the eight-year period, and sweetener consumption was only measured from tabletop sweeteners and soft drinks, which excludes many other sources of food where LNCSs are found. Sucralose was also not included given its later entry to the market, but may have been part of the participants' diet over the eight years.[3]

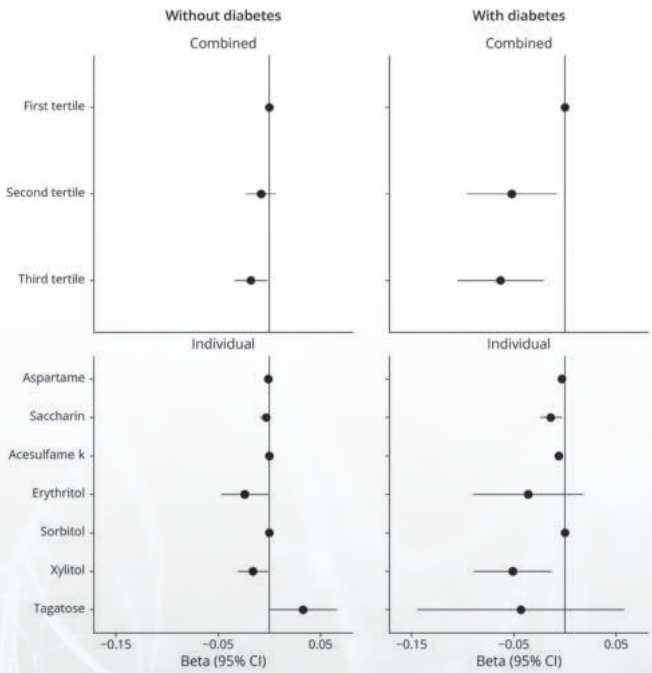

Figure 3: Association of combined and individual LCNS consumption at the study baseline with global cognition decline over a median of 8 years of follow-up in participants without (n = 11,363) and with (n = 1,409) diabetes.[3]

Regardless, Gonçalves et al. encourage deeper investigation on the relationship between LNCSs and cognitive decline, ignite a healthy dose of skepticism and further caution over sweetener consumption. It also places further scrutiny on the factors causing the pressing and growing prevalence of dementia, currently around 7% globally; LNCS consumption has risen along with the consumption of ultra-processed foods, which have also been linked with an increased risk of dementia.[3, 10]

Conclusion: Erring On The Side Of Caution?

Dietary choices have critical impacts on long-term health. The study reinforces the importance of preventive interventions against cognitive decline in middle-aged adults, given that memory, attention, and processing speed peak during early adulthood and decline gradually starting in the 30s; dementia biomarkers also become evident 20–30 years before onset of clinical disease.[3] However, other longitudinal studies have also shown conflicting effects, marking this an ongoing area of research.[3] Future studies may use neuroimaging to assess structural brain changes and confirm plausible mechanisms behind this relationship.[11]

In the study, generally all investigated LNCSs other than tagatose were associated with faster cognitive decline, and the authors suggest choosing natural sweeteners like honey, especially in patients with diabetes.[3] The almost decade long follow-up does inform the future of public health efforts to maintain healthy societies, but ultimately, health is not a siloed concept, and messaging to the public must be done with care.

Abbreviations:

MIND, Mediterranean- (Dietary Approach to Systolic Hypertension) Intervention for Neurodegenerative Delay.

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LDL-C Management with Inclisiran in Patients with Recent Acute Coronary Syndrome (ACS): A Clinical Trial Snapshot of the VICTORION-Inception Trial

by Migee Tang

Many patients fail to reach guideline-recommended low-density lipoprotein cholesterol (LDL-C) goals of <55 mg/dL or <70 mg/dL (<1.4mmol/L or <1.8mmol/L) in the first year after acute coronary syndrome (ACS), increasing their risk of recurrent ischemic events[1-4]. The 2025 AHA/ACC guidelines recommend adding inclisiran if LDL-C remains elevated after 4–6 weeks of maximally tolerated statin and non-statin lipid lowering agents[5]. While inclisiran has shown sustained LDL-C reduction in patients with atherosclerotic cardiovascular disease (ASCVD), its efficacy in recent ACS patients remains unestablished, highlighting the need for further investigation in this high-risk group[6].

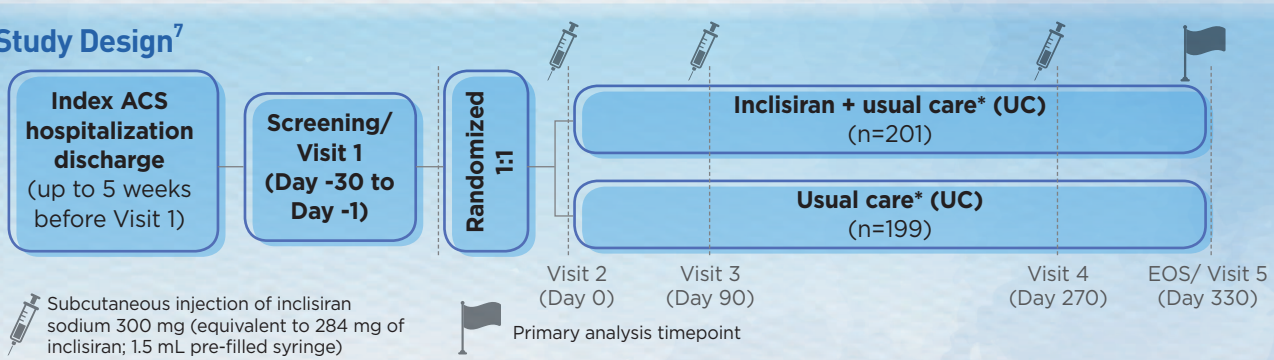
VICTORION-Inception[7]:

A phase 3b, randomized, controlled, open-label trial to mimic real-world practice of inclisiran and evaluate whether inclisiran in addition to usual care, compared with usual care alone, improves LDL-C goal attainment and LDL-C reduction in participants with recent ACS

Key Inclusion Criteria[7]

- **≥18** Years of age
- LDL-C ≥70 mg/dL (≥1.8mmol/L) or non-HDL-C ≥100 mg/dL (≥2.6 mmol/L)
- Discharged from hospitalization within 5 weeks of screening for ACS (STEMI/ NSTEMI/unstable angina)
- Discharged on statin therapy or with documented statin intolerance

Study Design[7]



Coprimary endpoints[7]

- % change in LDL-C from baseline to Day 330
- Achievement of LDL-C <70mg/dL (<1.8mmol/L) at Day 330

Secondary endpoints[7]

- Achievement of prespecified LDL-C goals at Day 330
- Changes in lipid-lowering therapy (LLT)
- Overall safety & tolerability of inclisiran

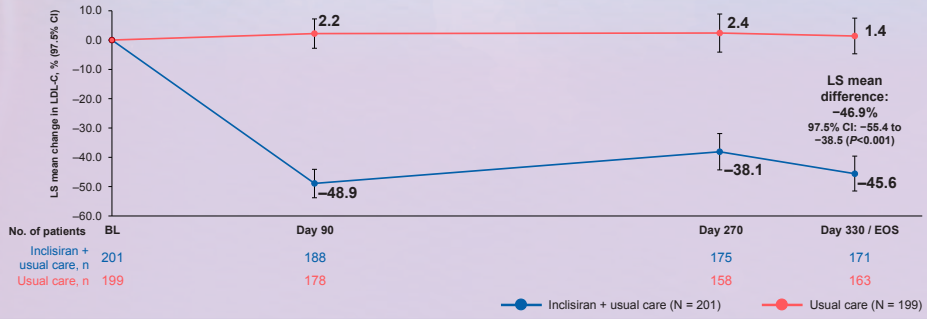
Exploratory endpoint[7]

- Occurrence of major adverse cardiovascular events (MACE)
  - cardiovascular death, nonfatal MI, resuscitated cardiac arrests, or nonfatal ischemic stroke

*Usual care in both arms included statin therapy and non statin LLT (ezetimibe, anti-PCSK9 mAbs, bempedoic acid, and inclisiran if acquired through commercial means) as considered appropriate by treating clinicians; participants receiving inclisiran could not receive anti-PCSK9 mAbs[7]

Significantly greater LDL-C reduction with inclisiran + UC vs. UC at Day 330[7]

Mean percentage change in LDL-C from baseline at Day 330:

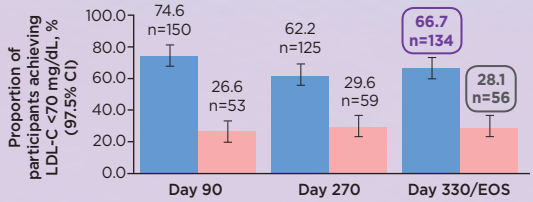


45.6% inclisiran + UC

vs.

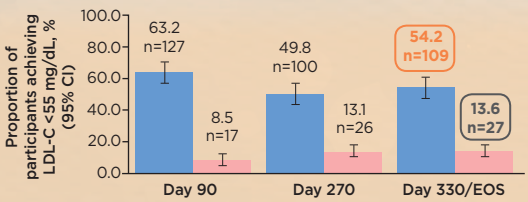
1.4% UC

Significantly more patients achieved <70 mg/dL (<1.8mmol/L) at Day 330[7]:



OR (97.5% CI)	Day 90	Day 270	Day 330/EOS
	10.84 (6.13-19.16)[a]	4.42 (2.68-7.30)[a]	5.42 (3.29-8.91)[a]

Significantly more patients achieved <55 mg/dL (<1.4mmol/L) at Day 330[7]:



OR (97.5% CI)	Day 90	Day 270	Day 330/EOS
	26.58 (14.14-49.98)[a]	7.44 (4.45-12.45)[a]	8.24 (4.97-13.65)[a]

Fewer patients experienced composite MACE by end of study[7]

Inclisiran + UC **3.5%** (n=7) *vs.* UC **7.5%** (n=15)

Comparable Safety Profile Between Inclisiran + UC & UC Arms[7]

AE Category[b]	Inclisiran + UC (n=203, n (%))	UC (n=197, n (%))
≥1 AE	119 (58.6)	105 (53.3)
≥1 Treatment-related AE[c]	21 (10.3)	0
≥1 AE leading to treatment withdrawal	1 (0.5)[d]	0
≥1 SAE	32 (15.8)	34 (17.3)
≥1 Treatment-related SAE[c]	0	0
Fatal AE	0	2 (1.0)
AE at the injection-site	17 (8.4)	0
Treatment-related AE at the injection site[c]	16 (7.9)	0

Early initiation† of inclisiran after ACS‡ provides a novel strategy to increase the number of patients at high risk of recurrent cardiovascular events achieving LDL-C goals

Units are converted from mg/dL to mmol/L by multiplying by 0.02586.

[a] Nominal P values were <0.001. [b] AEs were treatment emergent (ie, occurred during the treatment period, and were not present before treatment initiation, and did not increase in severity). [c] An AE was considered related if the relationship to study treatment was reported as related by the investigator. [d] Treatment withdrawal was due to urticaria[7].

†Median [Q1-Q3] time to treatment initiation: 34 (26-43) days after index hospitalization discharge. ‡ Discharge from hospital for ACS ≤5 weeks before screening[7]

ACC, American College of Cardiology; **ACS**, acute coronary syndromes; **AE**, adverse events; **AHA**, American Heart Association; **anti-PCSK9 mAbs**, anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibodies; **BL**, baseline; **CI**, confidence interval; **EOS**, end of study; **HDL-C**, high-density lipoprotein cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **LLT**, lipid-lowering therapy; **LS**, least squares; **MACE**, major adverse cardiovascular events; **MI**, myocardial infarction; **NSTEMI**, non-ST elevation myocardial infarction; **OR**, odds ratio; **SAE**, serious adverse events; **STEMI**, ST elevation myocardial infarction; **UC**, usual care

References: 1. Rao SV, et al. Circulation 2025;151(13):e771-e862. **2.** Grundy SM, et al. J Am Coll Cardiol 2019;73(24):3168-3209. **3.** Gu J, et al. Am J Prev Cardiol 2022;10:100336. **4.** Alanezi M, et al. Cardiology 2024;149(3):266-274. **5.** Banach M, et al. Drugs. 2024;84(12):1541-157. **6.** Ray KK, et al. N Engl J Med 2020;382(16):1507-1519. **7.** Knowlton KU et al. Presented at: National Lipid Association's 2025 Annual Scientific Sessions; May 29-June 1, 2025; Miami, FL. P99

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On-the-Pulse

Neurology

by Dr. Feng Xue

Sildenafil Reduces Risk of Alzheimer's Disease by Half[1]

The first meta-analysis on the association between use of sildenafil, a Phosphodiesterase-5 (PDE5) inhibitor, and risk of Alzheimer's disease (AD) was conducted by Singaporean researchers. MEDLINE and Embase were searched from inception to March 11, 2024 to identify cohort, case-control studies comparing the frequency of AD in patients taking sildenafil with those without. Risk ratios (RR) and hazard ratios (HR) were computed with accompanying 95% confidence intervals (CIs) for each study, and the results pooled using a random-effects meta-analysis.

Out of 415 studies that were screened initially, 5 studies comprising 885,380 patients were included for analysis. Sildenafil use was associated with a reduced risk of developing AD by 53% compared to non-use (HR: 0.47, 95% CI: 0.27-0.82, $p<0.001$). There was a similar association in risk reduction of AD in patients on PDE5 inhibitors compared to non-use (RR: 0.55, 95% CI: 0.38-0.80, $p=0.002$). Although the meta-analysis showed that the use of sildenafil is associated with a reduced risk of developing AD, further randomized control trials to ascertain the effect of sildenafil on AD pathology would be useful.

Environmental Health

by Michelle Lee

Sick Building Syndrome[2]

Sick building syndrome (SBS) refers to a condition where occupants of a building experience non-specific symptoms such as fatigue, drowsiness, headaches, and respiratory issues, which often improve when they leave the building. A study investigated SBS prevalence and its association with perceived indoor environmental quality (IEQ) in both aboveground and underground workspaces in Singapore. The findings revealed a decline in SBS prevalence from 17.9% to 8.5% over 12 months, with fatigue and drowsiness being the most common symptoms. This research highlighted that higher satisfaction with indoor air quality was linked to reduced SBS risk in aboveground workspaces, while better perceived temperature comfort was associated with lower SBS odds in underground environments. The study underscores the importance of addressing IEQ factors like air quality and thermal comfort to mitigate SBS symptoms, offering insights for healthier building policies. These results emphasise the role of occupant perceptions in shaping workplace health outcomes.

Nutrition

by Migee Tang

The Dairy-Dream Connection[3]

New research uncovers an intriguing connection between late-night dairy and disturbing dreams, especially in those with lactose intolerance. A survey of over 1,000 students revealed that individuals who consumed cheese or other dairy products before sleep were more likely to experience bizarre dreams, with gut discomfort being the likely trigger. Gastrointestinal symptoms such as bloating and cramping may interfere with sleep and affect the dream state. Participants who reported food intolerances, particularly to lactose, were more prone to nightmares, poor sleep, and vivid dream recall. While only a small percentage believed food had a direct effect, many suspected dairy and sweets behind their unsettling sleep experiences. The findings support a growing body of evidence suggesting that what you eat, especially close to bedtime, can shape not only the quality of your sleep but also the emotional tone of your dreams.

Dentistry

Fighting Cavities at School[4]

Dental caries remain one of the most common chronic childhood diseases, particularly among underserved communities with limited dental care access. In the recent CariedAway trial, over 7,000 children were randomized to receive either silver diamine fluoride (SDF) or atraumatic restorative treatment (ART) as part of a school-based program. Surface-level failure was slightly lower with SDF (38.3%) than ART (45.5%). Over four years, SDF successfully controlled 62% of carious surfaces while ART controlled 55%, showing comparable long-term results. These simple, topical interventions offer a promising alternative to invasive procedures in reducing oral health disparities among vulnerable populations where access to routine dental care is limited.

Pulmonology

Brensocatib: A Promising Advance in Bronchiectasis Care[5]

Chronic neutrophilic inflammation drives exacerbations and lung damage in bronchiectasis, but a new drug, brensocatib, may offer new hope for patients. Results from the Phase 3 ASPEN trial were recently published, in which over 1,700 patients were randomized to receive brensocatib or placebo once daily for 52 weeks. Both doses significantly reduced pulmonary exacerbations rates by about 20%, with nearly half of brensocatib users remaining exacerbation-free. The higher dose also slowed lung function decline and improved quality of life measures. Brensocatib is a selective dipeptidyl peptidase 1 (DPP1) inhibitor and suppresses harmful neutrophil activity at its source. With a favorable safety profile, it represents a potential first-in-class treatment that targets disease progression—not just symptoms—in bronchiectasis.

Cardiology

Unpacking Fat: The Role of Body Fat Distribution in Cardiovascular Aging[6]

Obesity is linked to accelerated cardiovascular aging, but the role of different fat distribution patterns remains unclear. Using machine learning and whole-body imaging in 21,241 participants, researchers predicted cardiovascular age and analyzed body fat distribution. They found that visceral adipose tissue, muscle fat infiltration, and liver fat were the strongest predictors of increased cardiovascular age in both sexes. Notably, while most fat deposition patterns accelerated cardiovascular aging in men, higher lower-body fat and total trunk fat were associated with slower cardiovascular aging in women. These findings highlight the importance of adipose tissue distribution as a key target for interventions aimed at promoting healthy lifespan.

On-the-Pulse

Hematology

Advancing ITP Care: Rilzabrutinib's Promising Results[7]

Immune thrombocytopenia (ITP) involves impaired platelet production with complex underlying immune dysregulation. Current therapies offer inconsistent efficacy and unresolved quality of life concerns. Rilzabrutinib, an oral BTK inhibitor recently approved by the FDA, has shown rapid, durable platelet increases in chronic ITP patients. Phase 2 (LUNA2) and phase 3 (LUNA3) trials demonstrated significant platelet response, fatigue reduction, and bleeding improvement, with a well-tolerated safety profile. Early use of rilzabrutinib also enhanced its efficacy. Longer-term studies, and investigations in pediatric patients and other immune-mediated diseases are underway, which position rilzabrutinib as a promising step forward in redefining ITP management and patient care.

Endocrinology

Why Semaglutide Users Are Quitting: The Cost of Weight Loss[8]

Despite semaglutide's proven efficacy, a recent Danish study has revealed a surprising reality: over half of adults stop using the drug within a year. While highly effective at curbing appetite and promoting weight loss, semaglutide's high cost, side effects like nausea, and potential health complications lead many to discontinue treatment. Younger adults, men, and those in low-income areas are especially prone to quitting, raising concerns as stopping the medication often results in weight regain. These findings underscore the critical challenges of maintaining long-term adherence to GLP-1 receptor agonists. Addressing these barriers, such as affordability and equitable access, will be essential to fully harness the potential of these breakthrough drugs in combatting the obesity epidemic.

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1. Chua WY, et al. Aging (Albany NY). 2025;17(3):726-39. **2.** Thach T-Q, et al. Building and Environment. 2019;166:106420. **3.** Nielsen T, et al. Front Psychol. 2025;16:1544475. **4.** Ruff RR, et al. JAMA Netw Open. 2025 Jun 2;8(6):e2513826. **5.** Chalmers JD, et al. N Engl J Med. 2025;392(16):1569-1581. **6.** Losev V, et al. Eur Heart J. Published online August 22, 2025. **7.** Kuter DJ, Ghanima W. Immunotherapy. 2025 Aug;17(11):767-782. **8.** Half Quit "Miracle" Weight-Loss Shots Ozempic and Wegovy Within One Year [Internet]. SciTechDaily. 2025 [cited 2025 Sep 22].

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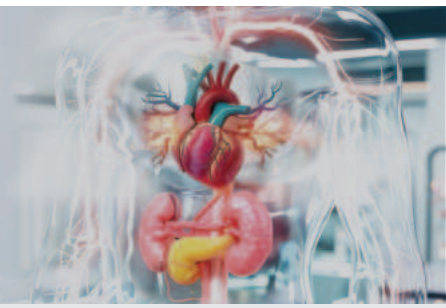
by Dr. Feng Xue

HKKF CKM Symposium Conducted with Success



On **26th September 2025**, the Hong Kong Kidney Foundation (HKKF), in collaboration with the Hong Kong Society of Nephrology, the Department of Family Medicine, New Territories East Cluster, Hospital Authority and the Shatin District Health Center Express, hosted a symposium titled **"Cardiovascular-Kidney-Metabolic Syndrome: Why and How It Matters for Every Primary Care Physician."**

The symposium aimed to raise awareness among primary care physicians about the interconnected nature of cardiovascular, kidney, and metabolic diseases—collectively referred to as **Cardiovascular-Kidney-Metabolic (CKM) Syndrome**. These chronic conditions often coexist and significantly impact patient outcomes, making early detection and integrated care essential.

Dr. CHOW Kai Ming

The keynote speaker, Dr. CHOW Kai Ming, a nephrologist and council member of both the HKKF and the Hong Kong Society of Nephrology, delivered a comprehensive presentation on the clinical significance of CKM Syndrome. He emphasized the importance of a multidisciplinary approach in managing patients with overlapping risk factors such as hypertension, diabetes, and chronic kidney disease.

A distinguished panel of experts joined the discussion, including:

Dr. LUI Siu Fai

Chairman of the HKKF

Dr. WONG Tsz Kau

Medical Consultant at Sha Tin District Health Centre Express

Dr. LEUNG Kwan Wa Maria

Service Director of Primary & Community Health Care, New Territories East Cluster (NTEC)

Dr. YAP Yat Hin Desmond,

Chairman of the Hong Kong Society of Nephrology

The event featured a structured agenda, beginning with on-site registration and lunch, followed by a welcome address and the main presentation. There were 73 onsite participants and over 130 online participants. **A Webinar Q&A session** allowed remote participants to engage with the speaker, while an **on-site Q&A** provided further opportunities for in-depth discussion.

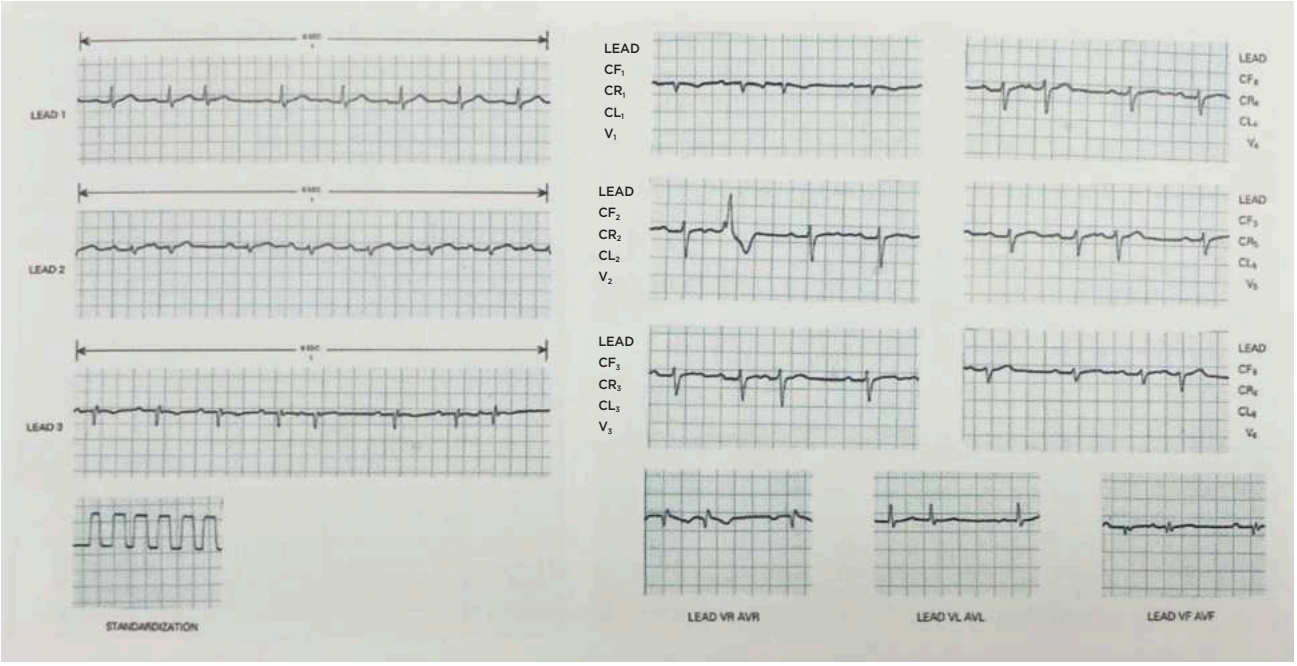
This event underscored the critical role of primary care physicians in the early identification and management of CKM Syndrome and highlighted the need for collaborative care models to improve long-term patient outcomes.


Cardiovascular-Kidney-Metabolic Syndrome:
Why and How It Matters for Every Primary Care Physician


45
IN 6 WEEKS

ECG CME OCTOBER 2025 (0.5 CME POINTS)

This ECG belongs to a 59-year-old man. He is a chronic smoker and has had diabetes mellitus for over 10 years. He came to see you complaining of reduced exercise tolerance recently. Examination of pulse revealed presence of ectopic beats.



Questions:

What is the ECG diagnosis?

A) Normal ECG

B) Left ventricular hypertrophy

C) First degree A-V block

D) Complete A-V block

E) Left bundle branch block

This ECG CME was prepared by Dr. Pun Chiu On, Specialist in Cardiology.

Please complete the Self-Study by visiting our website: https://cmevideo.hkdu.org/ or scan the QR code to submit your answers on or before ***28-November-2025***

SCAN ME

by Dr. Feng Xue

2025 China Doctors' Day Hong Kong Celebration Successfully Held with Over a Thousand Medical Professionals in Attendance

The 2025 China Doctors' Day Hong Kong Celebration was successfully held on the evening of 11 August, attracting more than a thousand participants from across the medical sector. The event was co-organized by the Department of Health, Hospital Authority (HA), Hong Kong Academy of Medicine, Li Ka Shing Faculty of Medicine of the University of Hong Kong (HKU), Faculty of Medicine of the Chinese University of Hong Kong, the Hong Kong Chinese Medical Association, and the Hong Kong Registered Chinese Medicine Practitioners Association. The HA Chairman Mr. Henry Fan presented the "2025 HA Outstanding Interns Award" to ten exceptional young doctors in recognition of their exemplary performance and dedication.

The Secretary for Health Professor Lo Chung-mau delivered a speech expressing gratitude to the central government for establishing China Doctors' Day. He emphasized the importance of role models in the medical profession, noting that senior doctors have inspired younger generations to pursue careers in medicine.

The event featured a keynote speech by Dr. Kang Min, Director of the Infectious Disease Prevention and Control Institute at the Guangdong Provincial Center for Disease Control and Prevention. Dr. Kang, recipient of the 2023 "Most Beautiful Doctor" award, shared insights and experiences from his career, offering valuable inspiration to attendees.

To underscore the importance of mentorship and legacy, the celebration included a "cross-generational dialogue" between senior and junior doctors. Notable participants included Professor Rosie Young, Honorary Professor at HKU's Li Ka Shing Faculty of Medicine, and Professor Sydney Tang, Chair Professor at the same institution.

A musical segment added a heartfelt touch to the evening. Dr. Thomas Tsang accompanied Dr. York Chow and Dr. David Fang on the piano as they performed "Danny Boy" and "You Raise Me Up," uplifting the spirits of their peers. A joint band formed by members of the St. John Ambulance Brigade and the Academy of Medicine performed "No More Salt and Oil," reminding everyone of the importance of health. The Hospital Authority Chinese Orchestra (HACO) contributed a special performance of traditional Chinese music as part of the celebrations. The celebration concluded with a rousing group performance of "Below the Lion Rock," leaving a lasting impression on all attendees.

Photographs excerpted from HKCMA e-Bulletin
Photographs reproduced by courtesy of HKCMA and President, Dr. Jane Chan

Psychiatry:

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(desvenlafaxine, as succinate)

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Composition[1]:

- DESPAXOR® is available in the following dosage forms: 50 mg and 100 mg extended-release oral tablets
- Each tablet contains 76 mg or 152 mg of desvenlafaxine succinate equivalent to 50 mg or 100 mg of desvenlafaxine, respectively

Indication[1]:

- A serotonin and norepinephrine reuptake inhibitor (SNRI), indicated for the treatment of adults with major depressive disorder (MDD)

Hepatology:

ENTECAVIR TEVA®

(entecavir))

TEVA

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Composition[2]:

- Available in the dosage form of 0.5 mg film-coated tablets

Indication[2]:

- Indicated for chronic hepatitis B virus (HBV) infection in adults. This medicine can be used in people with either compensated or decompensated liver disease
- Indicated for chronic HBV infection in children and adolescents aged 2 to less than 18 years. This medicine can be used in children with compensated liver disease

Hematology:

HYMPAVZI®

(marstacimab)

PFIZER

HK Reg. No. HK-68832 (28 Aug, 2025)

Composition[3]:

- Hympavzi 150 mg solution for injection in pre-filled pen: Each pre-filled pen contains 150 mg marstacimab in 1 mL of solution

Indication[3]:

Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with

- Severe hemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or
- Severe hemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors

LEQVIO®
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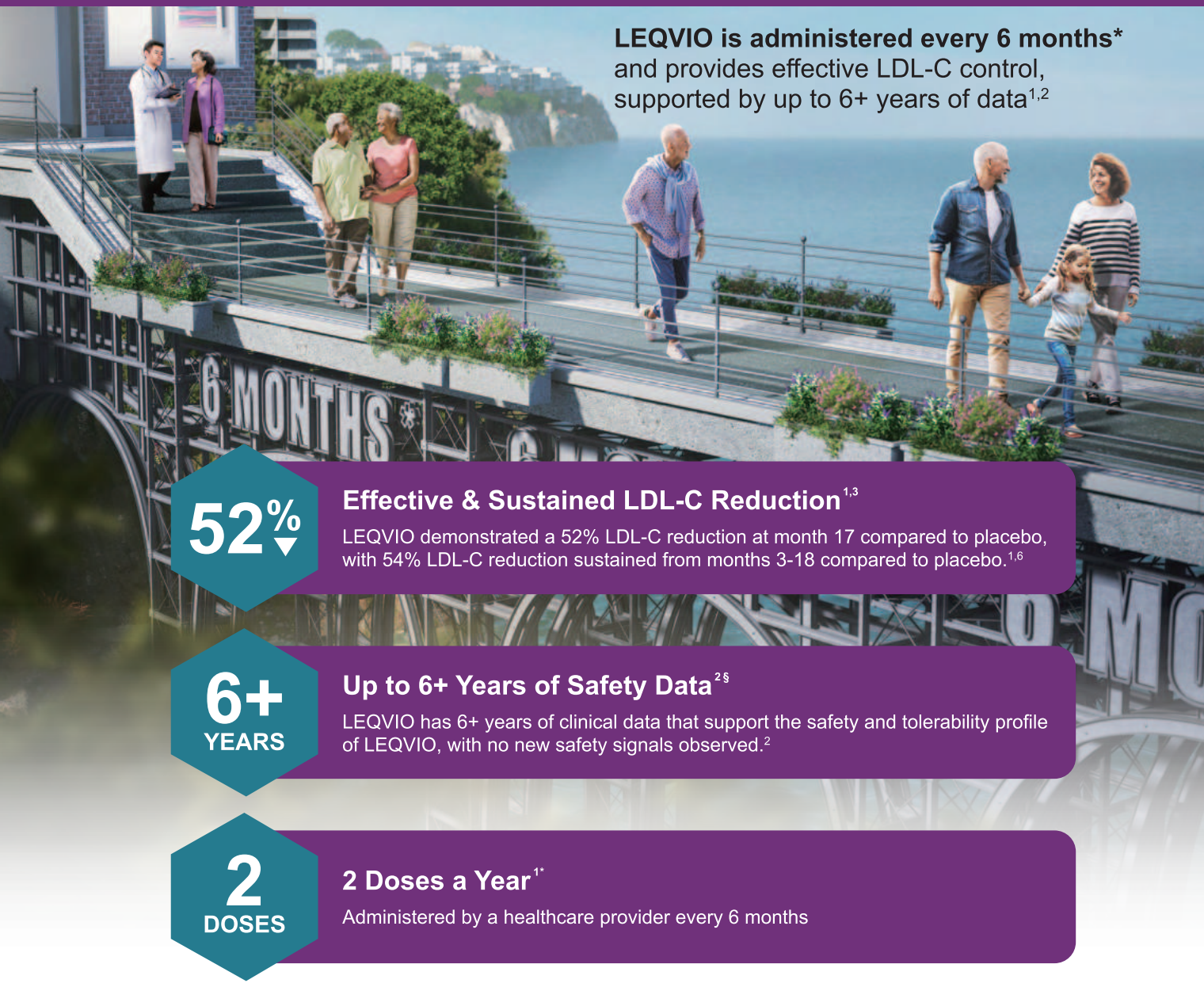
UNITED FOR LONG-LASTING† LDL-C CONTROL[1]



LEQVIO is administered every 6 months* and provides effective LDL-C control, supported by up to 6+ years of data[1,2]

52%▼

Effective & Sustained LDL-C Reduction[1,3]

LEQVIO demonstrated a 52% LDL-C reduction at month 17 compared to placebo, with 54% LDL-C reduction sustained from months 3-18 compared to placebo.[1,6]

6+ YEARS

Up to 6+ Years of Safety Data[2§]

LEQVIO has 6+ years of clinical data that support the safety and tolerability profile of LEQVIO, with no new safety signals observed.[2]

2 DOSES

2 Doses a Year[1*]

Administered by a healthcare provider every 6 months

* Two doses a year after the two initial doses. Single subcutaneous injection at the start of treatment, again at 3 months, and thereafter every 6 months.[1] ‡ † LDL-C reduction was maintained during each 6-month dosing interval after 2 initial doses of inclisiran. ‡ §Most common (>1 to <10%) adverse events at the injection site (includes injection site reaction, injection site pain, injection site erythema, and injection site rash).

References: 1. LEQVIO, Hong Kong Prescribing Information. Novartis Pharmaceuticals Corp. 2021. **2.** RS Wright, FJ Raal, W Koenig, U Landmesser, LA Leiter, S Vikarunnessa, A Lesogor, P Maheux, Z Talloczy, X Zang, GG Schwartz, KK Ray, Inclisiran administration potently and durably lowers LDL-C over an extended-term follow-up: the ORION-8 trial, Cardiovascular Research, 2024;, cvae109, https://doi.org/10.1093/cvr/cvae109. **3.** Ray KK, Wright RS, Kallend D, et al; ORION-10 and ORION-11 Investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. N Engl J Med. 2020;382(16):1507-1519. doi:10.1056/NEJMoa1912387.

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

HK2406276815

NOVARTIS

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Tel: 2882 5222 Fax: 2577 0274

Oncology:

LYTGOBI®

(futibatinib)

DKSH

HK Reg. No. HK-68839 (04 Sep, 2025)

Composition[4]:

- Each film-coated tablet contains 4 mg of futibatinib

Indication[4]:

- Lytgobi monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy

References

1. Drugs.com. Desvenlafaxine ER Tablets: Package Insert / Prescribing Info. 5 August 2025. Available from: https://www.drugs.com/pro/desvenlafaxine-er-tablets.html. [Accessed 18 September 2025]. **2.** Health Products Regulatory Authority, Ireland. Package leaflet: Information for the user: Entecavir Teva 0.5 mg Film-coated Tablets. Revised May 2017. **3.** EMA. Hympavzi Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/hympavzi-epar-product-information_en.pdf. [Accessed 18 September 2025]. **4.** EMA. Lytgobi Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/lytgobiepar-product-information_en.pdf. [Accessed 18 September 2025].

Keep Up With the Pace of Drug Development Evolution and Discover the Newly Launched Treatment in Hong Kong

Help patients with cGVHD

ROCK ON with

REZUROCK®
(belumosudil) tablets

***First-in-class** ROCK2 inhibitor*
*to treat **cGVHD**[1-3]*

featuring

RAP

Reduction of fibrosis[3]
Anti-inflammation[2,3]
Promising safety profile[1]

Meaningful Response
within a real-world demographic of cGVHD patients
ORR 75%[1,4,5,*]

Immunomodulator
to restore immune homeostasis with favorable safety[6]
ZERO CMV infection[6]
<4% grade ≥3 cytopenias[6]

NCCN Guidelines
Suggested Systemic Agent
for steroid-refractory cGVHD[7,†]

INDICATION[1]

REZUROCK® (belumosudil) is indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

* Based on a final analysis by the FDA (n=65)
† NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network®; ORR, overall response rate; ROCK2, rho-associated coiled-coil-containing protein kinase-2.

References: 1. REZUROCK® Hong Kong Prescribing Information. 2. Zanin-Zhorov A, Weiss JM, Nyuydzefe MS, et al. Proc Natl Acad Sci USA. 2014;111(47):16814-16819. 3. Flynn R, Paz K, Du J, et al. Blood. 2016;127(17):2144-2154. 4. Data on file 1. Kadmon Pharmaceuticals, LLC; 2021. 5. Data on file 2. Kadmon Pharmaceuticals, LLC; 2020. 6. Cutler C, Lee SJ, Arai S, et al. Blood. 2021;138(22):2278-2289. 7. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Cell Transplantation (HCT) Version 3.2023 - October 9, 2023. 8. Items supported by the Samaritan Fund. Hospital Authority. (Effective from 30 May 2025).

Abbreviated Prescribing Information
Presentation: REZUROCK (belumosudil) Tablets 200mg. **Indications:** For treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy. **Dosage & Administration:** 200 mg given orally once daily until progression of chronic GVHD that requires new systemic therapy. Swallow REZUROCK tablets whole. Take REZUROCK with a meal at approximately the same time each day. If a dose of REZUROCK is missed, instruct patient to not take extra doses to make up the missed dose. Monitor total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at least monthly. Modify REZUROCK dosage for adverse reactions including hepatotoxicity. Increase REZUROCK dosage to 200 mg twice daily when co-administered with strong CYP3A inducers or proton pump inhibitors. Avoid use in patients with moderate or severe hepatic impairment without liver GVHD. *For full dosage information, please refer to the full prescribing information*. **Contraindications:** None. **Precautions:** Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm when administered to pregnant woman. Advise pregnant women of the potential risk to fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during REZUROCK treatment and for one week after the last dose. **Drug Interactions:** Strong CYP3A Inducers and Proton Pump Inhibitors. **Pregnancy and lactation:** Advise pregnant women and females of reproductive potential of the potential risk to fetus. Because of the potential for serious adverse reactions from belumosudil in breastfed child, advise lactating women not to breastfeed during REZUROCK treatment and for one week after the last dose. Verify pregnancy status of females of reproductive potential prior to initiating REZUROCK treatment. **Undesirable effects:** Infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension. *For other undesirable effects, please refer to the full prescribing information*. **Preparation**: 200mg x 30's. **Legal Classification:** Part 1, First & Third Schedules Poison. ***Full prescribing information is available upon request.***

API-HK-RZR-24.05

For Healthcare Professionals Use Only

sanofi

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MAT-HK-2500508-1.0-09/2025

IN THE TREATMENT OF RELAPSED/REFRACTORY MULTIPLE MYELOMA, NINLARO® BRINGS[1]

Tourmaline MM1 study (n=722) was a double-blinded, placebo-controlled, phase 3 trial to compare efficacy and safety of Ixazomib(I), lenalidomide(R) & dexamethasone(d) vs placebo-Rd in relapsed/refractory multiple myeloma patients. The primary endpoint was progression free survival (PFS). The median PFS of IRd vs placebo-Rd was 20.6 months vs 14.7 months. The most common adverse events (>30%) included neutropenia, thrombocytopenia, diarrhea, rash and constipation.

NINLARO® in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Abbreviated Prescribing Information (EU-DEC21-HK-FEB22)

NINLARO®
ixazomib capsules
恩萊瑞®

Ninlaro 2.3mg, 3mg and 4mg Capsules

Presentation: Ixazomib 2.3 mg, 3 mg and 4 mg gelatin hard capsules. Indication: NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Dosage and administration: Recommended starting doses: NINLARO 4 mg (one capsule) administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle at least 1 hour before or at least 2 hours after food; lenalidomide 25 mg administered daily on Days 1 to 21 of a 28-day treatment cycle; dexamethasone 40 mg administered on Days 1, 8, 15, and 22 of a 28-day treatment cycle. Treatment should be continued until disease progression or unacceptable toxicity. Treatment with NINLARO in combination with lenalidomide and dexamethasone for longer than 24 cycles should be based on an individual benefit risk assessment, as the data on the tolerability and toxicity beyond 24 cycles are limited. Antiviral prophylaxis should be considered in patients being treated with NINLARO to decrease the risk of herpes zoster reactivation. No dose adjustment is necessary in patients over 65 years of age. Reduced 3 mg starting dose recommended in moderate or severe hepatic impairment. Reduced 3 mg starting dose recommended in severe renal impairment or end-stage renal disease requiring dialysis. Contraindications: Hypersensitivity to the active substance or to its excipients. As NINLARO is administered in combination with lenalidomide and dexamethasone, refer to the package insert for these medicinal products for additional contraindications. Warnings and precautions: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Platelet counts should be monitored at least monthly during NINLARO treatment. Thrombocytopenia can be managed with dose modifications and platelet transfusions as per standard medical guidelines. Diarrhoea, constipation, nausea and vomiting have been reported with NINLARO, occasionally requiring use of antiemetic and antidiarrhoeal medicinal products and supportive care. The dose should be adjusted for severe (Grade 3–4) symptoms. Patients experiencing new or worsening peripheral neuropathy may require dose modification. Patients with peripheral oedema should be evaluated for underlying causes and provided supportive care, as necessary. The dose of dexamethasone should be adjusted per its package insert or NINLARO for Grade 3 or 4 symptoms. Rash should be managed with supportive care or with dose modification if Grade 2 or higher. Stevens-Johnson syndrome (SJS) has also been reported with NINLARO. If SJS occurs, discontinue NINLARO. Cases of Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) have been reported in patients who received NINLARO. Some of these have been fatal. Signs and symptoms of TMA should be monitored for and NINLARO stopped if diagnosis is suspected. Hepatic enzymes should be monitored regularly and dose should be adjusted for Grade 3 or 4 symptoms. Pregnancy: Women should avoid becoming pregnant while being treated with NINLARO. In patients developing Posterior reversible encephalopathy syndrome (PRES), discontinue NINLARO. Interactions: Co-administration of strong CYP3A inducers with NINLARO is not recommended. No dose modification is required for NINLARO with co-administration of strong CYP3A inhibitors or strong CYP1A2 inhibitors. Women should avoid becoming pregnant while being treated with NINLARO. Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment. Women using oral hormonal contraceptives should additionally use a barrier method of contraception. Breast feeding should be discontinued. Undesirable effects: Very common (all grades): Upper respiratory tract infection, bronchitis, thrombocytopenia, neutropenia, peripheral neuropathies, diarrhoea, constipation, nausea, vomiting, rash, back pain, oedema peripheral. Common (all grades): Herpes zoster. Serious adverse reactions: Serious adverse reactions reported in ≥2% of patients included diarrhoea (3%), thrombocytopenia (2%) and bronchitis (2%). As Ixazomib is administered in combination with lenalidomide and dexamethasone, refer to the package insert for these medicinal products for additional undesirable effects.

For details, please refer to full prescribing information.

Takeda
ONCOLOGY

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Reference: 1. Moreau P et al. N Engl J Med. 2016 Apr 28;374(17):1621-1634.

For reporting suspected side effects for Takeda products at AE.HongKong@takeda.com
For asking medical information and other inquiries for Takeda products at medinfohk@takeda.com

C-APROM/HK/NINL/0034 (03/2024)