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# 香 港 醫 訊

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## Cardiology


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**References: 1.** Data on file. Amgen [1]: 2015. **2.** Repatha® Hong Kong Prescribing information (HKPI20150007) Jan-2016. **3.** Data on file. Amgen [2]: 2015.

**Repatha® (Evolocumab) Abbreviated Prescribing Information**
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# Contents





## Disclaimer



## The Cover Shot


The Hong Kong Rope Skipping Team, jointly developed and nurtured by the Hong Kong College of Cardiology and The Hong Kong Rope Skipping Association, China since 2000, rose to top honour after capturing 27 gold, 27 silver and 26 bronze medals in the 2016 World Rope Skipping Championships held in Malmo, Sweden.

In the Male Team Championship, Hong Kong dominated by sweeping gold, silver and bronze. Our Female Team won bronze medal in the team championship. Two world records were broken by Hong Kong Team!

This photo was taken right after the Closing Ceremony cum Medal Presentation on July 31, 2016. The major event was the rope skipping "World Cup" competed by 6 countries/regions, and this was also won by our Hong Kong Team!

In this epic photo, Dr Patrick Ko, the Hon. Team Manager, was surrounded by the entire team of 137 rope skippers (many of them wearing the medals awarded to them), and 10 coaches or staff. They all looked super-cheerful, exuding confidence and positive energy!

Their hard work has finally paid off. They deserve the recognition they have long deserved, and we are so proud of them!

**Dr Patrick KO**

MCPS, MD(Alberta), FACC, FRCPC, FHKCP, FHKAM(Med)

*Specialist in Cardiology*
*Hon. Clinical Associate Professor in Medicine (HKU)*
*Hon. Adjunct Associate Professor in Medicine (CUHK)*

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# Editorial

## Dr Ngai-yin CHAN

MBBS(HK), FRCP(Lond), FRCP(Edin), FRCP(Glasg), FACC, FHKCP, FHKAM(Med)

*Specialist in Cardiology*
*Consultant Physician and Deputy Chief-of-Service, Department of Medicine & Geriatrics, Princess Margaret Hospital*
*Honorary Treasurer, Hong Kong College of Cardiology*

***Editor***

Dr Ngai-yin CHAN

Heart failure is a common clinical condition which is managed not only by cardiologists but also physicians of other subspecialties and family physicians. On the other hand, it is also an economically significant and life-threatening disease as evidenced by over 18,000 hospital admissions and 800 deaths per year in Hong Kong.[1] Therefore, I believe it is a topic of interests for the readers of the Hong Kong Medical Diary.

It is indeed exciting for us in the recent decade when we see phenomenal advancement in the management of heart failure. New drugs have been emerging and have been shown to improve the prognosis and symptoms of heart failure. Cardiac resynchronisation therapy with a pacemaker or implantable cardioverter-defibrillator continues to evolve and possibly results in a higher response rate and benefits a wider patient population. We have seen leaping development in the area of catheter-based valvular interventions in recent years. Mitral regurgitation can now be treated by percutaneous catheter-based technique and a subset of heart failure patients do benefit a lot. Last but not the least, surgical interventions remain integral in the whole management armamentarium for heart failure. To put all these together, I am fortunate to have support of all the contributors, who are certainly experts in this area. I am deeply indebted to Prof Chu-pak Lau, Prof David Siu, Dr Katherine Fan, Dr Cally Ho, Dr Ryan Ko, Dr Will Chan and Dr Michael Wong for their contribution to this issue.

Prevention is always better than cure but at the same time it is nothing easier because it usually requires a modification of human behaviour in diseases like heart failure. Dr Patrick Ko nicely shares with us the cover photo taken right after the closing ceremony cum medal presentation at the 2016 World Rope Skipping Championships held in Malmo, Sweden. This highlights the longstanding effort of the Hong Kong College of Cardiology in the promotion of regular exercise in Hong Kong citizens, especially our younger generation. Apart from primary prevention in coronary artery disease which is a main risk factor for the development of heart failure in Hong Kong, regular physical activity is also recommended for heart failure patients for improvement in functional status.[2]

Being a doctor, in particular, a cardiologist is undoubtedly a stressful occupation. Besides sedentary lifestyle, psychosocial stress is also a well-known risk factor for heart disease. I must thank Dr Ngai-shing Mok, who makes this issue special by sharing with us his interesting and stress-relieving hobby of stargazing. We all have a passion for fighting diseases, curing our patients and promoting health. Yet, we are leading lives with long working hours and stressful working environment. Maybe it is the time for us, if you have not yet done so, to develop a more balanced and healthy lifestyle both for ourselves and for setting good examples for our patients and our society in Hong Kong.

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# Novel Therapeutic Targets for Heart Failure

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*This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 April 2017.*

## Introduction

The challenge raised against the global epidemic of heart failure (HF) is unprecedented. Success in advancing medical treatment and interventional techniques in heart diseases, be it coronary, congenital, or valvular, has led to reduced mortality rates from these prior lethal causes in the past decades, resulting in prolonged longevity of heart disease patients overall. Coupled with the ageing population structure in developed countries and the transitional lifestyle patterns in developing jurisdictions where burgeoning rates of hypertension, diabetes and obesity are seen, HF will be the leading cause of death, morbidities and hospitalisation worldwide.[1]

Despite currently established effective medical therapies for HF, a significant proportion of patients remain refractory in terms of clinical symptoms, outcomes and quality of life. Thus there remains a pressing need to further empower our anti-HF armamentarium. Furthermore, unlike the success observed in medical and device-based therapies of HF with reduced ejection fraction (HFrEF), so far no therapeutic strategy has been proved effective in altering clinical outcomes of HF with preserved ejection fraction (HFpEF), which totalled half of HF disease burden and is projected to be the more common type of HF in the coming decades. Recently, a deeper understanding into the pathophysiology of HFpEF versus HFrEF made us to realise distinctive mechanistic origins and has opened up exciting opportunities to potentially intervene the disease process via novel pathways.[2, 3]

## Pathophysiology of Heart Failure with Preserved Ejection Fraction (HFpEF)

The pathophysiology of HFpEF has classically been centred upon left ventricular (LV) diastolic dysfunction. Recent research showed that HFpEF is indeed far more than lone LV diastolic dysfunction, and represents an orchestrated interplay between LV and systemic arterial stiffness, left atrial dysfunction, increased pulmonary vascular resistance, and chronotropic incompetence. [2-5]

Speckle tracking echocardiographic imaging showed that there is predominant subendocardial fibre damage in HFpEF, resulting in impaired LV longitudinal shortening with circumferential and radial compensatory response.[6] There is functionally impaired pressure decay in LV relaxation explained in terms of myofilament dissociation, abnormal calcium reuptake and altered sarcoplasmic reticulum stress[7]. Simultaneously, the passive stretching is further mechanically impaired due to altered viscoelastic properties of the extracellular matrix, sarcomere/ titin-based stiffness, and pericardium.[5]

Such cardiomyocyte and systemic vascular dysfunction can be commonly explained by systemic oxidative stress and microvascular inflammation[8], which eventually results in depressed nitric oxide (NO) function and downregulation of NO-mediated cyclic guanosine monophosphate (cGMP)-Protein Kinase G (PKG) signalling. Such downregulation of the cGMP-PKG pathway is now believed to be a key pathophysiological pathway in HF, especially HFpEF, and thus provides various novel targets for therapeutic intervention through cGMP-PKG augmentation at various mechanistic stages.[4]

## Targeting the Cyclic GMP-PKG Pathway

Mechanotransduction studies of the myocardium showed that titin, a sarcomere protein that is functionally pivotal in determining myocardial passive tension and stiffness, can be modulated via phosphorylation through the cGMP-PKG pathway, such that reduced myocardial cGMP and PKG activities are associated with titin hypo-phosphorylation, heightened nitrosative/oxidative stress, and titin-based myocardial stiffness. In a study of HEpEF by Heerebeek et al[9], it was beautifully showed that levels of myocardial cGMP and PKG activities were significantly reduced among patients with HFpEF, versus patients with HFrEF or aortic stenosis. Thus augmentation of the cGMP activity may help alleviate titin-based myocardial tension and stiffness, and this concept is the backbone of numerous therapeutic trial attempts to the treatment of HF.

cGMP, an intracellular second messenger that provides signal transduction to effector molecule PKG, can be modulated via the guanosine cyclases (GC)s. The GCs are a group of enzymes which convert precursor guanosine triphosphates into intracellular cGMP. There are 2 types of GCs: transmembrane-associated particulate GC, a receptor for the natriuretic peptides (ANP, BNP, CNP); and soluble GC, an intracellular receptor for NO secreted by endothelial cells.[4, 5]

As nicely summarised by Greene et al, the ways to alter cGMP activity will be (1) use of NO mimetics i.e. nitrovasodilators; (2) sGC activators/ stimulators; (3) increased natriuretic peptides activity; (4) reduced phosphodiesterase (PDE) hydroxylation of cGMP.[4]

## NO Mimetics/ nitrovasodilators

The First Vasodilator Heart Failure Trial (V-HeFT I) showed that combined isosorbide dinitrate with antioxidant hydralazine had clinical benefits in patients with mild-to-severe heart failure.[10] The subsequent African-American Heart Failure Trial (A-HeFT) further demonstrated that isosorbide dinitrate plus hydralazine, when added to standard therapy for heart failure including neurohormonal blockers, improved survival, reduced first hospitalisation for heart failure, and improved quality of life survival among black patients with advanced HFrEF.[11] Nevertheless, the use of NO mimetics is often limited by symptoms of hypotension. There is concern regarding the raised systemic oxidative stress levels at high doses or prolonged use of NO mimetics. The potential ethnic difference in therapeutic efficacy is worthwhile for further investigation. So far, there is no evidence of NO use resulting in benefits in patient with HFpEF.

## Clinical Efficacy of Angiotensin-Neprilysin Inhibitor (ANRI)

The beneficial effects of renin-angiotensin-aldosterone blockade in HF have been well described. The further development of the Angiotensin-Neprilysin Inhibitor (ANRI) Valsartan/sacubitril (LCZ696) was one the most exciting findings in recent years of research in clinical therapeutics of HF. In the landmark trial PARADIGM-HF, LCZ696 (200 mg twice daily) was shown to be superior compared to enalapril (10 mg twice daily) in 8442 patients with NYHA class II, III, or IV HFrEF with ejection fraction of 40% or less, in reducing cardiovascular death and HF hospitalisation.[12] The study was prematurely terminated after 27 months due to study drug benefit. LCZ696 also decreased the symptoms and physical limitations of HFrEF. In a subsequent secondary analysis, it was further shown that LCZ696 resulted in reduced chance to require intensive care, or to receive intravenous positive inotropic agents, or requirement for device-based HF therapy or cardiac transplantation, and improved symptom scores/ favourable biomarkers in surviving patients with HFrEF. Noting the clinical benefits, the LCZ696 is also noted to have higher rates of hypotension and non-serious angioedema which may limit its use and/ or dose in patients with borderline blood pressure. Furthermore, any benefit of its use among patients with HFpEF remains obscured.[13, 14]

## Phosphodiesterase-5 (PGE-5) Inhibitors

Inhibition of PGE-5 results in reduced hydroxylation of myocardial cGMP, and thus theoretically increases cGMP levels and PKG medicated titin phosphorylation. This idea in the treatment of diastolic dysfunction and HFpEF is thus attractive. In the Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX) multicentre trial, 216 stable ambulatory HFpEF patients were randomised to receive sildenafil versus placebo. It was noted that there was no significant change in peak exercise oxygen consumption, clinical status rank score, or 6-minute walk distance at 24 weeks.[15] Albeit disappointing, it was noted that plasma cGMP levels were not significantly altered after sildenafil. It might be possible that it is the upstream reduced NO bioavailability rather than downstream PGE-5 over-expression that is predominant in these patients. If this is the case, then it might not be surprising to see no significant effect of sildenafil was seen among these patients. This hypothesis will require further testing.

## Soluble Guanylate Cyclase (sCG) Stimulator/ Activator

A number of trials including the SOluble guanylate Cyclase stimulatoR in heArT failurE Studies (SOCRATES), is ongoing which will test the sGC stimulator vericiguat, in its clinical efficacy for HF protection in patients with HFrEF or HFpEF. Trials for the other sGC stimulator, riociguat, and sGC activator, cinaciguat, are also ongoing.[4, 5, 16, 17]

## Summary

The cGMP-PKG signalling pathway represents a key mechanistic pathway in modulating titin phosphorylation and myocardial stiffness. Augmentation of the cGMP activity at various mechanistic stages may thus help alleviate titin-based myocardial tension and stiffness, and potentially represent novel therapeutic targets in the treatment of HF. While angiotensin-neprilysin inhibitor was shown to be effective in reducing cardiovascular death and heart failure hospitalisation, further therapeutic modalities will need to be tested in ongoing and upcoming randomised controlled trials.

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## MCHK CME Programme Self-assessment Questions

**Please read the article entitled "Novel Therapeutic Targets for Heart Failure" by Yap-hang CHAN and Prof David Chung-wah SIU and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 April 2017. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.**

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

1. The worldwide disease burden of heart failure is increasing.
2. Diastolic dysfunction is equivalent to heart failure with preserved ejection fraction (HFpEF).
3. HFpEF represents an orchestrated interplay between left ventricular and systemic arterial stiffness, left atrial dysfunction, increased pulmonary vascular resistance, and chronotropic incompetence.
4. The cyclic guanosine monophosphate (cGMP)-Protein Kinase G (PKG) signalling pathway represents a key mechanistic pathway in modulating titin phosphorylation and myocardial stiffness.
5. The Angiotensin-Neprilysin Inhibitor (ANRI) Valsartan/sacubitril (LCZ696) was shown to be superior compared to enalapril (10 mg twice daily) in reducing cardiovascular death and heart failure hospitalisation.
6. The use of LCZ696 is associated with higher rates of hypotension and non-serious angioedema in the PARADIGM-HF trial.
7. In the Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction (RELAX) trial, sildenafil has not been shown to be effective in reducing HF symptoms in patients with HFpEF.
8. Combined isosorbide dinitrate with antioxidant hydralazine had clinical benefits in patients with mild-to-severe heart failure.
9. Isosorbide dinitrate plus hydralazine, when added to standard therapy for heart failure including neurohormonal blockers, improved survival, reduced first hospitalisation for heart failure, and improved quality of life survival among black patients with advanced HFrEF.
10. Augmentation of the cGMP activity may help alleviate titin-based myocardial tension and stiffness, and potentially represents a novel pathway that provides targets for therapeutic interventions in HF. This concept will need to be tested in ongoing and upcoming randomised controlled trials.

## ANSWER SHEET FOR APRIL 2017

**Please return the completed answer sheet to the Federation Secretariat on or before 30 April 2017 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.**

# Novel Therapeutic Targets for Heart Failure

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*Specialist in Cardiology*
*Professor of Department of Medicine*

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## Answers to March 2017 Issue

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† Based on 2016 ESC HF Guidelines and 2016 ACC/AHA/HFSA Guideline Update.

‡ Primary end point.

§ Secondary end point that measured the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ).

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

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# Current Overview of Cardiac Resynchronisation Therapy for Heart Failure

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## INTRODUCTION

While optimal pharmacological therapy (OPT) remains the cornerstone of treatment for systolic heart failure (HF), the residual mortality and morbidity risks of HF remain high. Even with the advent of neprilysin inhibitors, the two-year cardiovascular mortality remains significant at 13.3%[1], and is higher in those with more advanced HF. This calls for the need of additional non-pharmacological therapy.

## MECHANISM OF CARDIAC RESYNCHRONISATION THERAPY

A wide QRS ECG complex such as a left bundle branch block (LBBB) occurs in about 30% of patients with moderate to severe HF[2]. In classical LBBBs, the electrical and mechanical activation of the left ventricle (LV) is delayed compared to the right ventricle (RV). This results in inappropriate sequence of RV and LV contractions (inter-ventricular dyssynchrony). More importantly, various regions in the LV contract at a different time, resulting in ineffective LV contraction (intra-ventricular dyssynchrony). There is often prolonged atrial to ventricular conduction, leading to inadequate diastolic filling of the ventricles. These 3 mechanisms further aggravate systolic dysfunction. By electrical pacing simultaneously the RV and the LV (through a pacing lead in the coronary sinus that paces the LV epicardially), both cardiac synchronicity and the left ventricular ejection fraction (LVEF) will be improved and the heart undergoes reverse remodelling[3] (Fig. 1). This biventricular pacing method has been termed cardiac resynchronisation therapy (CRT).

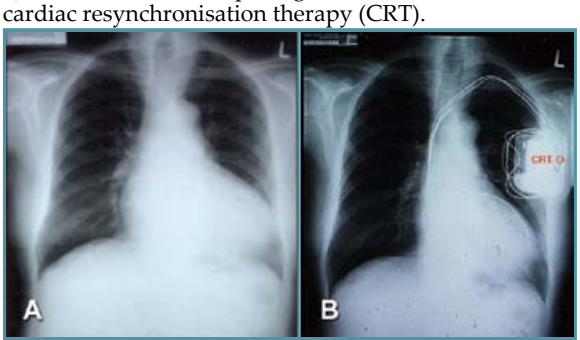


*Fig. 1. Chest radiographs of a patient with dilated cardiomyopathy with ejection fraction of 25%, before (A) and after (B) cardiac resynchronization therapy with defibrillator (CRT-D). This shows significant reduction in heart size. A 3 lead system, right atrial, right ventricle and left ventricle.*

## CLINICAL EVIDENCE

The COMPANION trial[4] is the landmark study which compared, in advanced HF patients, CRT with (CRT-D) or without defibrillator (CRT-P) over OPT. These patients had poor LVEF (EF ≤ 35%), a wide QRS > 120ms and severe HF symptoms (New York Heart Association Class, NYHC, III/IV). The combined endpoint of HF hospitalisation and death was lower with CRT-D/CRT-P vs OPT, with survival benefits in the CRT-D arm in secondary analysis. In less severe HF (NYHC II/III), the RAFT study[5] showed a similar benefit. The MADIT-CRT study[6] randomised patients with no or only mild HF symptoms (NYHC I/II) to receive either CRT-D or an implantable cardioverter defibrillator (ICD) and demonstrated a 34% reduction in the risks of all causes mortality or first HF event. The REVERSE study[7] further showed reverse remodelling in patients with LVEF ≤ 40% and minor HF symptoms, who received CRT-P and prevention of HF events, suggesting HF prevention by CRT. A recent meta-analysis of these trials confirmed these major trial findings[8].

## GUIDELINES FOR CRT

Class I indication for CRT nowadays is for patients in sinus rhythm with QRS ≥ 150ms, LBBB, EF ≤ 35% and NYHC II-III[9-10] (Table 1). In the European Society of Cardiology (ESC) guideline, a QRS duration between 130-150ms is also an indication but with a lower level of evidence and also not advocated by the guideline in the United States (US). Both US and European guidelines will consider the use of CRT for non-LBBBs if the QRS duration is ≥ 150 ms (Class IIa). Shorter QRS durations for non-LBBBs are not generally indicated for CRT. Especially for patients with a normal QRS interval, CRT can potentially cause harm even after echocardiographic determination of LV dyssynchrony. [11-12]

*Table 1.European Society of Cardiology Guideline for Cardiac Resynchronization Therapy (CRT) [9]. The United State guideline for CRT is similar, but Class 1B condition is not considered an indication[10]. OPT = Optimal pharmacological therapy; NYHC = New York Heart Association Class.*

| | | |
|---|---|---|
| **Class I:** | OPT (>3months)<br>NYHC II-IV (ambulatory)<br>LVEF ≤ 35%<br>Sinus Rhythm<br>QRS ≥ 130ms<br>LBBB | IA if QRS ≥ 150 ms<br><br><br><br>IB if QRS 130-149 ms |
| **Class II:** | Non-LBBB + Above | IIa if QRS ≥ 150 ms<br>IIb if QRS 130 - 149 ms |
| **Class III:** | QRS < 130 ms | -- |

## THE NON-RESPONDERS

In almost all prospective studies, at least 1/3 of patients do not improve after CRT. There are four important mechanisms for response to CRT: a large area of functional block in the LV with delayed activation, this delayed area can be reached by a pacing lead in the coronary sinus, pacing at that site can reverse the dyssynchrony and finally sufficient LV contracting myocardium should remain for a response (Fig. 2). Even when all elements are present, the presence of sinus rhythm and appropriately adjusted atrio-ventricular and RV to LV timings are needed to optimise the response. These factors are important to select the proper candidate, consider for the lead placement site and proper programming.

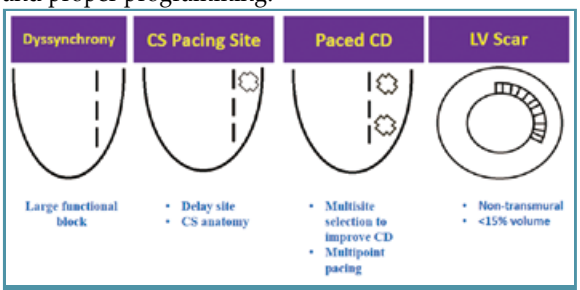


*Fig. 2. Elements for cardiac resynchronization therapy (CRT) response in LBBB and sinus rhythm (SR). CD = conduction delay; CS = coronary sinus; LV = left ventricle. See text for discussion.*

The clinical factors that are useful for predicting CRT response include non- ischaemic cardiomyopathy and the female sex. Among 453 women in the 1,800 patients recruited in the MADIT-CRT trial[6], women had better outcome both in the ICD and CRT-D arms compared with men, even after adjusting for baseline demographic differences. A greater degree of dyssynchrony in females at the same QRS duration compared to males is suggested. Atrial fibrillation (AF) significantly impairs clinical response, as there is loss of atrio-ventricular synchrony and biventricular pacing can be inhibited, resulting in a decreased CRT efficacy. Indeed for optimal CRT response, a > 98% biventricular pacing is an important criterion for an adequate dose of CRT and clinical response[13]. Thus optimal rate control in a CRT patient who has AF is critical, which can include rate controlled drugs or atrio-ventricular nodal ablation[14].

Pre-implant ECG with LBBB ≥ 150ms remains the gold standard for indication and also for optimal outcome. CRT use in non-LBBB conditions such as RBBBs and intra-ventricular conduction delay is controversial. At the time of implantation, a longer delay from surface Q wave to the onset of LV electrogram as recorded by the LV lead (so called Q-LV duration) is associated with a good clinical outcome[15], emphasising the importance of electrical dyssynchrony and the appropriate pacing site.

Can baseline echocardiography be used to predict response? Echo-Doppler techniques including tissue Doppler and speckle tracking are excellent non-invasive measures of mechanical dyssynchrony. Unfortunately, using a myriad of up to 12 echo-parameters, it was not possible to predict the response or no-response to CRT[16]. There are several reasons for this unexpected finding, including echo-Doppler technique variabilities in different centres, the possibility that mechanical dyssynchrony is not equivalent to electrical dyssynchrony and that the pacing lead site and presence of myocardial scar may have limited the benefit of CRT as aforementioned. Indeed, magnetic resonance imaging of the LV has shown that a LV scar area < 15% is predictive of good CRT outcome[17]. The ability to use echo-Doppler to guide the proper positioning of the LV lead has been suggested[18]. Innovations to improve CRT response include the use of quadripolar leads (to increase the chance of reaching a responsive LV area and to pace a larger area using multiple electrodes)[19] and to harness the still functioning right bundle[20]. With the availability of leadless pacing[21], LV endocardial pacing may become a possibility. LV endocardial pacing can achieve a faster and more uniform conduction than pacing the epicardium from the coronary sinus and thus improves synchroncity. In addition, an optimal pacing site will not be constrained by the coronary sinus anatomy that restricts where a LV lead can be placed.

It must be remembered that the efficacy of CRT is based on a background of OPT, which may change overtime. In addition, concurrent or new onset medical diseases such as anaemia, thyroid dysfunction or coronary artery disease can lead to a change in the CRT outcome. These emphasise the importance of medical follow-up and assessment in addition to device programming.

## CONCLUSION

In conclusion, CRT is a major advance in non-pharmacological therapy for HF. The presence of LBBB in patients with systolic HF should alert the clinician to a possible target to reverse or improve HF.

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# Update on Left Ventricular Assist Devices as Mechanical Circulatory Support for End-Stage Heart Failure

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## Introduction

Heart failure is a disease with significant morbidity and mortality and stage D represents end-stage heart failure with poor prognosis of 20% 5-year survival rate.[1] Although heart transplantation is the gold standard treatment for end-stage heart failure, donor availability remains the major limitation worldwide.[2] Thus left ventricular assist devices (LVAD) have emerged as a new therapy for end-stage heart failure.

## Concept and History of LVAD

The concept of left ventricular assist devices is very simple. A mechanical pump is connected between the failing left ventricle and the aorta providing mechanical force to pump blood from the left ventricle to the aorta in parallel to the intrinsic blood flow. This can offload the left ventricle to reduce filling pressure as well as to augment cardiac output. The pump is connected via a driveline to an external power source and a control module to adjust pump settings.

The history of LVAD can be traced back to the first clinical use of an implantable artificial ventricle by Liotta[3] in 1963 and a first pneumatic LVAD by Debakey[4] in 1966. However, these primitive ventricular assist devices could only support patients in terms of days. Subsequent improvement in pulsatile LVAD designs eventually led to FDA approval for the indication of bridge to transplantation (BTT) by the mid-1990s.[5]

In 2001, the first landmark study REMATCH trial compared the use of a pulsatile LVAD (HeartMate XVE) (Fig. 1) and optimal medical therapy among 129 patients with end-stage heart failure who were not heart transplant candidates in a randomised fashion. The study demonstrated significant improvement of 1 year survival with the use of pulsatile LVAD compared to optimal medical therapy (52% vs 25%, p=0.002)[6] and resulted in FDA approval for its use as destination therapy (DT) in 2003. However the 2-year survival was only 23% in the LVAD group due to sepsis and LVAD device failure signifying the need for improvements in pump design to improve long term outcome.

The development of a smaller continuous axial-flow LVAD (HeartMate II) (Fig. 2) resulted in wide spread use of LVAD for advanced heart failure after the publication of the HeartMate II BTT trial in 2007 which demonstrated 6-month and 1-year survivals of 75% and 68% [7] and led to FDA approval for its use as BTT in 2008[5]. The annual LVAD implantation number increased from less than 500 before 2007 to more than 2,000 in 2012 with continuous flow LVADs accounted for more than 90% of the implants in the United States.[8] With the improvement of clinical experience, a subsequent study demonstrated very good 18-month survival of 72% as BTT[9] and showed significant better survival at 2 years compared to pulsatile LVAD HeartMate XVE (58% vs 24%, p=0.008) as DT.[10]

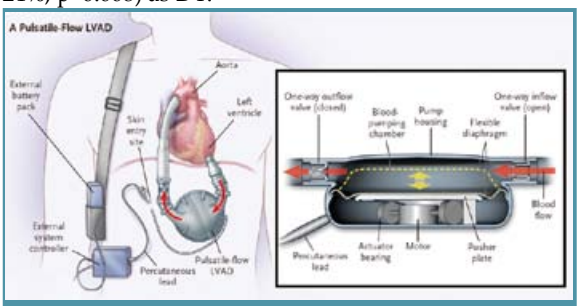


*Fig. 1. Diagram of pulsatile-flow left ventricular assist device (HeartMate XVE)*

Slaughter MS et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med. 2009;361:2241-51.*

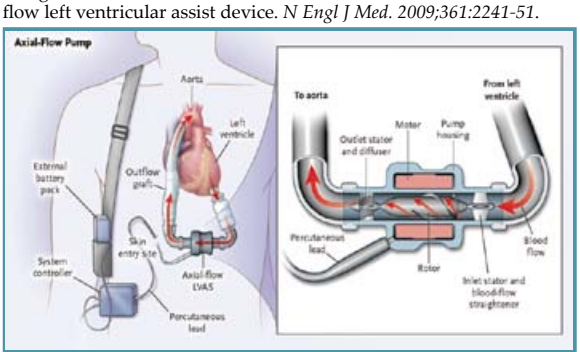


*Fig. 2. Diagram of continuous axial-flow left ventricular assist device (HeartMate II)*

Slaughter MS et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med. 2009;361:2241-51.*

The latest generation LVADs are small centrifugal-flow intra-pericardial LVADs. (Fig. 3-4) In the HVAD ADVANCE BTT study, the HeartWare LVAD device (HVAD) was shown to be non-inferior to current LVADs available in the market as BTT with 6-month survival of 94% and 1-year survival of 86% compared to control of 90% and 85% respectively.[11] In the recently published MOMENTUM 3 trial, 294 patients were randomised to receive a fully magnetically levitated centrifugal-flow LVAD (HeartMate 3) and axial-flow LVAD HeartMate II for both BTT and DT indications. Primary end point was reached in 86.2% in HeartMate 3 group vs 76.8% in HeartMate II group at 6 months (p<0.001 for non-inferiority and p=0.04 for superiority) with the

difference mostly contributed by less re-operation for pump malfunction 0.7% with HeartMate 3 vs 7.7% with HeartMate II and the pump thrombosis rate was 0% in HeartMate 3. This signifies improvements in technology and design of the LVAD can result in smaller, more reliable, durable and effective LVAD devices with fewer complications.

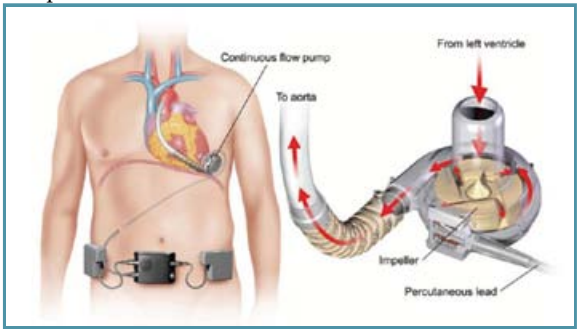


*Fig. 3. Diagram of continuous centrifugal-flow intra-pericardial left ventricular assist device HeartWare Ventricular Assist Device (HVAD)*

Aaronson KD et al. Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation 2012;125:3191-200.*

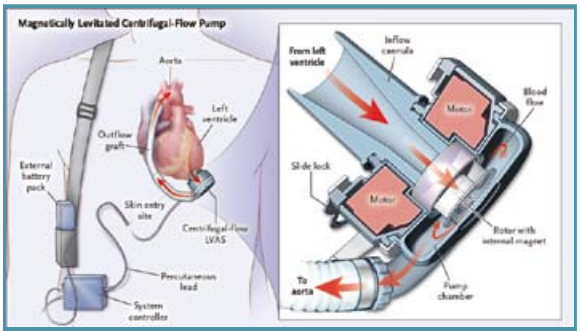


*Fig. 4. Diagram of fully magnetically levitated centrifugal-flow left ventricular assist device (HeartMate 3)*

Mehra MR et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med. 2016.*

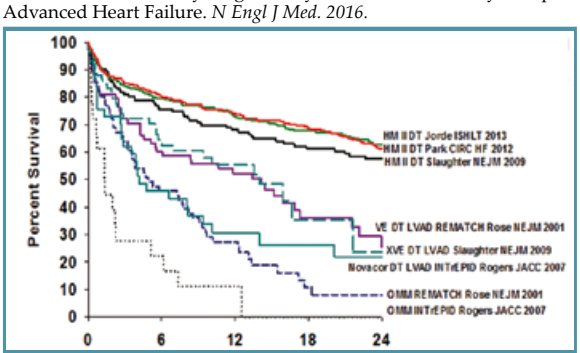


*Fig. 5. Figure demonstrating the clinical outcome of left ventricular assist device as destination therapy*

Jorde UP, Kushwaha SS, Tatooles AJ, et al.: Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *Journal of the American College of Cardiology 2014;63:1751-7.*

## Indications and Contraindications of LVAD Therapy

The pivotal role of LVAD is bridge to transplantation (BTT). In fact, it is recommended that all potential candidates for LVAD should be assessed for their transplant candidacy prior to implant.[12] Patients with more than 2 months of severe symptoms despite optimal medical and device therapy with at least two additional characteristics (Table 1) are considered as potential LVAD candidates to improve symptoms, reduce the risk of heart failure hospitalisation and the risk of premature death while on the heart transplant waiting list.[13] In patients who have contraindications for heart transplantation such as fixed pulmonary hypertension, significant renal impairment due to cardio-renal syndrome not responded to conventional therapy, recently treated malignancy, substance abuse and obesity, the use of LVAD therapy may potentially reverse or allow time to settle these situations and its use is termed bridge to candidacy (BTC). [13-15]

*Table 1.[13-15] Common Terminology used in Mechanical Circulatory Support or Left Ventricular Assist Device Therapy*

| Common Terminology used in Mechanical Circulatory Support or Left Ventricular Assist Device Therapy | | |
|---|---|---|
| BTT | Bridge to Transplant | Use of MCS (LVAD or BiVAD) to keep patient alive who is otherwise at high risk of death before transplantation until a donor organ becomes available |
| BTC | Bridge to Candidacy | Use of MCS (usually LVAD) to improve end-organ function in order to make an ineligible patient eligible for heart transplantation |
| DT | Destination Therapy | Long-term use of MCS (LVAD) as an alternative to transplantation in patients with end-stage HF ineligible for transplantation or long-term waiting for heart transplantation. |
| BTD/ BTB | Bridge to Decision/ Bridge to Bridge | Use of short-term MCS (e.g. ECLS or ECMO) in patients with cardiogenic shock until haemodynamics and end-organ perfusion are stabilised, contraindications for long-term MCS are excluded (brain damage after resuscitation) and additional therapeutic options including long-term VAD therapy or heart transplant can be evaluated. |
| BTR | Bridge to Recovery | Use of MCS (typically LVAD) to keep patient alive until cardiac function recovers sufficiently to remove MCS. |
| **Indication (Bridge to Transplantation [IIa-C] or Destination Therapy [IIa-B])** | | |
| More than 2 months of severe symptoms despite optimal medical and device therapy and more than one of the following characteristics:<br>1. left ventricular ejection fraction < 25% and, if measured, peak VO2 < 12 ml/kg/min;<br>2. more than or equal to 3 heart failure hospitalisations in the previous 12 months without an obvious precipitating cause;<br>3. dependence on intravenous inotropic therapy;<br>4. progressive end-organ dysfunction (worsening renal or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (pulmonary capillary wedge pressure > 20mmHg and systolic blood pressure <= 80-90mmHg or cardiac index <=2 L/min/m2); and<br>5. absence of severe right ventricular dysfunction together with severe tricuspid regurgitation. | | |
| **Indication to enable heart transplant (Bridge to Candidacy)** | | |
| 1. Pulmonary vascular resistance > 5 Woods units secondary to chronic heart failure not responded to conventional therapy and expected to reverse after LVAD<br>2. Glomerular filtration rate < 25-30 mL/min/1.73 m2 secondary to chronic heart failure and likely to improve after LVAD | | |
| ECLS: extracorporeal life support; ECMO: extracorporeal membrane oxygenation; HF: heart failure; LVAD: left ventricular assist device; VAD: ventricular assist device; MCS: mechanical circulatory support. | | |

Absolute or relative contraindications for LVAD therapy have been previously published and are summarised in Table 3. In general patients with active systemic infection or bacteraemia, severe bleeding tendency and terminal organ failure or malignancy with limited life expectancy are contraindicated for LVAD therapy. Patients with physical or psychosocial conditions that impair their ability to care or maintain LVAD devices after implantation should not receive LVAD therapy. Right ventricular function should be carefully assessed by echocardiography and cardiac catheterisation and optimised prior to LVAD implantation. Although

patients with hypertrophic cardiomyopathy and restrictive cardiomyopathies are generally considered not suitable for LVAD due to restricted left ventricular size, a single centre experience showed good results when LVAD is used in this group of patients. [12, 14-16]

LVAD therapy is also indicated in patients considered not heart transplant candidates as destination therapy (DT) to improve survival and quality of life.[6, 7, 17] General indications and contraindications for DT LVAD are the same as BTT. [13] (Table 1-2) Occasionally, LVAD therapy has been used as bridge to recovery (BTR) therapy such as in cases of myocarditis. However this indication accounts for less than 1% in the total population supported by LVAD therapy.[8]

*Table 2.*[12,14-15]

| Absolute Contraindications for Left Ventricular Assist Device (LVAD) |
|---|
| 1. Acute infective endocarditis or infection of cardiac implantable electronic devices with active bacteraemia |
| 2. Irreversible multi-organ failure; |
| 3. Confirmed cirrhosis or an increased Model for End Stage Liver Disease (MELD) score; |
| 4. Permanent dialysis unless suitable for combined heart-kidney transplantation |
| 5. Severe pulmonary dysfunction (FEV1 < 1 L or home oxygen dependent) |
| 6. Active malignancy and a life expectancy of less than 2 years; |
| 7. Active severe bleeding |
| 8. Active substance abusers (including alcohol); |
| 9. Neuromuscular disease or active psychiatric illness that severely compromises the ability to care for or maintain their device; |
| 10. Active pregnancy; or |
| 11. Poor compliance to medical recommendations |
| **Relative Contraindications for LVAD** |
| 1. Severe peripheral vascular disease; |
| 2. Recent or evolving stroke; |
| 3. Poor diabetes mellitus control with severe retinopathy, neuropathy, nephropathy, or vasculopathy; |
| 4. Psychosocial limitation including lack of any caregiver or living in an unsafe environment e.g. no secure electricity supply or homeless |
| 5. Morbid obesity with body mass index >=40 kg/m2; |
| 6. Severe malnutrition (body mass index < 21 kg/m2 in males and < 19 kg/m2 in female) |
| 7. Significant right ventricular dysfunction; |
| 8. Non-systolic heart failure with small ventricular chamber size. |
| 9. Mechanical ventilation |
| 10. Abdominal aortic aneurysm >=5cm |
| 11. Body surface area < 1.2-1.5 m2 or other dimensional or technical limitation |

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) sub-classified advanced heart failure into 7 stages (Table 3).[8, 13] More than 80% of patients implanted with continuous flow LVAD or biventricular VAD (BiVAD) belonged to the INTERMACS level 1-3 signifying they are either receiving inotropic therapy or in cardiogenic shock state. However, it is expected that patients in the most critical INTERMACS level 1 status had the poorest 1 year survival of about 53% compared to 80% 1-year survival rate in the overall LVAD population.[8, 13] This highlights the importance of timely recognition and referral.

The general trigger for referral depends on the recognition of advanced heart failure. Characteristic features of the advanced heart failure have been well defined and were shown in Table 4.[18] In addition, pulmonary hypertension not responding to treatment, progressive cardiac cachexia, refractory angina not amendable by medication and revascularisation, as well as refractory ventricular arrhythmia not amendable by conventional therapy should also trigger consideration of LVAD therapy. [14, 15]

## Potential complications

Gastrointestinal bleeding is common especially with continuous flow LVAD among which the bleeding rate was 63 per 100 patient-years compared to 6.8 per 100 patient-years in pulsatile flow LVAD.[19] Possible explanations include loss of pulsatility contributed to the development of arteriovenous malformations[20, 21] and development of acquired von Willebrand syndrome due to destruction of von Willebrand factors by the rotating components of the continuous flow LVAD.[22] On the other hand, pump thrombosis occurred in up to 10% of patients supported with LVAD in 6 months[17] that may require pump exchange if not responded to medical therapy. Infection of the driveline connecting the pump to the external power source is the Achilles heel of LVAD therapy which may end up with devastating pump infection requiring pump exchange, urgent heart transplantation or death. Both ischaemic and haemorrhagic strokes can occur after LVAD implantation and the incidence can be up to 10.9% while disabling strokes can be up to 6% in 6 months. Right heart failure occurred in about 25-30% LVAD recipients and remained a major source of short

*Table 3.*[8-13]

| INTERMACS stages | | NYHA | Description | 1 year survival with LVAD therapy | Percentage of continuous flow LVAD/BiVAD Implanted |
|---|---|---|---|---|---|
| 1 | Cardiogenic shock | IV | Haemodynamic instability in spite of increasing doses of catecholamine and/or mechanical circulatory support with critical hypoperfusion of target organs (severe cardiogenic shock) | 52.6% +/- 5.6% | 15% |
| 2 | Progressive decline | IV | Intravenous inotropic support with acceptable blood pressure but rapid deterioration of renal function, nutritional state, or signs of congestion. | 63.1+/- 3.1% | 37.5% |
| 3 | Inotropic dependent | IV | Haemodynamic stability with low or intermediate doses of inotropes, but necessary due to hypotension, worsening of symptoms, or progressive renal failure. | 78.4 +/- 2.5% | 28.8% |
| 4 | Resting symptoms | IV Ambulatory | Temporary cessation of inotropic treatment is possible, but patient presents with frequent symptom recurrences and typically with fluid overload | 78.7 +/- 3.0% | 13.7% |
| 5 | Exertion-intolerant | IV Ambulatory | Complete cessation of physical activity, stable at rest, but frequently with moderate fluid retention and some level of renal dysfunction | 93.0 +/- 3.9% | 2.7% |
| 6 | Exertion-limited | III | Minor limitation on physical activity and absence of congestion while at rest. Easily fatigued by light activity. | - | 1.2% |
| 7 | Advance NYHA III | III | Patient in NYHA class III with no current or recent unstable fluid balance. | - | 0.6% |

LVAD: Left ventricular assist device; BiVAD: Biventricular assist device

and long term morbidity and mortality.[17] Ventricular arrhythmia occurred more frequently in patients after LVAD implantation with 18.1% over 1 year period compared 5.8% among those on conventional therapy probably due to scar formation around the apical core created during LVAD implantation as well as mechanical irritation of the LVAD inflow cannula.[23] It is recommended that an implantable cardioverter defibrillator (ICD) should be implanted prior to and reactivated after LVAD implantation.[12]

*Table 4.*[18]

| Definition of Advanced Heart Failure |
|---|
| 1. Severe symptoms of heart failure with dyspnoea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV) |
| 2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral oedema) and/or of reduced cardiac output at rest (peripheral hypoperfusion) |
| 3. Objective evidence of severe cardiac dysfunction, shown by at least one of the following:<br>i. A low LVEF (< 30%)<br>ii. A severe abnormality of cardiac function on Doppler-echocardiography with a pseudonormal or restrictive mitral inflow pattern<br>iii. High LV filling pressures (mean PCWP > 16 mm Hg, and/or mean RAP > 12 mm Hg by pulmonary artery catheterisation)<br>iv. High BNP or NT-ProBNP plasma levels, in the absence of non-cardiac causes |
| 4. Severe impairment of functional capacity shown by one of the following:<br>i. Inability to exercise<br>ii. 6-MWT distance < 300 m or less in females and/or patients aged ≥75 years<br>iii. peak VO2 < 12 to 14 ml/kg/min |
| 5. History of ≥1 heart failure hospitalisation in the past 6 months |
| 6. Presence of all the previous features despite "attempts to optimise" therapy including diuretics, inhibitors of the renin–angiotensin–aldosterone system, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated |

Abbreviations: ACHF, advanced chronic heart failure; NYHA, New York Heart Association; LV, left ventricular; EF, ejection fraction; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; BNP, brain natriuretic peptide; NT, N-terminal; 6-MWT, 6-minute walk test; VO2, oxygen consumption; CRT, cardiac resynchronisation therapy.

## Current status in Hong Kong and Conclusion

The first LVAD implantation in Hong Kong was performed in August 2010 and since then 46 LVADs were implanted up to December 2016 with 42 BTT and 4 DT LVADs. Overall survival is excellent with 88.2% at 1 year 88.2% at 2 years and 73.2% at 4 years compared to benchmark survival of 80% at 1 year, 70% at 2 years and 48% at 4 years reported in the INTERMACS registry.[8] Currently, durable LVAD implantation is only for BTT indication as a life-saving strategy being eligible for reimbursement by the Hospital Authority. The indication of LVAD as DT LVAD is still as yet to be decided.

In conclusion, LVAD therapy has become the standard therapy for patients with advanced heart failure with very limited therapeutic options other than heart transplantation and palliative care. It can be used as bridge to transplant, bridge to candidacy, destination therapy and even as bridge to recovery. Timely recognition and referral of patients with advanced heart failure is the key to achieve the best outcome in this sick population.

*Table 5. Summary of clinical outcome of ventricular assist devices used as bridge to transplantation (BTT).*

| Study | Publish Year | Device | Sample Size | One-year Survival | Reference |
|---|---|---|---|---|---|
| HeartMate II Pivotal Trial | 2007 | HeartMate II | 133 | 68% | Miller LW, Pagani FD, Russell SD, et al.: Use of a continuous-flow device in patients awaiting heart transplantation. The New England journal of medicine 2007;357:885-96. |
| HeartMate II Pivotal Trial | 2009 | HeartMate II | 281 | 74% | Pagani FD, Miller LW, Russell SD, et al.: Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. Journal of the American College of Cardiology 2009;54:312-21. |
| Post Approval Study | 2011 | HeartMate II | 169 | 85% | Starling RC, Naka Y, Boyle AJ, et al.: Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). Journal of the American College of Cardiology 2011;57:1890-8. |
| Commercial versus Trial | 2011 | HeartMate II | 1469 | 85% | John R, Naka Y, Smedira NG, et al.: Continuous flow left ventricular assist device outcomes in commercial use compared with the prior clinical trial. The Annals of thoracic surgery 2011;92:1406-13. |
| HVAD ADVANCE BTT Study | 2012 | HeartWare Ventricular Assist Device (HVAD) | 140 | 86% | Aaronson KD, Slaughter MS, Miller LW, et al.: Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. Circulation 2012;125:3191-200. |

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# Radiology Quiz

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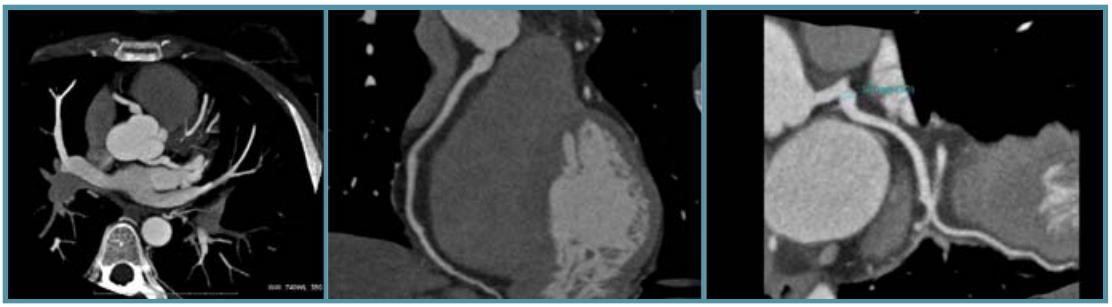

This is a 25-year-old lady with known cardiac conditions.
A CT coronary angiogram was performed for reassessment.

## Questions

1. What is the abnormality?
2. What is the most likely cause of such abnormality in this patient?
3. What will be the prognosis and management?

*(See P.39 for answers)*

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# Heart Transplant in Hong Kong

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Dr Cally HO

The Heart transplant programme began in Hong Kong in 1992. Under this programme the first heart transplant was performed by Professor Chi-keung MOK at the Grantham Hospital in December for a 55 year old patient who suffered from Ischaemic Cardiomyopathy. The operation was a success and the post-operative management proved to be flawless given the fact that the patient is still alive and has a reasonable quality of life up till today. In late 2008, the surgical side of the heart transplant programme relocated from the Grantham Hospital to the Queen Mary Hospital, along with the whole cardiothoracic surgical service unit. The remaining part of the heart transplant programme is still based in the Cardiac Medical Unit, Grantham Hospital. Most of the pre-transplant workup, assessments, education, postoperative care, cardiac rehabilitation and training of staff are still carried out there.

Since the programme's inception, a total of 179 heart transplants, 4 heart-lung transplants and 2 heart-liver transplants have been performed. During this period, heart transplant surgery has also evolved from the initial simple primary cardiac surgery to the highly complex re-operative surgery conducted nowadays. It involves more patients implanted with different kinds of mechanical circulatory support or left ventricular assist devices. During the last 3 years, nearly half of the heart transplant recipients had previous cardiac operations or left ventricular assist device/ mechanical circulatory support implanted.

Heart transplantation is generally reserved for patients with end-stage heart failure. They should have very poor ejection fraction ~10-15% on echocardiogram, with a functional status of NYHA class IV, despite the best medical or surgical therapy. Their pulmonary vascular resistance should not be higher than 5 Wood Units, and they should have no other end-organ malfunction or disease that would lead to a poor quality of life or a shorter life span. The most common cause of heart transplantation is Ischaemic cardiomyopathy followed by Idiopathic dilated cardiomyopathy. Other causes for heart transplant include valvular heart disease, congenital heart disease, arrhythmogenic right ventricular dysfunction, post-myocarditis and cardiac non-compaction.

The success of a heart transplant depends on appropriate donor selection and management. Maintaining optimum function of the donor heart is paramount. Most of the potential donors have succumbed to brain death and should be optimally managed in an intensive care unit so as to have the best chance to preserve the donor organs. Specifically for a heart donor, the most sophisticated monitoring should be available, like arterial line, central venous pressure line and even a Swan-Ganz catheter so that the volume status and cardiac output can be monitored and assessed continuously. Brainstem-dead donors often run into neuro-hormonal crisis that adversely affects the cardiovascular, endocrine and metabolic systems, such that hormonal replacement in these patients is essential and crucial to maintain the quality of the donor heart and thus its haemodynamics. Other than methylprednisolone, desmopressin, insulin and intravenous thyroxine should be given in order to benefit in organ retrieval. In Hong Kong, all potential heart donors should undergo echocardiographic assessment; and male donor > 40 years and female donor > 50 years, should have diagnostic coronary angiogram to rule out coronary artery disease before being accepted as a heart donor.

The fact that the donor heart functions well within the donor body does not mean it will function equally well in any recipient. Matching in heart transplantation is an art. Size matching is an extremely important process. Generally, larger donor graft to recipient is better. However, the donor's body surface area should better not be more than 20% larger than that of the recipient. Usually if the recipients' PA pressure or transpulmonary gradient is higher, a bigger size graft is required. Female to male donations should be limited. A better quality donor heart should be given to a poorer condition recipient so as to optimise the chance of survival after surgery.

During harvesting, the donor heart graft is preserved using standard strategies including decompression, local hypothermia with ice and antegrade delivery of Custodiol ® HTK solution to the aortic root. The ischaemic time of the donor heart also determines the initial function of the heart graft after implantation surgery. In Hong Kong, all donor hearts come from brainstem-dead donors from local hospitals. The harvesting team can usually bring the donor heart within one hour from any local hospital to Queen Mary Hospital, such that the total ischaemic time for the donor organ is reasonably short. However, for marginal donor hearts, like severe left ventricular hypertrophy, donor age >60 years old , minor coronary artery disease or high inotrope requirements, stringent control of the ischaemic time is essential for the initial successful return of the heart graft function early after surgery. This relies deeply on the close coordination between the harvesting team and the implanting team.

The surgical technique of heart transplantation surgery has not changed much. In the last 15 years, heart transplantation has been performed using the bicaval

technique. Recipients are put under general anaesthesia with haemodynamic monitoring (TEE, CVP and PA catheter). Median sternotomy incision is performed, followed by standard cardiopulmonary bypass with bicaval cannulation. The diseased heart is explanted after aortic cross-clamping with transection at the Superior vena cava (SVC) and Inferior vena cava (IVC), leaving behind the Left atrial (LA) cuff and two major arterial trunks, i.e. aorta and Pulmonary artery (PA). The donor heart implantation begins with LA cuff anastomosis followed by the aorta, PA, IVC and SVC anastomosis. Once completed, aortic reperfusion is resumed, temporary pacing wires are inserted, and the donor heart starts to beat. If the blood pressure generated by the new heart is adequate, bypass can be weaned. Perioperative inhaled nitric oxide is always ready for those patients with high PA pressure and marginal RV function.

Following transplant surgery, the patient needs several medications to prevent rejection and infection. Other than induction immunosuppressive therapy, in the immediate postoperative period, recipients are subjected to a maintenance dose of triple immunosuppressants including steroids, calcineurin-inhibitors and antimetabolites. They are followed-up with regular surveillance endomyocardial biopsy by our transplant cardiologist to look for rejections. All patients follow a regular cardiac rehabilitation programme in Grantham Hospital. They have to make some changes in their life-style after heart transplant because of the immunosuppressive status, even so, their quality of life improves and they usually re-integrate into the society after a short period of rehabilitation.

Heart transplant surgery is already a well-established and standardised treatment in Hong Kong for end stage heart failure patients. Despite this, early mortality is around 8-12%. Immediate cause of death is mainly attributed to primary graft failure, right heart dysfunction, uncontrolled sepsis and multi-organ failure. For those patients with post heart transplant graft failure or right heart failure, Extracorporeal Membrane Oxygenation (ECMO) therapy gives a chance of survival. In Hong Kong, after heart transplantation, the 5-year and 10-year survival rate is about 80% and 66% respectively.

Heart transplantation improves survival and enhances quality of life in heart failure patients. Like all the other countries in the world, the supply of donor hearts in Hong Kong is never able to meet the demand and as a result there has been an increase in the number of patients on transplant waiting lists as well as in the number of patients dying while on the waiting list. The death rate on the waiting list is more than 25% in Hong Kong. Because of this, the implantable Left Ventricular Assist Device (LVAD) programme has been implemented in Queen Mary Hospital since 2010, in order to buy time for those decompensated potential heart transplant recipients. Even after receiving an LVAD, the mean waiting time for the availability of a suitable donor heart is usually more than 3.5 years in Hong Kong. Until a more durable and a more ideal device is available in the market, the ultimate solution for all these end stage heart failure patients is still heart transplantation. And our team at Queen Mary Hospital is committed to continually endeavoring to improve the outcome of the heart transplant programme.

# Percutaneous Catheter-Based Treatment for Mitral Regurgitation for Heart Failure

**Dr Ryan KO**

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*Specialist in Cardiology*

Dr Ryan KO

Mechanical treatments to improve the pumping function of a failing heart have always been an attractive option in heart failure management. From guideline-indicated cardiac resynchronisation therapy (CRT) and left ventricular assisted device (LVAD) to recent developments in percutaneous ventricular restoration therapy using the parachute device[1]; we have made great strides in the past decade to improve contractile function of the diseased left ventricle (LV).

However, forward cardiac output requires competent valves. But yet, an important and common complication from a dilating left ventricle is ironically severe functional mitral regurgitation (FMR).

As oppose to degenerative mitral regurgitation (DMR) which only involves structural abnormalities with the valve leaflets or its subvalvular apparatus (such as a ruptured chordae), FMR results from a dysfunction of the supporting structures for the mitral valve complex. In a failing and dilated left ventricle, this process is often thought to begin with mitral annular dilatation, but it can also occur as a result of the increase in interpapillary muscle distance, asynchrony of papillary muscle contraction or tethering of the leaflets from tightened chordae[2]. The end result from the combination of these processes will lead to a failure of coaptation between the leaflets and thereby mitral regurgitation (MR).

Increasing FMR and its resulting decrease in forward cardiac output will lead to further increase in myocardial stress and damage. This will then result in further left ventricular dysfunction and therefore causes even more FMR. This perpetual FMR circle will ensure and accelerate the heart failure process and is therefore a logical target for therapy.

Unfortunately, management of severe FMR in heart failure patients had remained in an uncharted territory for many years, largely because of the lack of safe and effective treatment options. While open mitral valve (MV) repair surgery with annuloplasty are effective in reducing FMR, it carries significant morbidity and mortality; especially in patients with impaired LV function. Also, surgical series for the treatment of FMR have so far all been small and observational[3]. Therefore, given the unproven long term mortality benefit, open MV surgery can only be recommended in very carefully selected FMR patients before they deteriorate and stand at a prohibitive risk for open-heart surgery.

Introduction of the MitraClip technology in 2003 with the first-in-human implant quickly altered our thinking and shed new hope for heart failure patients with severe FMR. The MitraClip system is a first-in-class, fully percutaneous mitral valve repair technology (Fig 1). It gains access to the left atrium via a standard trans-septal puncture and by using a double clipping system, it grips on and creates a vertical line of coaptation between the anterior and posterior mitral valve leaflets. Modelling off the surgical technique of an edge-to-edge Alfieri stitch[4], the approximation of the leaflets by the MitraClip will form a double-orifice mitral valve allowing uninterrupted forward blood flow into the left ventricle, while effectively reduces mitral regurgitation. The procedure is done over a beating heart under trans-oesophageal echocardiogram guidance. This reduces the stress on the body and allowing patients to typically be discharged from the hospital within 1 to 2 days (Fig 2). The percutaneous nature of this mitral valve repair technique and its ability to 're-coapt' the mitral leaflets make the MitraClip technology extremely attractive in treating FMR patients.

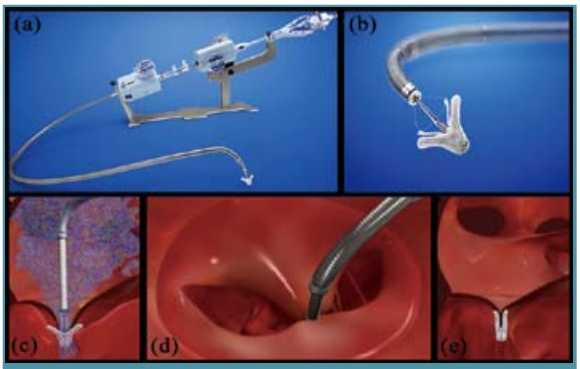


*Fig. 1*
*(a) MitraClip Clip Delivery System*
*(b) MitraClip device with grippers down and clip at 120°*
*(c) Animation of the MitraClip grasping the anterior and posterior mitral valve leaflet*
*(d) Animation of the MitraClip device in closed position*
*(e) Animation of MitraClip device deployed*

The MitraClip device has been well studied. The EVEREST II clinical trial[5] randomised patients with severe MR (both FMR and DMR) who were candidates for MV surgery to either the MitraClip device or conventional MV surgery (control group) in a 2-to-1 fashion respectively. Both the short and long term safety of the MitraClip device was clearly demonstrated. As expected with a percutaneous procedure, the 30 days major adverse events were significantly higher in the surgical group compared with the MitraClip group

(48% versus 15%); although mainly driven by the need for blood transfusion. Given these patients were all originally suitable candidates for open MV surgery, the mortality rate and the adverse events rate were noticeably low in both groups, but importantly not significantly different between both groups at 1 year through to 5 years.

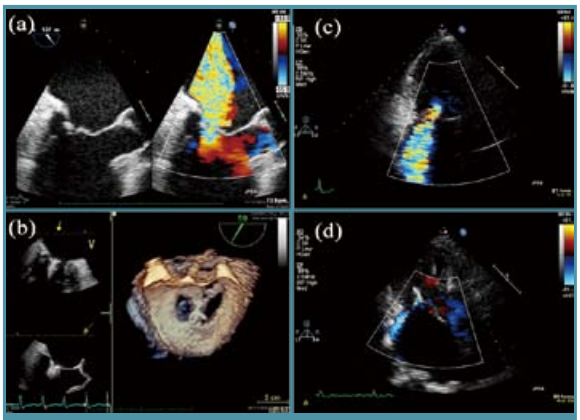


*Fig. 2*
*(a) Trans-oesophageal Echocardiogram (TOE) at Left Ventricular outflow tract view showing severe mixed degenerative and functional mitral regurgitation.*
*(b) TOE with real-time 3D imaging of the mitral valve viewed from the left atrium. A single MitraClip device is seen deployed creating a double orifice opening.*
*(c) Pre-MitraClip Trans-Thoracic Echocardiographic (TTE) image of the same patient.*
*(d) Post-MitraClip TTE image at 4 weeks after the procedure.*

In terms of clinical benefit, the trial was able to demonstrate durable MR reduction and significant improvements in left ventricular volumes and functional status (NYHA functional class improvements and reduced hospitalisation for heart failure) at 1 year, which was sustained through to 5 years. The result of this pivotal trial finally lead to the FDA (US Food and Drug Administration) approval of the MitraClip system for the indication of severe degenerative mitral regurgitation (DMR) in patients who are too high risk for open MV surgery.

Despite this FDA approval for use in DMR patients, we still do not have a definitive answer for the MitraClip device in patients with severe FMR. Only around a quarter of the patients in the Everest II trial were FMR patients and while numerous case series in recent years have shown improvements in functional class as well as evidence of reversed remodelling of the left ventricle in patients with FMR[6], we still do not have enough prospective randomise data. This is especially important; because as opposed to DMR which is a structural disease of the mitral valve, FMR is primarily a ventricular disease. Therefore, given the more complex pathology in patients with heart failure and severe FMR, whether the MitraClip device and its resulting MR reduction alone is enough to produce sustained clinical benefits remains inconclusive at this juncture.

Randomised controlled trials focusing on severe FMR patients are currently ongoing to answer this precise question. The 5 ongoing randomised trials have had slow recruitments, but the most promising one: The COAPT trial is close to 80% enrolled. It's aim is to randomise 610 patients with symptomatic heart failure and severe FMR in a 1-to-1 fashion, targeting a conservative primary endpoint of recurrent heart failure related hospitalisation within 2 years. The result of this trial is expected in the next few years.

Since its CE mark approval in 2008, the MitraClip has been implanted in over 35,000 patients worldwide with extremely high successful implant rates. Very different from clinical trial settings, the real world experiences have seen well over 60% of patients being treated for the off-label indication of severe FMR. There is clearly a large group of FMR patients, and they are often very sick, symptomatic and without many effective treatment options. The introduction of the MitraClip device in the past 8 years has certainly shed hope and if performed very early on in the heart failure process, it can often produce a long lasting beneficial effect for the failing heart.

One common criticism for the MitraClip is it is too simple a technology for a very structurally complex mitral valve. Surgical experiences have often stressed on the importance of an undersized annuloplasty ring to produce effective MR reduction. Therefore, percutaneous mitral annuloplasty techniques have also been a subject of intense research. Early experiences with coronary sinus devices were complicated with frequent coronary artery occlusions and was therefore unpopular. But more recent developments with the Cardioband device proves much more promising[7]. The ultimate goal of a totally percutaneous transcatheter mitral valve replacement is also in the horizon[8] and it is likely in the near future that the combination of these technologies will make up for a complete percutaneous mitral valve solution.

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# I Have a Date with the Starry Sky
# 我和星空有個約會

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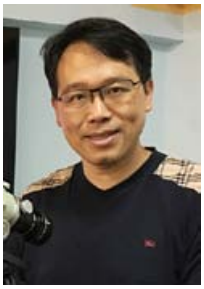

Dr Isaac Ngai-shing MOK

Recent few years have witnessed many youngsters chasing after the K-Pop stars. You may be surprised I have also become a star chaser not long ago – chasing the stars hanging in the night sky!

During my secondary school days at King's College I indulged in astronomy. Every other Friday night I joined the Astronomy Club to walk up the Kotewall Road from school for the star party in the Peak and saw many constellations with my naked eyes and celestial wonders through telescopes. I have seen the beautiful Jupiter with her red spot, the spectacular Saturn ring and the lunar eclipses, just to name a few. You cannot imagine how I spent the whole summer in Form 4 grinding a 6-inch lens at home for building a Newtonian telescope. Looking back, I am amazed by my own passion and stamina in learning astronomy during those years. Time flies and those were the days. Every time when I look up at the starry sky and recognise the long-forgotten constellations now, I reminisce about those precious and memorable moments I spent on star gazing.

I chose doctor as my career because practising medicine is a meaningful job that can save lives. But as an interventional cardiologist, I have to work round the clock to perform emergency angioplasty to save lives of patients from heart attacks. Although it brings me a lot of job satisfaction, it imposes much work stress on my life at the same time. The excessive clinical workload coupled with the heavy hospital administrative duties have stretched me to the limit. It made "Work Life Balance" become too far-fetched and unrealistic to me.

Recently I read with great interest the book 「星空獵人」 written by Mr Bill Yeung, the president of the Hong Kong Astronomical Society. Bill's extraordinary experience dawned on me and immediately rekindled my interest and passion in astronomy. Following a calling in his heart, Bill quitted his job and spent 6 years in his mobile observatory in the desert of Arizona chasing after the asteroids with his four 18-inch reflectors. With pluck and perseverance, he discovered over 2000 asteroids, ranking second in the world in terms of the number of asteroids discovered. His passion and commitment in his quest into the universe were indeed admirable and respectable. Inspired by Bill, I embarked on my star-chasing journey again to enjoy and appreciate the marvel and splendour of the extraterrestrial wonders. In December 2014, I saw the fascinating and entrancing aurora borealis (northern lights) in the Arctic Circle in Finland with my wife for the first time on our 20th wedding anniversary. In January 2015, the Comet Lovejoy approached Earth. I spent a few nights driving to Tai Au Mun after work to watch the comet with my naked eyes through a binocular. The excitement of this debut encounter with a comet was nothing short of meeting my first love! In December 2015, I led a group of church friends to see the spectacular Geminid meteor shower in CingJing, Taichung, 3000m above sea level. When the meteor shower peaked at midnight, we saw over 100 meteors radiating from the constellation of Gemini and flashing across the clear sky within an hour. It was just awesome and unforgettable.

Last year I learnt from some experienced astronomers in the Hong Kong Astronomical Society the ABC of taking star photos. After installing some basic equipment including a 6cm refractor , an equatorial mount for tracking stars, a tripod for the telescope, and a second-hand Canon EOSM mirrorless camera with its low pass filter replaced by a Baader BCF filter to capture the hydrogen alpha light from nebulae, I began my wonderful journey of astrophotography. In August 2016, my family and I visited Coonabarabran, the astronomy city in Australia. It is situated at the border of Queensland and New South Wales, about 7-hour drive from Brisbane or 6 -hour drive from Sydney. Coonabarabran has exceptionally long sunny days and no air or light pollution which makes her a perfect place for star gazing and astrophotography. It is the reason why the largest 4-metre Newtonian telescope in Australia was housed in the Siding Spring Observatory in Coonabarabran. We stayed in an Air B&B with a private observatory where we could use a 12.5-inch Newtonian telescope for free for star gazing under the guidance of the B&B owner Gary, who is a passionate amateur astronomer. For 2 consecutive nights, we witnessed and captured with our camera the spectacular winter Milky Way and celestial wonders of the Southern Hemisphere including the constellation of the Southern Cross, the Eta Carina Nebula and the Large and Small Magellanic Clouds. The appearance of a dazzling Perseid meteor fireball across the Southern sky in the second night was a bonus to our amazing star party in Coonabarabran.

I enjoy gazing stars in a dark and tranquil night and the feeling of being embraced by the universe during star gazing. In front of the immense universe I feel like I am no bigger than a grain of sand. She teaches me to be humble, not to care too much about success or failure and brings me peace of mind. Star gazing is actually a hobby ideal for relieving stress and getting rejuvenated. People say there are four astronomical phenomena we should never miss in our lifetime, namely, meteor shower, comet, northern lights and total solar eclipse.

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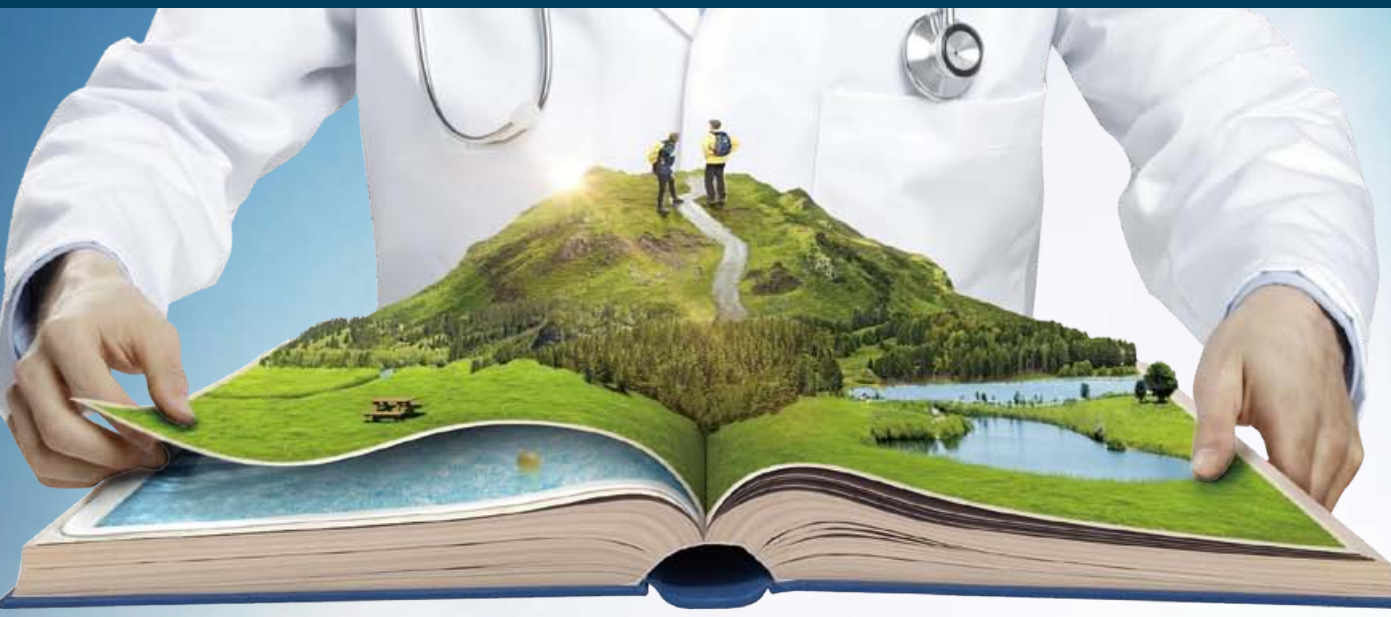

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In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias ◆**hyperglycemia with beta agonists:** clinically notable changes in blood glucose (4.1%) at the recommended dose than on placebo (2.3%), ULTIBRO BREEZHALER has not been investigated in patients for whom diabetes mellitus is not well controlled. **Women of child-bearing potential:** There are no special recommendations for women of child-bearing potential. **Pregnancy:** should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus. **Breast-feeding:** should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **Fertility:** reproduction studies or other data in animals did not reveal a problem or potential problem concerning fertility in either males or females. **Labor and delivery:** *Information related to indacaterol* - ULTIBRO BREEZHALER may inhibit labor due to a relaxant effect on uterine smooth muscle. **Interactions:** ◆No specific drug-drug interaction studies were conducted with ULTIBRO BREEZHALER. Information on the potential for interactions is based on the potential for each of its two components. ◆should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use ◆should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT-interval. Drugs known to prolong the QT-interval may Novartis Page 3 BSS ULTIBRO BREEZHALER increase the risk of ventricular arrhythmia. ◆concomitant administration of other sympathomimetic agents may potentiate the undesirable effects ◆concomitant treatment with methylxanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate the possible hypokalemic effect of beta2-adrenergic agonists. ◆inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses. ◆co-administration with other inhaled anticholinergic-containing drugs has not been studied and is therefore not recommended. ◆no clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of the organic cation transport. **Adverse reactions:** *Adverse reactions from ULTIBRO BREEZHALER* ◆**Uncommon (≥0.1 to <1%) and potentially serious:** Glaucoma, hypersensitivity, diabetes mellitus and hyperglycemia, ischemic heart disease, atrial fibrillation, paradoxical bronchospasm ◆**Very common (≥10%):** Upper respiratory tract infection ◆**Common (≥1% to <10%):** Nasopharyngitis, urinary tract infection, sinusitis, rhinitis, dizziness, headache, cough, oropharyngeal pain including throat irritation, dyspepsia, dental caries, gastroenteritis, musculoskeletal pain, pyrexia, chest pain ◆**Uncommon (≥0.1% to <1%):** Insomnia, paresthesia, tachycardia, palpitations, epistaxis, dry mouth, pruritus/rash, muscle spasm, myalgia, pain in extremity, bladder obstruction including urinary retention, peripheral edema, fatigue. **Packs and prices:** 30 Inhalation Powder Hard Capsules/Pack **Legal classification:** P1S1S3 Ref: EMA Oct 2013

**References: 1.** Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol–glycopyrronium versus salmeterol–fluticasone for COPD. N Engl J Med. 374;23:2222-2234. **2.** Ultibro® Breezhaler®. Summary of Product Characteristics. Oct 2015. **3.** Wedzicha JA, et al. Lancet Respir J 2013:1:199–209. **4.** Zhong NS, et al. Int J COPD 2015;10:1015-1026.

*Full Prescribing Information is available on request*

NOVARTIS
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ONCE DAILY
ultibro®
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indacaterol maleate/glycopyrronium bromide
inhalation powder

HK1610540846 Oct 2016

I am lucky to have already experienced the joy of eye-witnessing the first three. As for the last one, I am already planning to see and take images of the Great American Eclipse on 21 August 2017 near Yellow Stone National Park in USA to fulfil my dream! Indeed, life will not be complete without dreams and dreams are not the privilege of the younger generations. Between you and me, let me tell you that I have been dreaming of seeing the return of Comet Halley to Earth in 2062, the year of my 100th birthday! It will certainly be a perfect birthday gift for me to conclude my life-long terrestrial journey in star gazing.

So, what about you? What is your dream? It is never too late to pursue your dreams and make them come true.

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近幾年「韓風襲港」，認識幾位年青人對韓劇及 K-Pop 非常着迷，後來他們更變成了「追星一族」。最近我也加入了另類的「追星一族」，要追的卻不是韓星，而是天上的月亮星宿。

中學時期醉心於天文學，多少個星期五晚上隨天文學會從般含道出發沿旭龢道步行上山頂觀星，甚麼木星的大紅斑、土星的光環和月全蝕等天文現象很早就看過了。還記得中四那年用了整個暑假去磨製一塊直徑六吋的牛頓式反射望遠鏡片，回想起來那種對天文的熱情和那份傻勁，覺得有點可笑。時光荏苒，物換星移，現在每次抬頭望見天空中繁星點點和那些久違了的星座，總會憶起那些年登山觀星的愉快時光，教我回味無窮。

人家都說醫生拯救病人生命，濟世為懷，工作滿有意義，自己從醫亦是為了這個目標。但醫生的生涯絕不輕鬆，特別是當心臟科醫生經常要捱更抵夜，隨時候命替瀕死病人施行心臟介入手術，工作帶來很大的滿足感，但面對的工作壓力卻不足為外人道。因工作加上家庭的關係，很早就放下對天文學的追尋，觀星已經成了奢侈的玩意。在醫院裡繁重的臨床及行政工作就像排山倒海般接踵而來，令人透不過氣，而對經常掛在嘴邊的「工作與生活平衡」(Work Life Balance) 總是有點遙不可及的感覺。

最近拜讀了香港天文學會會長楊光宇先生所寫的「星空獵人」，精神為之一振，而對天文學那份冷卻了的熱情頓時被燃點起來。作者分享了他為了追尋小行星而放下工作，搬到亞到桑那州沙漠地帶建立流動天文臺，每天與四枱 18 吋口徑天文望遠鏡跟浩瀚的星空為伍，幾經困難和波折，六年間發現超過 2000 多顆小行星。他那份對追尋夢想的堅持和對天文觀測的全程投入，令我肅然起敬。受到作者的感召，我又從新踏上「追星」的行列，再次享受觀星和觀測各種天文現象的樂趣。大前年聖誕前我和太太到了芬蘭北極圈第一次親眼目睹了北極光的壯麗，畢生難忘。前年初彗星 Lovejoy 臨近地球，肉眼可見。記得當時每天都會將相機、望遠鏡和三腳架放在車廂內，每當放工時看到晴天，便會駕車到西貢大拗門追尋她的芳踪並拍下照片留念，第一次目睹彗星那種興奮的感覺就像初戀。同年十二月帶領教會朋友到清境觀賞雙子座流星雨，極大期時一小時內看到百多顆流星劃過清澈的台灣夜空，真教我們目瞪口呆、嘆為觀止。

去年年中我從香港天文學會前輩當中學了攝星技考的一招半式，並添置了一些攝星的基本器材，隨即踏上天文攝影的繽紛旅程。八月我和家人到澳洲旅行，因利成便我們駕車到了新南威爾斯和昆士蘭交界的澳洲天文之都庫納巴拉布蘭市 (Coonabarabran ) 觀星和攝星。Coonabarabran 得天獨厚，晴朗的日子特別多，又沒有光害和空氣污染，星空特別燦爛。我們租住在一間擁有私人天文台的旅館，可以免費利用屋主的一枝直徑十二吋半的牛頓反射式望遠鏡觀星，並得到他提供的私人觀星指導。那兩個晚上我們一次過目睹並拍下壯麗奪目的銀河和南半球獨有的星空奇觀，興奮和滿足之情，溢於言表，而當晚剛巧撞上英仙座流星雨的極大期，一顆燦爛奪目的火流星突然劃過長空，良久不散，為這觀星之旅錦上添花。

我享受在漆黑的靜夜裡觀星，融入天地的懷抱裡。面對穹蒼的浩瀚，人也變得渺小，她教曉我不用去執著成敗得失，幫我洗滌心靈，讓我豁然開朗。有人說一生中有四個不可錯過的天文現象，包括流星雨、彗星、北極光和日全蝕，前三個我有幸已經親眼看過了，我正計劃 2017 年 8 月 21 日到美國觀賞難得一見的日全蝕，達成我的夢想。人生不可以沒有夢想，而夢想也絕不是年青人的專利。靜靜地告訴你，我正夢想著 2062 年我 100 歲那年能親眼目睹哈雷彗星回歸地球呢！ 那你又有甚麼夢想呢？

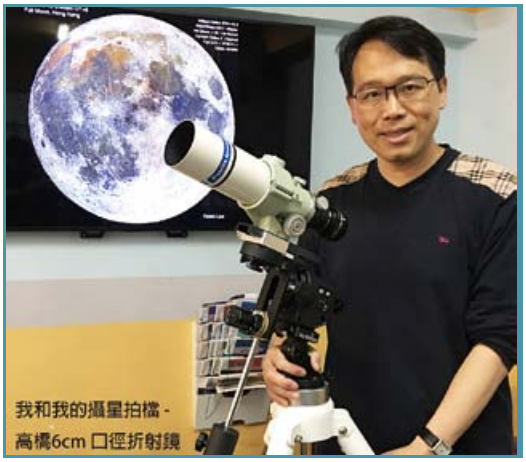
昨夜晴空萬里，我目睹了一輪明月和伴著她身旁的獵戶、大犬、雙子、御夫和金牛等星座，當我陶醉於與星月為伍之際，腦袋裡不期然響起盧冠廷用他那獨特的嗓子演譯著他的名曲「天籟 -- 星河傳說」 “……萬千的皎潔星座，圍著朗月分佈就座，在千秋不變星座，存著你或我……。”

萬籟俱寂，我再一次沉醉在美麗的星河中去追尋我的夢想。

***## For those of you who would like to enjoy star gazing and learn more about astronomy, I recommend you to download the following apps for free to your mobile phone:***

***## 你若有興趣追星可免費下載以下手機應用程式 (Apps) :***

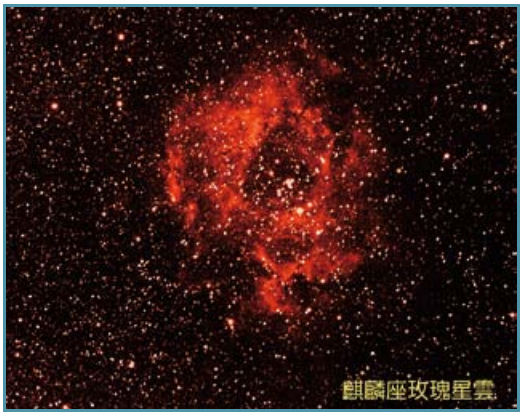
***(1) 星夜行 (2) 香港天文 (3) Stellarium (4) Sky Safari***


我和我的攝星拍檔 -
高標6cm 口徑折射鏡


澳洲Coonabarabran南方星流跡


獵戶座大星雲 M42


土星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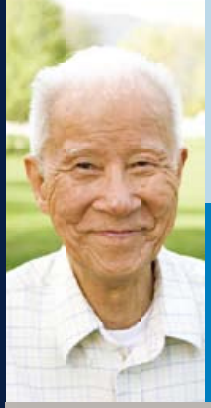
The only FDA-approved MRI portfolio for pacemaker, ICD, CRT-D, and ICM patients

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New opportunities to redefine the patient experience and reduce complications associated with traditional pacing technology.

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**51%**
Fewer Major Complications

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- No chest scar
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### Eliminated Pocket-related Complications

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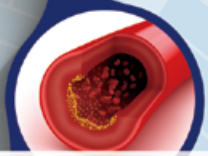
### Long-term Lead- and Pocket-related Complications with Traditional Systems

- Pocket-related complications **8% at 5 years**
- Lead-related complications **11% at 5 years**

| Sunday | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday |
|---|---|---|---|---|---|---|
| | | | | | | 1 |
| 2 | 3 | 4 | ★ HKMA Central, Western & Southern Community Network - Allergic Rhinitis and Obstructive Sleep Apnea<br>5 | ★ HKMA Hong Kong East Community Network - Imaging in Common Primary Malignancies & Comparison of US, CT, MRI and PET in Detecting Metastases<br>★ HKMA Kowloon East Community Network - The Benefit of HPV Prevention to Each Individual and Society<br>★ HKMA New Territories West Community Network - Updates in Diabesity Management<br>★ MPS Workshop - Mastering Shared Decision Making<br>6 | ★ HKMA Kowloon City Community Network - How New Basal Insulin Help DM Management in Private Practice?<br>7 | ★ Refresher Course for Health Care Providers 2016/2017<br>8 |
| 9 | 10 | ★ HKMA Yau Tsim Mong Community Network - Practical Tips in Managing Your Osteoporosis Patient<br>★ HKMA Kowloon West Community Network – Management in Diabetes with Renal Complication<br>★ FMSHK Officers' Meeting<br>★ HKMA Council Meeting<br>11 | ★ Hong Kong Neurosurgical Society Monthly Academic Meeting –Virtual Reality in Neurosurgery<br>12 | 13 | 14 | 15 |
| 16 | 17 | ★ HKMA Tai Po Community Network - Update on the Management of Hypertension<br>18 | 19 | ★ MPS Workshop - Mastering Difficult Interactions Patients<br>★ FMSHK Executive Committee Meeting<br>20 | 21 | 22 |
| 23 | | ★ HKMA Kowloon West Community Network – Updates on NOACs and Specific Reversal Agent<br>25 | ★ HKMA Central, Western & Southern Community Network - Management of DM Complications<br>★ MPS Workshop - Mastering Professional Interactions<br>26 | ★ HKMA Hong Kong East Community Network - Certificate Course on Diabetes Mellitus (Session 1) - Prevention of Microvascular Complication of DM<br>★ HKMA New Territories West Community Network - Updates in Joint Pain Management<br>★ FMSHK Foundation Meeting<br>27 | ★ HKMA Yau Tsim Mong Community Network - Clinical Update: Audiology & Speech Therapy for Older Adults - Topic 1: Audiology Service for Older Adults; Topic 2: Speech and Swallowing Therapy for Older Adults<br>28 | ★ MPS Workshop - Mastering Your Risk<br>29 |
| ★ HKMA Snooker Tournament 2017<br>30 | 24 | | | | | |

CNE/CME/CPD accreditations are in application



# British Medical Association (Hong Kong)

# Advance in Therapeutics Course 2017

**Date** : 8th May – 29th May, 2017 Every Monday Evening
**Time** : Light refreshments from 6:45 pm / Lecture: 7:15pm – 9:15pm
**Venue** : Asia Medical Specialists, 8/F China Building, 29th Queen's Road Central, Hong Kong

## 8th May - Oncology

**Cutting Edge on Radiotherapy**
**Dr Stephen Chun-key LAW**
*Specialist in Clinical Oncologist, HKSH Healthcare (Central)*

**Target Therapy & Cancer**
**Dr Chung-kong KWAN**
*Consultant, Department of Oncology, United Christian Hospital*

*Chairman – Dr Raymond See-kit LO, President of BMA (HK)*

## 15th May - Metabolic Health

**Cholesterol: How Low Can We Get?**
**Prof Brian TOMLINSON**
*Specialist in Internal Medicine & Clinical Pharmacology*
*Adjunct Professor, Department of Medicine and Therapeutics, The Chinese University of Hong Kong*
*Council Member of BMA (HK)*

**Facts and Uncertainties on Treatment of Diabetes**
**Dr Peter Chun-yip TONG**
*Specialist in Endocrinology, Diabetes & Metabolism*
*Qualigenics Medical*

*Chairman - Prof Bernard Man-yung CHEUNG*
*President of Hong Kong Pharmacology Society,*
*Hon Secretary of the Federation of Medical Societies of Hong Kong*

## 22nd May - Paediatrics

**Food Allergy: To Eat or Not To Eat ?**
**Dr Alson Wai-ming CHAN**
*Specialist in Paediatric Immunology & Infectious Diseases*
*Honorary Clinical Assistant Professor, Department of Paediatric & Adolescent Medicine, University of Hong Kong*

**Survival Guide for Family Doctors & Paediatricians on Frequently Encountered Paediatric Orthopaedic Problems - Fracture, Crooked Back & Deformed Limbs**
**Dr King-lok LIU**
*Specialist in Orthopaedics & Traumatology*
*Visiting consultant at hospitals in China*

*Chairman – Dr Adrian Young-yuen WU, Vice-President of BMA (HK)*

## 29th May - Geriatrics & Palliative Care

**Update on Management of Mild Cognitive Impairment**
**Prof Timothy C.Y. KWOK**
*Professor, Department of Medicine and Therapeutics, CUHK*
*Director of Jockey Club Centre for Positive Ageing*

**Advance Care Planning: What It Is & What It Isn't?**
**Dr Raymond See-kit LO**
*Specialist in Geriatric Medicine*
*Clinical Professor (Hon) Department of Medicine & Therapeutics, Chinese University of Hong Kong*

*Chairman – Prof Brian TOMLINSON, Council Member of BMA (HK)*

***Seats limited. Register early.***

**Free for BMA members** Join BMA as Ordinary or Associate member at $350 and course fees waived.
**For non-members** $50 registration fee per evening or $100 for 4 evenings.

**Enquiries and Registration:**
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The Federation of Medical Societies of Hong Kong

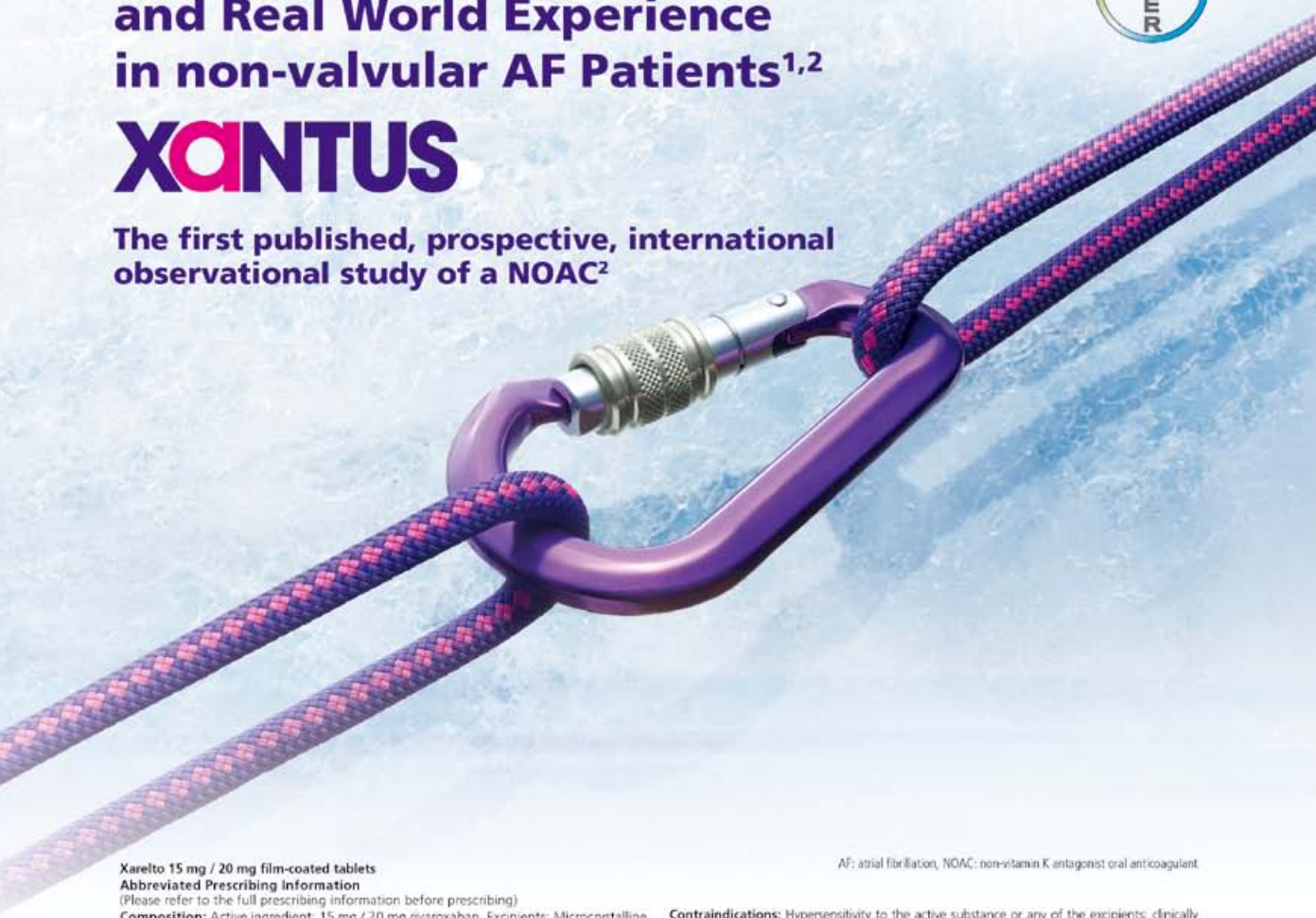
| Date / Time | Function | Enquiry / Remarks |
|---|---|---|
| **5 WED** 1:00 PM | **HKMA Central, Western & Southern Community Network - Allergic Rhinitis and Obstructive Sleep Apnea**<br>Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. POON Man Kay; Speaker: Dr. LAM Chung Mei, Jamie; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong | Mr. Ziv WONG<br>Tel: 2527 8285<br>1 CME Point |
| **6 THU** 1:00 PM | **HKMA Hong Kong East Community Network - Imaging in Common Primary Malignancies & Comparison of US, CT, MRI and PET in Detecting Metastases**<br>Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. GOH Kim Yeow; Speaker: Dr. Lawrence TEE; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| 1:00 PM | **HKMA Kowloon East Community Network - The Benefit of HPV Prevention to Each Individual and Society**<br>Organiser: HKMA Kowloon East Community Network; Chairman: Dr. CHU Wen Jing, Jennifer; Speaker: Dr. SIU Shing Shun, Nelson; Venue: Lei Garden Restaurant, Shop No. L5-8, APM, No. 418 Kwun Tong Road, Kwun Tong, Kowloon | Mr. Ziv WONG<br>Tel: 2527 8285<br>1 CME Point |
| 1:00 PM | **HKMA New Territories West Community Network - Updates in Diabesity Management**<br>Organiser: HKMA New Territories West Community Network; Chairman: Dr. TSUI Fung; Speaker: Dr. WU, Enoch; Venue: Plentiful Delight Banquet, 1/F, Ho Shun Tai Building, 10 Sai Ching Street, Yuen Long, N.T. | Mr. Ziv WONG<br>Tel: 2527 8285<br>1 CME Point |
| 6:30 PM | **MPS Workshop - Mastering Shared Decision Making**<br>Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. FUNG Shu Yan, Anthony; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong | HKMA CME Dept.<br>Tel: 2527 8452<br>2.5 CME Points |
| **7 FRI** 1:00 PM | **HKMA Kowloon City Community Network - How New Basal Insulin Help DM Management in Private Practice?**<br>Organiser: HKMA Kowloon City Community Network; Chairman: Dr. CHAN Man Chung, JP; Speaker: Dr. LAU Wing Yan, Winnie; Venue: President's Room, Spotlight Recreation Club (博藝會), 4/F., Screen World, Site 8, Whampoa Garden, Hunghom, Kowloon | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| **8 SAT** 2:15 PM | **Refresher Course for Health Care Providers 2016/2017**<br>Organiser: Hong Kong Medical Association; HK College of Family Physicians; HA-Our Lady of Maryknoll Hospital; Speaker: Dr. LAM Wing Wo; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon | Ms. Clara TSANG<br>Tel: 2354 2440<br>2 CME Points |
| **11 TUE** 1:00 PM | **HKMA Yau Tsim Mong Community Network - Practical Tips in Managing Your Osteoporosis Patient**<br>Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. HO Lap Yin; Speaker: Dr. WONG Sze Hung; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| 1:00 PM | **HKMA Kowloon West Community Network – Management in Diabetes with Renal Complication**<br>Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LEUNG Gin Pang; Speaker: Dr. WU, Enoch; Venue: Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T | Mr. Ziv WONG<br>Tel: 2527 8285<br>1 CME Point |
| 8:00 PM | **FMSHK Officers' Meeting**<br>Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong | Ms. Nancy CHAN<br>Tel: 2527 8898 |
| 9:00 PM | **HKMA Council Meeting**<br>Organiser: The Hong Kong Medical Association; Chairman: Dr. CHOI Kin; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong | Ms. Christine WONG<br>Tel: 2527 8285 |
| **12 WED** 7:30AM | **Hong Kong Neurosurgical Society Monthly Academic Meeting –Virtual Reality in Neurosurgery**<br>Organiser: Hong Kong Neurosurgical Society; Chairman: Dr PANG Kai Yuen; Speaker: Dr CHAN Shing Kit, Robert; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital | Name: Dr. LEE Wing Yan, Michael<br>Tel: 2595 6456 Fax. No.: 2965 4061<br>1.5 points<br>College of Surgeons of Hong Kong |
| **18 TUE** 1:45 PM | **HKMA Tai Po Community Network - Update on the Management of Hypertension**<br>Organiser: HKMA Tai Po Community Network; Chairman: Dr. CHOW Chun Kwan, John; Speaker: Dr. YAN Chun Ting; Venue: Chiuchow Garden Restaurant (潮江春), Shop 001-003, 1/F, Uptown Plaza, No. 9 Nam Wan Road, Tai Po, N.T. | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| **20 THU** 6:30 PM | **MPS Workshop - Mastering Difficult Interactions Patients**<br>Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. FUNG Shu Yan, Anthony; Venue: Eaton, Hong Kong, 380 Nathan Road, Kowloon | HKMA CME Dept.<br>Tel: 2527 8452<br>2.5 CME Points |
| 8:00PM | **FMSHK Executive Committee Meeting**<br>Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong | Ms. Nancy CHAN<br>Tel: 2527 8898 |
| **25 TUE** 1:00 PM | **HKMA Kowloon West Community Network – Updates on NOACs and Specific Reversal Agent**<br>Organiser: HKMA Kowloon West Community Network; Chairman: Dr. TONG Kai Sing; Speaker: Dr. TSANG Chi Yan, Vincent; Venue: Panda Hotel, 3 Tsuen Wah Street, Tsuen Wan, N.T | Mr. Ziv WONG<br>Tel: 2527 8285<br>1 CME Point |
| **26 WED** 1:00 PM | **HKMA Central, Western & Southern Community Network - Management of DM Complications**<br>Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. CHAN Hau Ngai, Kingsley; Speaker: Dr. WU, Enoch; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong | Mr. Ziv WONG<br>Tel: 2527 8285<br>1 CME Point |
| 6:30 PM | **MPS Workshop - Mastering Professional Interactions**<br>Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. LEE Wai Hung, Danny; Venue: Eaton, Hong Kong, 380 Nathan Road, Kowloon | HKMA CME Dept.<br>Tel: 2527 8452<br>2.5 CME Points |
| **27 THU** 1:00 PM | **HKMA Hong Kong East Community Network - Certificate Course on Diabetes Mellitus (Session 1) - Prevention of Microvascular Complication of DM**<br>Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. LAM See Yui, Joseph; Speaker: Dr. YEUNG Chun Yip; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |

| Date / Time | Function | Enquiry / Remarks |
|---|---|---|
| **27 THU** 1:00 PM | **HKMA New Territories West Community Network - Updates in Joint Pain Management**<br>Organiser: HKMA New Territories West Community Network; Chairman: Dr. TSANG Yat Fai; Speaker: Dr. WONG Sze Hung; Venue: Atrium Function Rooms, Lobby Floor, Hong Kong Gold Coast Hotel, 1 Castle Peak Road, Gold Coast, Hong Kong | Mr. Ziv WONG<br>Tel: 2527 8285<br>1 CME Point |
| 8:00PM | **FMSHK Foundation Meeting**<br>Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong | Ms. Nancy CHAN<br>Tel: 2527 8898 |
| **28 FRI** 1:00 PM | **HKMA Yau Tsim Mong Community Network - Clinical Update: Audiology & Speech Therapy for Older Adults - Topic 1: Audiology Service for Older Adults; Topic 2: Speech and Swallowing Therapy for Older Adults**<br>Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. HO Kit Man; Speaker: Ms. BOK Sze Wan, Cara; Ms. NG Wing Yee, Cymie; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon | Ms. Candice TONG<br>Tel: 2527 8285<br>1 CME Point |
| **29 SAT** 2:30 PM | **MPS Workshop - Mastering Your Risk**<br>Organiser: The Hong Kong Medical Association & Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong | HKMA CME Dept.<br>Tel: 2527 8452<br>2.5 CME Points |
| **30 SUN** 2:00 PM | **HKMA Snooker Tournament 2017**<br>Organiser: The Hong Kong Medical Association; Venue: Youth Billiard Club, LG/F, Houston Centre, 63 Mody Road, Tsim ShaTsui East, Kowloon | Miss Ada SIU/<br>Miss Denise KWOK<br>Tel: 2527 8285 |

# Confidence from Evidence and Real World Experience in non-valvular AF Patients[1,2]

# XANTUS

## The first published, prospective, international observational study of a NOAC[2]



AF: atrial fibrillation, NOAC: non-vitamin K antagonist oral anticoagulant

**Xarelto 15 mg / 20 mg film-coated tablets**
**Abbreviated Prescribing Information**
(Please refer to the full prescribing information before prescribing)

**Composition:** Active ingredient: 15 mg / 20 mg rivaroxaban. Excipients: Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate, macrogol 3350, titanium dioxide (E171), iron oxide red (E172).

**Indication:** Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

**Posology:**
*Prevention of stroke and systemic embolism*
Recommended dose is 20 mg once daily, which is also the recommended maximum dose.
*Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE*
The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE.

**Renal impairment**
No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min).
In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily.
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 20 mg once daily.
- Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased; therefore, Xarelto is to be used with caution in these patients.
- Use is not recommended in patients with creatinine clearance < 15 ml/min.

**Hepatic impairment**
Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.

**Contraindications:** Hypersensitivity to the active substance or any of the excipients; clinically significant active bleeding; pregnancy and breast feeding.

**Warnings and Precautions:** Not recommended: in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- and P-gp-inhibitors, i.e. azoleantimycotics or HIV protease inhibitors; in patients with severe renal impairment (creatinine clearance < 15 ml/min); in the treatment of acute pulmonary embolism; due to lack of data: in patients below 18 years of age, in patients with prosthetic heart valves, in patients concomitantly treated with dronedarone. Use with caution: in patients with severe renal impairment (creatinine clearance 15 – 29 ml/min) or with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicinal products affecting haemostasis or with strong CYP3A4 inducers; in patients with increased bleeding risk. In patients at risk of ulcerative gastrointestinal disease prophylactic treatment may be considered. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Specific dose recommendations apply for patients with moderate to severe renal impairment. Xarelto contains lactose.

**Undesirable effects:** Common: anaemia, dizziness, headache, syncope, eye haemorrhage, tachycardia, hypotension, haematoma, epistaxis, gastrointestinal tract haemorrhage, gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, pain in extremity, urogenital tract haemorrhage, fever, peripheral oedema, decreased general strength and energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. Uncommon: thrombocythemia, allergic reaction, dermatitis allergic, cerebral and intracranial haemorrhage, haemoptysis, dry mouth, hepatic function abnormal, urticaria, cutaneous and subcutaneous haemorrhage, haemarthrosis, renal impairment, feeling unwell, localised oedema. Increases in: bilirubin, blood alkaline phosphatase, LDH, lipase, amylase, GGT. Rare: jaundice, muscle haemorrhage, bilirubin conjugated increased. Frequency not known: pseudoaneurysm following percutaneous intervention, compartment syndrome or (acute) renal failure secondary to a bleeding.

**References: 1.** Patel M.R., Mahaffey K.W., Garg J. et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–891. **2.** Camm J., Amarenco P., Haas S. et al. XANTUS: A Real-World, Prospective, Observational Study of Patients Treated with Rivaroxaban for Stroke Prevention in Atrial Fibrillation. Eur Heart J. 2015;[ePub ahead of print].

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LHK.MKT.06.2016.1150

Xarelto® rivaroxaban

## Answers to Radiology Quiz

**Answer:**

Case of Kawasaki disease with coronary artery involvement.

1. Aneurysms are present at the proximal left circumflex artery (LCX) and right coronary artery (RCA).

2. Kawasaki disease is the most common cause of coronary artery aneurysms, particularly in children. Other possible aetiologies include polyarteritis nodosa, systemic lupus erythematosus, atherosclerosis, trauma and iatrogenic causes.

3. Kawasaki disease is an acute vasculitis of childhood affecting small to medium sized vessels, with predilection for the coronary arteries.

   Diagnostic criteria established by the American Heart Association (AHA) are fever for at least 5 days and ≥4 of the 5 major clinical features: oedema or redness of extremities, conjunctival injection, polymorphous rash, oral mucosal changes and cervical lymphadenopathy.

   It is generally self-limiting yet its cardiovascular sequelae are the leading cause of morbidity, with the primary concern being coronary artery aneuryms (CAA), which could develop in 15-25% of untreated children. CAA are more frequently noted at the proximal segments. Aneurysms in the RCA are more prone to massive thrombosis, whereas those in the left coronary artery (LCA) are more prone to progressive focal stenosis.

   Angiographic spontaneous resolution may occur in about 50% of CAA, usually in small aneurysms. Treatment with high dose intravenous gamma globulin combined with aspirin has been proved to be highly effective in reducing the clinical manifestations as well the prevalence of CAA to less than 5%. However, about 10% of patients do not respond favourably to this treatment and therefore long term monitoring becomes important as they are at increased risk of developing CAA.

   Cardiac imaging plays an important role in evaluating patients with Kawasaki disease. The coronary anomalies should be evaluated as soon as possible after the acute phase in order to predict disease progression and for management planning. Cardiac CT and MR provide a non-invasive and reliable means to assess cardiovascular complications, as well as for long term follow-up especially after childhood.

### References

1. *Chung C, Stein L. Kawasaki disease: a review. Radiology. 1998;208:25–33.*
2. *Duarte, Ricardo et al. Kawasaki Disease: A Review with Emphasis on Cardiovascular Complications. Insights into Imaging 1.4 (2010): 223–231.*
3. *Friedman et al. Coronary Artery Aneurysms in Kawasaki Disease: Risk Factors for Progressive Disease and Adverse Cardiac Events in the US Population. Am Heart Assoc 2016 Sep 15;5(9).*
4. *Dahnert. Radiology Review Manual 7th edition.*

**Dr Grace Hoi-ting NG**
MBChB (CUHK), FRCR
*Department of Radiology, Queen Mary Hospital*

Feburic
(febuxostat)

# A new and simple way

to target sUA ≤ 6mg/dL[1]

6 mg/dL

Potent urate-lowering effect in achieving serum uric acid (sUA) levels of 6.0 mg/dL[1], which can reduce gout flares eventually to zero on long-term treatment.[2]

No dosage adjustment is necessary in patients with mild to moderate renal impairment.[3]

Renoprotective effect was shown in clinical studies.[4, 5]


Reference :
1. Becker MA et al. N Engl J Med 2005;353(23):2450-2641 2. Schumacher HR Jr. et al. Rheumatology 2009;48:188-194
3. FEBURIC®HK packaging Insert May 2014 4. Sezai A et al. Circ J 2013; 77 (8):2043-2049 5. Tanaka K et al. Clin Exp Nephrol. 2015 Dec; 19(6):1044-53


**FEBURIC® 80mg Abridged Prescribing Information**
**Indication:** Chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus &/or gouty arthritis.) **FEBURIC®** is indicated in adults. **Dosage and Adminstration**: 80 mg once daily. May be taken w/o regard to food or antacid use. **Contraindications**: Hypersensitivity. Pregnancy & lactation. **Special Precautions**: Ischaemic heart disease, Congestive heart failure, rare serious hypersensitivity reactions, gout flare, malignant disease, Lesch-Nyhan syndrome. Concomitant mercaptopurine, azathioprine, theophylline. Altered thyroid function. Organ transplantation. Galactose intolerance, glucose-galactose malabsorption, Lapp lactase deficiency. Severe renal impairment. Moderate to severe hepatic impairment. May impair ability to drive or operate machinery. Childn & adolescents. **Adverse Reactions**: Gout flares, headache, diarrhoea, nausea, rash, oedema, liver function test abnormalities. **Interactions**: Mercaptopurine, azathioprine, NSAIDs, probenecid, glucuronidation inducer.

(Full prescribing information is available upon request)



**Astellas Pharma Hong Kong Co., Ltd.**
Unit 1103-1108, 11/F, Tower 1, Grand Century Place,
193 Prince Edward Road West, Mongkok, Kowloon, Hong Kong
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# Betmiga®
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THE 1ST $\beta_3$-AGONIST FOR OAB* PATIENTS
WITH PROMISING SAFETY PROFILE
**PLACEBO-LIKE DRY MOUTH(1.7%) SIDE EFFECT**[1]

# Harnal OCAS®
tamsulosin

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

# YOUR POWERFUL 1ST LINE PHARMACOLOGICAL OPTIONS FOR LUTS+ MANAGEMENT[3,4]


*OAB: Overactive Bladder + LUTS: Lower Urinary Tract Symptoms

Reference: **1.** Chapple C.R. et al. Neurourol Urodynam 2013 [doi 10.1002/nau22505] **2.** Chapple C.R. et al. Eur Urol Supp. 2005; 4:33-44 **3.** Guidelines on the Management of Non-Neurogenic Male LUTS. European Association of Urology. 2015. **4.** DIAGNOSIS AND TREATMENT OF OVERACTIVE BLADDER (Non-Neurogenic) IN ADULTS: AUA/SUFU GUIDELINE. American Urological Association. 2014.

**HARNAL OCAS® Abridged Prescribing Information** **I:** Lower urinary tract symptoms (LUTS) associated w/ benign prostatic hyperplasia (BPH). **D:** 0.4mg once daily. **A:** Can be taken with or without food. Swallow whole, do not chew/divide/crush. **C:** Hypersensitivity. **AR:** Common: Dizziness (1.3%), ejaculation disorder. **Full prescribing information is available upon request.**

**BETMIGA® Abridged Prescribing Information** **I:** Symptomatic treatment of urgency, increased micturition frequency &/or urgency incontinence as may occur in adults w/ overactive bladder (OAB) syndrome. **D:** Adult including elderly 50 mg once daily. **A:** Swallow whole. Do not chew/divide/crush. **C:** Hypersensitivity. Severe uncontrolled hypertension. **AR:** Common: Urinary tract infection, tachycardia, nausea. **Full prescribing information is available upon request.**

**Astellas Pharma Hong Kong Co., Ltd.** Unit 1103-08, 11/F, Tower 1, Grand Century Place, 193 Prince Edward Road West, Mongkok, Kowloon. Tel: (852) 2377 9801 Fax: (852) 2856 1440

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Once-daily
# TRESIBA®
ULTRA-LONG
DURATION OF ACTION[3,4]


# GET HbA1c DOWN WITH CONTROL

- **Successful reductions in HbA$_{1c}$**[1,2]
- **Lower risk of nocturnal hypoglycaemia versus glargine U100**[1,2*]
- **Flexibility in day-to-day dosing time when needed**[3*]

...delivered in a once-daily dose.

## Abbreviated prescribing information

**Tresiba® (insulin degludec) 100U (100 units/mL insulin solution for injection) in a prefilled pen (FlexTouch®) Consult Summary of Product Characteristics before prescribing.Presentation:** Tresiba® FlexTouch®. All presentations contain insulin degludec. Tresiba® 100 units/mL – 1 mL of solution contains 100 units insulin degludec (equivalent to 3.66 mg). One pre-filled device contains 300 units of insulin degludec in 3 mL solution. **Indications:** Treatment of diabetes mellitus in adults. **Posology and administration:** Tresiba® is a basal insulin for once-daily subcutaneous administration at any time of the day, preferably at the same time of day. On occasions when administration at the same time of the day is not possible, Tresiba® allows for flexibility in the timing of insulin administration. A minimum of 8 hours between injections should be ensured. In patients with type 2 diabetes mellitus, Tresiba® can be administered alone, in combination with oral anti-diabetic medicinal products as well as in combination with bolus insulin. In type 1 diabetes mellitus, Tresiba® is to be used with short-/rapid-acting insulin. Administration by subcutaneous injection only. Tresiba® is available in 100 units/mL. For Tresiba® 100 units/mL a dose of 1–80 units per injection, in steps of 1 unit, can be administered. When initiating patients with type 2 diabetes mellitus the recommended daily starting dose is 10 units. Transferring from other insulins; in type 2 diabetes changing the basal insulin to Tresiba® can be done unit-to-unit, based on the previous basal insulin component; in type 1 diabetes the same applies apart from where transferring from twice-daily basal insulin or patients with an HbA1c <8.0%, the Tresiba® dose needs to be determined on an individual basis with a dose reduction considered. Doses and timing of concomitant treatment may require adjustment. In all cases doses should be adjusted based on individual patients' needs; fasting plasma glucose is recommended to be used for optimising glycaemic control. In elderly patients and patients with renal/hepatic impairment glucose monitoring should be intensified and the dose adjusted on an individual basis. Tresiba® comes in a pre-filled pen, FlexTouch®, designed to be used with NovoFine®/NovoTwist® needles. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Special warnings and precautions:** Too high insulin dose, omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. Reduction of warning symptoms of hypoglycaemia may be seen upon tightening control and also in patients with long-standing diabetes. Administration of rapid-acting insulin recommended in situations with severe hyperglycaemia. Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement. Transferring to a new type, brand or manufacturer of insulin should be done under strict medical supervision. When using insulin in combination with pioglitazone, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs. Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between the two strengths of Tresiba® and other insulins. Hypoglycaemia may constitute a risk when driving or operating machinery. **Pregnancy and lactation:** There is no clinical experience with use of Tresiba® in pregnant women and during breastfeeding. Animal reproduction studies with insulin degludec have not revealed any adverse effects on fertility. **Undesirable effects:** Refer to SmPC for complete information on side effects. Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1.000 to < 1/100); rare (≥ 1/10.000 to < 1/1.000); very rare (< 1/10.000); not known (cannot be estimated from the available data). Very common: Hypoglycaemia. Common: Injection site reactions. Uncommon: Lipodystrophy and peripheral oedema. Rare: Hypersensitivity and urticaria. With insulin preparations, allergic reaction may occur; immediate-type allergic reactions may potentially be life threatening. Injection site reactions are usually mild, transitory and normally disappear during continued treatment.

* Applies to the adult population only

**References: 1.** Rodbard HW, *et al.* on behalf of the BEGIN Once Long Trial Investigators. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. *DIABETIC Medicine* 2013;30(11):1298–304. **2.** Bode BW, *et al.* on behalf of the BEGIN Basal–Bolus Type 1 Trial Investigators. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal–bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN Basal–Bolus Type 1): 2-year results of a randomized clinical trial. *DIABETIC Medicine* 2013;30(11):1293–297. **3.** Tresiba® Packing Insert. **4.** Jonassen I, *et al.* Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. *Pharmaceutical Research.* 2012;29(8):2104-2114.




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