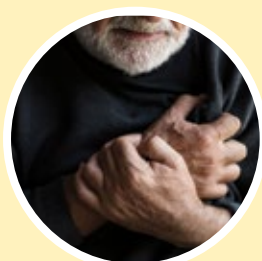
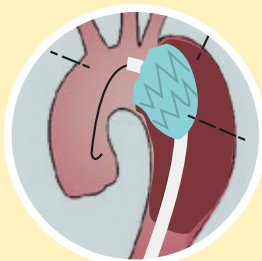


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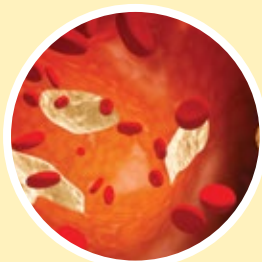
A publication of  
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Singapore (NHCS)



**TRANSTHYRETIN  
CARDIAC  
AMYLOIDOSIS:  
THE  
UNDERDIAGNOSED  
DISEASE**



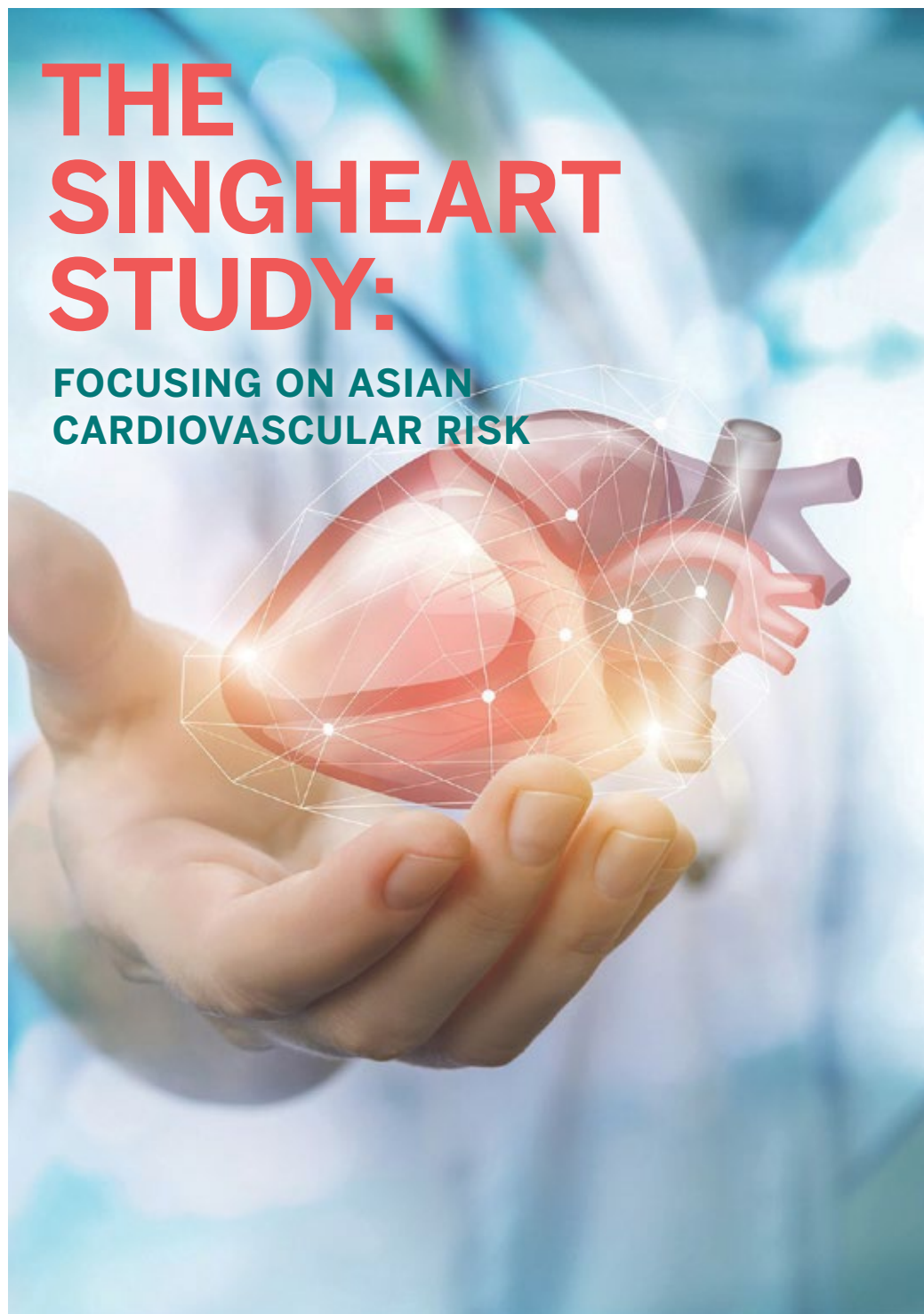
**EMERGING  
MINIMALLY INVASIVE  
SURGERY FOR  
AORTIC REPAIR**



**ALL YOU NEED  
TO KNOW ABOUT  
ANTICOAGULANTS**

## THE SINGHEART STUDY:

**FOCUSING ON ASIAN  
CARDIOVASCULAR RISK**



# THE SINGHEART STUDY:

## FOCUSING ON ASIAN CARDIOVASCULAR RISK

By Assoc Prof Yeo Khung Kheong, Senior Consultant, and Dr Kenneth Chew, Senior Resident, Department of Cardiology



To develop precise prevention, diagnosis and treatment plans for heart diseases in Asians, NHCS researchers are examining the genetics of local multi-ethnic population and more.

**H**eat disease is a modern epidemic, with cardiovascular disease as a leading cause of death in Singapore, contributing close to 30% of total mortality in 2018<sup>1</sup>. Similarly, this trend is noted globally with significant worldwide contribution towards morbidity and mortality.

The current understanding of heart diseases has evolved into a multi-factorial one, encompassing genetic programming, epigenetics, lifestyle (including fitness, physical activity and diet) and clinical 'phenotype' (such as a positive electrocardiogram (ECG) test or a cardiac magnetic resonance imaging (MRI) scan of a structurally abnormal heart.

Correspondingly, conventional knowledge of predisposing risk factors for cardiovascular disease had been derived from large, prospective, population based studies in Western cohorts, such as the landmark Framingham Heart Study<sup>2</sup>, from which total cholesterol (comprising low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)), blood pressure, smoking, diabetes and

age were identified as risk factors in a population free from overt coronary heart disease.

### Lack of Data in Asian Ethnic Groups

Ethnicity, with its accompanying differences in culture and diet, has long been known to be a contributing factor towards cardiovascular conditions. An example is the penchant of heart failure with preserved ejection fraction in younger Asians with multiple comorbidities<sup>3</sup>. With various other clear evidence on a unique Asian disease profile, further and advanced research is needed.

In the West, attempts have been made to improve traditional understanding of cardiovascular risk factors and include a wider array of patients, such as the Pooled Cohort, a key contemporary study group from the United States and from which the 2013 American College of Cardiology/ American Heart Association (ACC/AHA)'s Atherosclerotic Cardiovascular Disease risk calculator was derived from.

Despite these attempts, the ACC/AHA 2013 Prevention Guideline highlighted areas of need, such as the insufficient study data on non-white or non-African American ethnic groups, alternative risk factors and novel biomarkers.

### Reviewing the Unique Asian Profile

Recognising the gap in research on Asian ethnic groups, the SingHEART study aims to shed light on our uniquely Asian population, elucidating at risk groups and informing the wider medical community on risk reduction. Significantly, it will help clinicians and scientists understand the interaction on genes and lifestyle, for the causes of heart diseases.

SingHEART is led by Assoc Prof Yeo Khung Keong, Senior Consultant from Department of Cardiology at the NHCS, and uses the NHCS Biobank, which tracks the health of local participants between the ages of 18 and 65 from all ethnic groups in Singapore.

The SingHEART study also partners with SingHealth Duke-NUS Institute of Precision Medicine (PRISM), to perform the complex genetic and metabolomic analyses in the study. PRISM, led by Prof Patrick Tan, is a joint institute between SingHealth and Duke-NUS Medical School to develop precise medical therapy for each individual patient, using a combination of genetics and other advanced technologies.

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### NON-INVASIVE CARDIAC IMAGING, ECHOCARDIOGRAPHY AND NUCLEAR CARDIOLOGY

NHCS offers a comprehensive range of investigations to detect cardiovascular problems including the latest gamma camera technology for heart scans which reduces scanning time by 75 per cent, and a 320-slice cardiac computed tomography which reduces radiation exposure in heart scan machine by 90 per cent.

### OUR SPECIALISTS

Prof Terrance Chua Siang Jin	Senior Consultant, Medical Director
Assoc Prof Ding Zee Pin	Senior Consultant, Advisor of Echocardiography
Assoc Prof Ewe See Hooi	Senior Consultant, Director of Echocardiography
Assoc Prof Felix Keng Yung Jih	Senior Consultant, Director of Nuclear Cardiology
Assoc Prof Tan Ju Le	Senior Consultant, Director of Adult Congenital Heart Diseases
Assoc Prof Tan Swee Yaw	Senior Consultant, Director of Cardiovascular Rehabilitation & Preventative Cardiology
Asst Prof Calvin Chin Woon Loong	Senior Consultant, Deputy Director of Cardiac Magnetic Resonance Imaging
Assoc Prof Sahlen Anders Olof	Senior Consultant
Assoc Prof Tan Ru San	Senior Consultant
Asst Prof Angela Koh Su-Mei	Senior Consultant
Asst Prof Kurugulasigamoney Gunasegaran	Senior Consultant
Asst Prof Lee Chung Yin	Senior Consultant
Asst Prof Tang Hak Chiaw	Senior Consultant
Asst Prof Jeffrey Lau Man Chu	Consultant
Asst Prof Laura Chan Lihua	Consultant
Asst Prof Lohendran Baskaran	Consultant
Asst Prof Louis Teo Loon Yee	Consultant
Asst Prof See Chai Keat	Consultant
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Dr Khoo Chun Yuan	Consultant
Dr Lee Phong Teck	Consultant
Dr Mohammed Rizwan Amanullah	Consultant
Dr Ng Choon Ta	Consultant
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Dr Huang Zijuan	Associate Consultant
Dr Ignasius Aditya Jappar	Associate Consultant
Dr Koh Choong Hou	Associate Consultant
Dr Natalie Koh Si Ya	Associate Consultant

For the full list of NHCS services and specialists,  
please visit [www.nhcs.com.sg](http://www.nhcs.com.sg).

## The SingHEART study has a threefold objective:



To characterise cardiovascular health specifically in Asians.



To assess and validate pre-existing biomarkers (lipid markers, family history), measurements of cardiorespiratory fitness, and imaging studies identifying subclinical cardiovascular disease, all in Asian populations.



To use both traditional statistical analysis and newer data analytics (machine learning).

## The SingHEART Study – A Unique Asian Study

SingHEART is the first population-based study in Asia, which involves a multi-ethnic, healthy Asian population, and uses the latest technologies – including genomics, lipidomics, advanced imaging, wearable data and data analytics. Its target is to recruit 5,000 patients based on feasibility and funding availability.

As of December 2019, more than 920 patients have been recruited.

The SingHEART programme welcomes any forms of public participation or support such as study volunteers or funding. Such contributions will provide significant impact and help future generations have better and healthier lives through breakthrough prevention, diagnosis and treatment plans for heart diseases.

<sup>1</sup>Principle Causes of Death. Ministry of Health, Singapore. [www.moh.gov.sg](http://www.moh.gov.sg). 2018.

<sup>2</sup>Wilson PWF et al. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97:1837-47.

<sup>3</sup>Tromp J et al; ASIAN-HF Investigators. Heart failure with preserved ejection fraction in Asia. *European Journal of Heart Failure* (2019) 21, 2336

## TRANSTHYRETIN (TTR) CARDIAC AMYLOIDOSIS

# THE UNDERDIAGNOSED DISEASE

Cardiac amyloidosis is a form of disorder that is caused by deposits of amyloids (abnormal proteins) in the heart tissue, resulting in heart not being able to work properly. Light chain (AL) and transthyretin (TTR) are the two most common and clinically relevant amyloid that infiltrate the heart. TTR amyloid (ATTR) mainly deposits in heart muscles and nerves. There are two types of ATTR – hereditary or mutant (ATTRm) and wild type (ATTRwt).

Department of Cardiology

By Asst Prof Tang Hak Chiaw, Senior Consultant,  
Department of Cardiology

**T**ypically, in TTR cardiac amyloidosis, there will be left ventricular (LV) thickening that resembles hypertensive heart disease or hypertrophic cardiomyopathy (especially at its early stage). Hence, early accurate diagnosis can be elusive. Both ATTRm and ATTRwt cardiomyopathy can lead to heart failure. Any other cardiac manifestations include atrial fibrillation (AF) and conduction disorder. The risk of intracardiac thrombus increases in cardiac amyloidosis too.

ATTRwt are more commonly seen in men after 70 years old. Its extracardiac involvements include carpal tunnel syndrome (especially bilateral and can precede cardiomyopathy for several years), biceps tendon rupture and lumbar spinal stenosis.

ATTRm exhibit autosomal dominant inheritance, with variable penetrance. There are mutations mainly present with cardiomyopathy or neuropathy, and not uncommonly a mixture of both. Bilateral ascending motor-sensory neuropathy and/or autonomic neuropathy are the main manifestation of neurologic disease of ATTRm.

ATTR cardiomyopathy had always been thought to be a rare disease. However, recent studies suggest otherwise; ATTRwt was detected in about 13% of

heart failure with preserved ejection fraction (HFpEF) patients<sup>1</sup>, 5% of surgical severe aortic stenosis patients<sup>2</sup> and 16% of transcatheter aortic valve implantation (TAVI) patients<sup>3</sup>.

### Diagnosing ATTR

Heart failure patients who have neurologic features (carpal tunnel syndrome, peripheral paraesthesia, constipation/diarrhoea or significant postural hypotension) or family history of heart failure and/or neuropathy may be at risk of having ATTR. This also includes elderly with long standing hypertension who becomes hypotensive and intolerant to antihypertensive medications.

### CLINICAL CLUES FOR ATTR CARDIOMYOPATHY

- Chronic hypertension patient becomes hypotensive, intolerant to ACE-inhibitor or beta blockers
- Unexplained HFpEF in an elderly man
- Heart failure patients with bilateral carpal tunnel syndrome or bicep tendon ruptures
- Heart failure patients with peripheral neuropathy or profound autonomic neuropathy

### FINDINGS OF NON-INVASIVE TEST IN CARDIAC AMYLOIDOSIS

#### • Biomarkers

- Raised NT-proBNP out of proportion to the degree of heart failure
- Persistent elevated troponin level in non-ACS (acute coronary syndrome) patient

#### • Electrocardiogram (ECG)

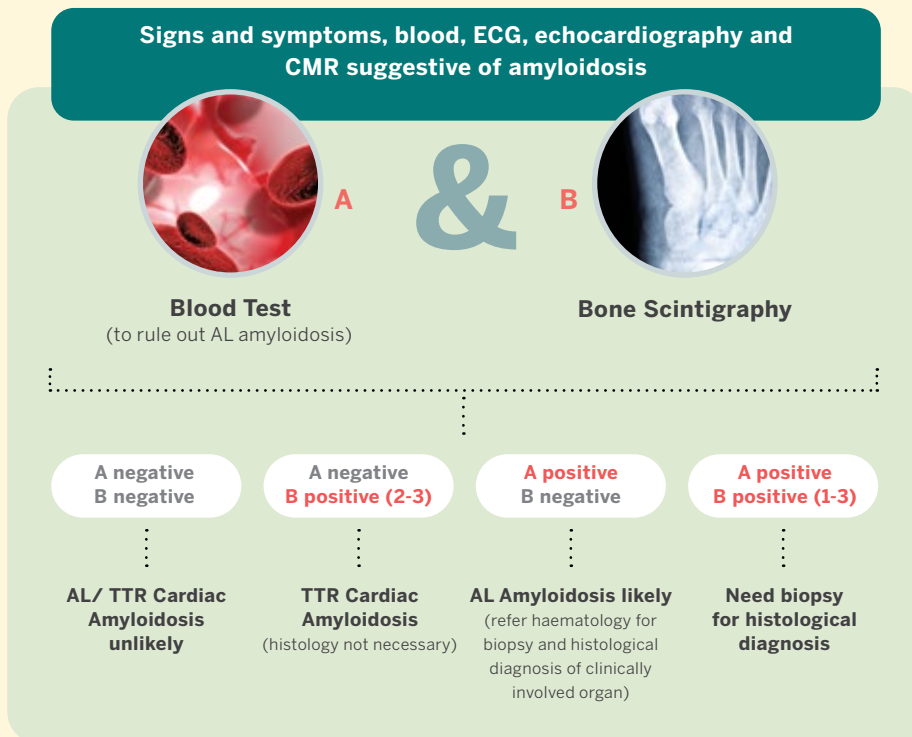
- Pseudo Q waves with no prior history of myocardial infarction
- Low ECG voltages with increased LV wall thickness (though low voltages is seen in less than half of TTR cardiomyopathy patients)

#### • Echocardiography

- Apical sparing in strain imaging
- Impaired LV longitudinal function in the presence of normal or near normal LV ejection fraction

#### • Cardiac Magnetic Resonance (CMR) Imaging

- Difficulty in nulling myocardial signal in late gadolinium enhancement (LGE) imaging due to altered contrast agent gadolinium kinetics
- Diffuse subendocardial or transmural LGE (not following coronary artery territory)
- Increased myocardial native T1 (a type of CMR imaging technique) and extracellular volume (ECV) values



## Bone bisphosphonate scintigraphy and endomyocardial biopsy (EMB):

The definitive diagnosis of amyloidosis is made based on the demonstration of amyloid tissue using Congo red stain, done through biopsy of a clinically affected organ (such as bone marrow, nerve, kidneys, heart, gut and others). As the yield of positive result of extracardiac biopsy for ATTR cardiomyopathy is poor, invasive EMB is usually necessary for histological diagnosis. This has resulted in delayed and under diagnosis of ATTR cardiomyopathy.

Bone scintigraphy/ bone scan with technetium-labelled bisphosphonates has long been noted to show great affinity for cardiac amyloid tissue. Technetium-labelled diphosphonopropanodicarboxylic acid (DPD), pyrophosphate (PYP) and hydroxymethylene diphosphonate (HMDP) scintigraphy are both sensitive and specific for identifying TTR cardiac amyloidosis.

The seminal work by Gilmore et al.<sup>4</sup> demonstrated a positive bone bisphosphonate scintigraphy that was 99% sensitive and 86% specific for cardiac TTR amyloid. The false positives were due to AL cardiac amyloidosis. After ruling out AL amyloidosis (negative blood and urine monoclonal protein studies), Gilmore et al. was able to show strong positive bone scintigraphy

that was 100% specific for TTR cardiac amyloid.

The use of bone scintigraphy has allowed ATTR cardiomyopathy to be diagnosed quickly and timely without the need for heart biopsy. Hence, there is great enthusiasm in developing and conducting clinical trials using pharmacological agents that block/ suppress TTR production in the liver, stabilise the TTR tetramer to prevent unfolding, or remove the deposited amyloid fibril.

## Treating ATTR

There are mainly two treatment approaches of ATTR cardiomyopathy - supportive and specific treatment.

### Supportive treatment

#### Heart Failure

The aim is to maintain patient in fluid balance state. Due to stiff heart from amyloid infiltration, fluid overload is common, and therefore diuretics are commonly used. However, it must be used judiciously as over diuresis would lead to hypotension and poor renal perfusion. ACE inhibitor and angiotensin receptor blocker (ARB) and beta blockers are usually poorly tolerated due to hypotension.

#### Atrial Fibrillation and Conduction Disorder

Rate control with calcium channel

blocker is not advisable due to high risk of heart block. Digoxin is best avoided as it binds to amyloid fibers and increases risk of toxicity. Amiodarone is commonly used in rate and rhythm control. Long term anticoagulation should be initiated in atrial fibrillation patient regardless of CHA<sub>2</sub>VAS<sub>2</sub>-Vasc score. Pacemaker implantation is not uncommon due to high prevalence of conduction disorder.

### Specific TTR treatment

#### TTR silencer (block protein synthesis)

Patisiran and Inotersen are two US FDA approved medications for treatment of ATTRm polyneuropathy, but not cardiomyopathy.

#### TTR tetramer stabiliser – Tafamidis and Diflunisal

Tafamidis binds to TTR and slows down the dissociation of TTR tetramers into monomers. A landmark trial<sup>5</sup> in 2018 showed tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalisations and reduced the decline in functional capacity and quality of life. Diflunisal is used in ATTRm polyneuropathy, with limited data on ATTR cardiomyopathy.

#### Amyloid fibril removal

Doxycycline and tauro-deoxychoilic acid (TUDCA) are currently being evaluated in clinical trial.

For selected patients with advanced ATTR cardiomyopathy, both hereditary and wild-type, heart transplantation (with combined liver transplantation in ATTRm) may be an option.

The availability of non-invasive diagnosis for ATTR cardiomyopathy using bone scintigraphy and blood test without biopsy of the heart have enabled the disease to be diagnosed in a more timely manner. Together with established and investigational therapeutic agents targeting at different points of amyloid pathway, clinicians are going to be better equipped to diagnose and treat this condition.

<sup>1</sup> Gonzalez-Lopez et al. Eur Heart J 2015;36:2585-94

<sup>2</sup> Treibel TA et al. Circ Cardiovasc Imag 2016

<sup>3</sup> Castaño A et al. Eur Heart J 2017;38:2879-89

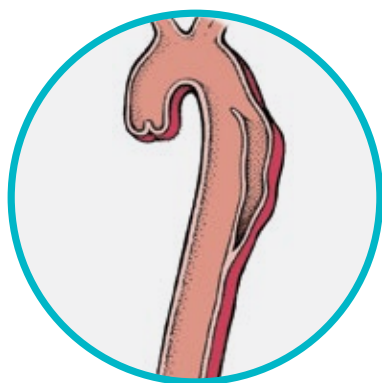
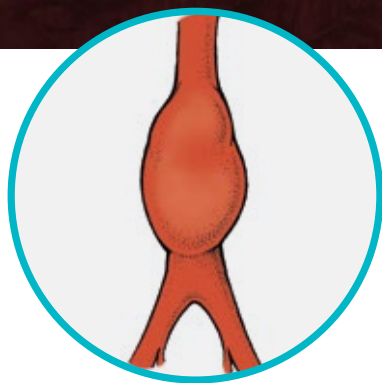
<sup>4</sup> Gilmore et al. Circulation. 2016;133:2404-2412

<sup>5</sup> Mathew S. Maurer et al. N Engl J Med 2018; 379:1007-1016

# EMERGING MINIMALLY INVASIVE SURGERY FOR AORTIC REPAIR

Our aorta is the biggest artery in our body which carries oxygenated blood from our heart to the rest of our body. Disease in the aorta can cause narrowing or, more commonly, abnormal dilation of the artery. Aortovascular diseases have been increasing in incidence over the years. This can be attributed to ageing population and increasing use of scans especially for screening. Two main conditions, which can be life-threatening, include aortic dissection and aortic aneurysms.

By Dr Sivaraj Pillai Govindasamy, Associate Consultant,  
Department of Cardiothoracic Surgery



▲ Aortic aneurysm (top) and aortic dissection (bottom).

**A**ortic dissection occurs when an injury to the innermost layer of the aorta allows blood to flow between the layers of aortic wall, forcing the layers apart. During this disruption of the aortic wall, blood supply to the various vital organs may be affected, compromising blood flow. Patients usually present with a sudden onset of severe tearing chest or back pain and this is an emergency condition. Depending on the location of the tears, patients need to undergo either emergency surgery or delayed intervention. Common causes include uncontrolled hypertension or genetic disorders like Marfan's Syndrome (conditions that weaken the wall of the blood vessel).

Aortic aneurysms is an abnormal dilatation of blood vessel that carries blood away from our heart to our organs. Aneurysms can potentially dissect or rupture and the risks increase with the size of the enlarged blood vessel. The causes of aortic aneurysm may be due to hypertension, smoking and genetics,

and symptoms present are chest pain or shortness of breath. At times, the condition can be picked up on routine pre-employment chest x-ray test. Generally, intervention is recommended for aortic aneurysms that are larger than 5.5cm or growing at a fast rate.

In the past, patients with aortic dissection or aneurysms are usually offered high risk conventional open-heart surgeries. With the emergence of Thoracic Endovascular Aortic Repair (TEVAR) procedure, there is now an alternative to conventional open-heart surgery for selected groups of patients such as those with aortovascular conditions who are elderly, frail and have a number of medical conditions, as well as those who were previously not recommended for any intervention due to health conditions.

## The TEVAR Procedure

The TEVAR procedure is performed in a hybrid operating theatre under x-ray guidance. Patients are typically

**In recent years, there were further enhancements to TEVAR technology. Stents can now be customised for each patient's vascular anatomy.**

procedure. This incision can be painful and at times, limits the mobility of many patients. This further attributes to an extended length of time required for recovery. In recent times, percutaneous closure devices have been a success in improving the TEVAR procedure. Now, the painful surgical incision in the groin has been replaced by percutaneous closure devices. A big painful surgical incision is replaced by a mere prick on the skin. The TEVAR procedure has evolved into a truly minimally invasive surgery.

In recent years, there were further enhancements to TEVAR technology. Stents can now be customised for each patient's vascular anatomy, which previously cannot be achieved with standard available stents. Thus, allowing

a broader population of patients to benefit from TEVAR procedures.

As in any procedure, the TEVAR procedure carries risks too but the main advantage is that it is less invasive than open-heart surgery and requires a shorter recovery time. It gives hope to patients who are at high or prohibitive surgical risk.

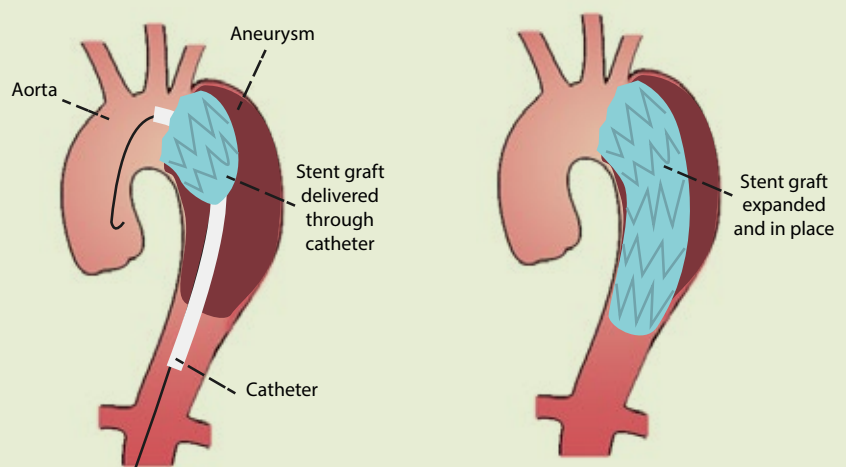
Not all aortovascular conditions require immediate or early interventions. In the mild cases, patients are serially monitored with use of scans. Blood pressure control helps slow the disease process. Stopping smoking further helps the patient's cause. Those with extensive aortic disease may require a combination of both open-heart and endovascular surgery.

The NHCS cardiovascular team has more than 10 years' experience in the TEVAR procedure. With the enhanced TEVAR technology, the outcomes achieved now are much better.

under general anaesthesia. During the TEVAR procedure, a tube or catheter is inserted into the femoral artery in the groin. A wire is guided through the artery into the aorta. A stent graft is delivered in a collapsed state through the catheter, positioned accurately using x-ray guidance. The stent graft is then expanded to span and cover the site of aortic injury or disease. As a result, the stent graft lines and reinforces the torn or diseased aortic wall to ensure continuity of blood flow and prevent further bleeding. The procedure usually takes about one to three hours. Patients typically stay in the hospital for three to four days and can resume all regular activities within a month. Complex cases may require a longer procedure time and hospital stay. Follow-up is lifelong with serial scans.

In the past, the femoral artery in the groin is accessed using a surgical incision for the procedure and subsequently repaired after the

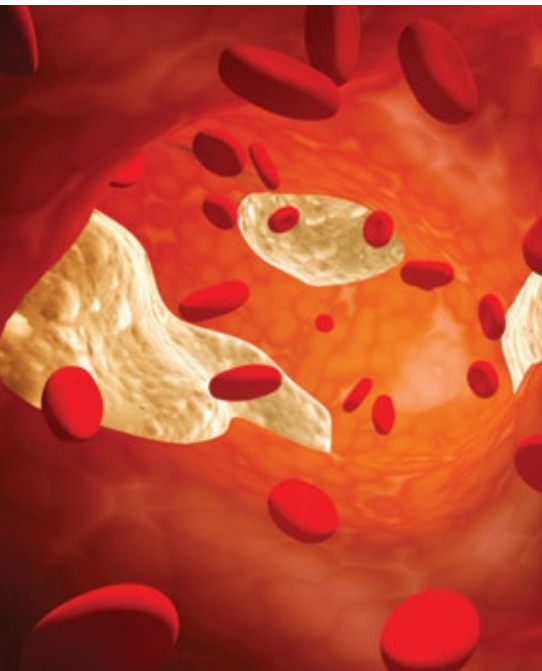
## THE TEVAR PROCEDURE



▲ TEVAR procedure – close-up of an aortic aneurysm where a catheter is inserted and a stent graft is delivered through the catheter to cover the site of the aortic injury.

## ALL YOU NEED TO KNOW ABOUT

# ANTICOAGULANTS



Anticoagulants are medications prescribed for prevention or treatment of blood clots. They are sometimes referred to as “blood thinners”, but they do not “thin” the blood. Instead, they delay the time for blood to clot, thereby slowing down the formation of blood clots. The most commonly prescribed oral anticoagulants are warfarin and non-vitamin K antagonist oral anticoagulants (NOACs) such as Rivaroxaban, Dabigatran and Apixaban. Anticoagulants also come in injectable forms such as heparin and low-molecular-weight heparin.

**A**nticoagulants stop certain clotting factors from forming or working. Different types of anticoagulants work in different ways. Warfarin block the formation of vitamin K-dependent clotting factors, while each NOAC blocks a different but specific blood clotting protein from functioning.

## Anticoagulants are usually used in patients with:

- Existing clots in the lungs, veins, arteries or heart
- Irregular heart rhythm that may cause blood clots to form in the heart and increases the risk of stroke
- Stroke
- Recent surgery which limits the patient’s movement, such as a hip replacement or knee replacement, as the period of inactivity can increase risk of developing a blood clot
- Heart valve replacement, as blood clots can form on the surface of the heart valve
- Thrombophilia, a condition where there is increased tendency to form clots in the body, e.g. Factor V Leiden
- Autoimmune diseases such as antiphospholipid syndrome where the immune system causes the blood to clot more easily
- Other conditions that may increase blood clot risk such as Left Ventricular Assist Device implantation and Chronic Thromboembolic Pulmonary Hypertension

## In particularly, NOACs have been approved for various indications:

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Prevention of recurrent DVT and PE
- Postoperative venous thromboembolism prophylaxis (knee/ hip replacement surgery)





## Dosing and Monitoring

Depending on the patient's health condition and doctor's assessment, anticoagulants may be prescribed for a duration of between three to six months, or even long-term. Patients should not stop their medication under any circumstances, unless otherwise advised by the doctors.

For patients who are on anticoagulants, it is crucial to check and monitor their International Normalised Ratio (INR), which is a test that measures the time it takes for blood to clot.

Dosage for the medications may be adjusted according to the desired INR that measures the effectiveness and impact of the medications. For instance, close monitoring may be required to determine the most appropriate dose of warfarin for each patient. The dosage may change after each visit, according to the INR results and patient's conditions, such as onset of any illnesses, recent hospitalisation, changes in medication or lifestyle changes.

The dosage for NOACs is given according to patient's kidney function; therefore frequent monitoring is required if the kidney function is weak.

## Watching Out for Signs and Symptoms

The most common side effect of anticoagulants is the increased risk of bleeding. Patients should inform the doctor at the next visit appointment should they notice any signs of bleeding such as:

- Bleeding from gums while brushing teeth (use a soft bristle toothbrush to minimise this)
- Excessive menstrual bleeding in women (increased menstrual flow may be common but patients should check with their doctor if feeling unwell)

- Nosebleed or prolonged bleeding from minor cuts despite applying pressure on the wound

They should contact their doctors immediately or admit themselves to the Emergency Department if they feel unwell, notice that the bleeding does not stop in 15 minutes, or experience any of the symptoms below:

- Blood in urine or cloudy and dark urine
- Black, sticky or tarry stools (not due to iron supplement)
- Coughing up blood or coffee ground-like vomit
- Unexplained large bruises or purplish area on skin
- Sudden severe headache with nausea or loss of consciousness

## NHCS Anticoagulation Clinic

NHCS Anticoagulation Clinic provides Patient Empowerment Programme (PEP) and POCT (Point-of-Care Testing) Programme for patients on warfarin therapy who require INR monitoring.

Suitable patients who have stable INR and do not require frequent testing, may be enrolled into the PEP to minimise their waiting time at the clinic. They may be scheduled for blood test only every two to three months and are empowered to monitor their INR. They do not need to attend the consultation clinic session if their INR is within desired range.

On the other hand, patients who have unstable INR and require frequent monitoring are enrolled under the POCT programme and required to own or loan a POCT device to perform INR self-monitoring. This provide convenience for those who have difficulty in travelling to NHCS for frequent blood tests. Patients are monitored and followed up

through phone calls by specially trained pharmacists or nurse clinicians who will adjust the warfarin dose according to the home INR result.

## MYTHS ABOUT ANTICOAGULANTS

- ✗ **Patients on NOACs do not require regular laboratory monitoring.**
- ✓ **Fact:** Although NOACs do not need monitoring to verify the efficacy of anticoagulation (unlike warfarin which requires INR monitoring), there is a need to do evaluations regularly to check on liver/renal functions, haemoglobin level, and medication compliance.
- ✗ **Patient who takes warfarin should limit foods with high levels of vitamin K like dark, leafy greens.**
- ✓ **Fact:** Patients are advised to maintain a consistent and balanced diet. There is no need to avoid foods with high levels of vitamin K totally.
- ✗ **Self-testing does not provide results as precise as testing performed by a clinic.**
- ✓ **Fact:** The accuracy of self-monitoring with today's Point-of-Care (POC) devices for anticoagulant therapy is comparable to laboratory measures, with favourable outcomes in anticoagulant control. The INR testing in NHCS uses POC devices that are recommended for INR range that is less than 3.5. A typical effective therapeutic range is between 2.0 to 3.0. When the INR range is higher than 3.5, patients will be required for blood test at the laboratory.

# OUR PRIDE, OUR JOY

## DOCTORS RECOGNISED FOR THEIR CONTRIBUTIONS

### Patients deserve your best care, whoever they may be

Prof Koh Tian Hai,  
Emeritus Consultant

perseverance is the key to success. My hope is for the course to grow even bigger in the coming years."

Widely regarded as a role model for his commitment to patients and public healthcare, Prof Koh's judicious decision-making skills, meticulous attention to

disease. As a recognised leader and expert in heart valve repair surgery in Singapore and the region, Assoc Prof Chua said that he chose to specialise in this field as fixing the valve can normalise the heart's rhythm, effectively lowering the risk of stroke in patients.

At a young age of 35, Assoc Prof Chua became the head of the Cardiothoracic Surgery team at NHCS. He led the department through tough times with unwavering dedication, and built on the team's capabilities with his firm focus on training the younger generations of doctors and medical staff, "You need to know each individuals' unique strengths and help them reach their fullest potential in every discipline to ensure leadership succession in the institution."

Assoc Prof Chua believes that healthcare should not be limited to local shores, and should look beyond at how to deliver healthcare to deprived places such as rural areas which face with malaria and emerging disease. Also holding the appointment as the Group Director for International Collaboration Office in SingHealth since 2014, Assoc Prof Chua and his team actively seek partnerships with philanthropic organisations to support outreach and humanitarian efforts to regions such as Papua New Guinea, Cambodia and Vietnam.

For his outstanding achievements, the humble veteran credits the team of specialists working together with him as well as the trust his patients have placed in him, "I have so many teachers in my life to thank for the incredible journey I have been on so far. To the younger ones - I say, do your best and learn to enjoy things that come your way."



### Conferment of Emeritus Consultant title - Prof Koh Tian Hai

*I would consider my most gratifying achievement in mentoring is to see how our NHCS colleagues have selflessly shared their skills and knowledge with successive generations of younger colleagues, without hesitation and fear of being surpassed by their students* – was Prof Koh Tian Hai's reply when asked about his most memorable experience as a mentor.

Not only is he a well-respected and reputable interventionist in the region, Prof Koh is a strong advocate for education. In the course of his career, he had trained numerous doctors local and abroad and a mentor to many. Under his able leadership as Medical Director from 2003 to 2014 in NHCS and subsequently, Senior Advisor from 2014 to 2019, Prof Koh has steered NHCS to always be at the forefront of cardiovascular care in clinical care, education and research, and in pursuit of clinical excellence through knowledge sharing platforms such as overseas exchanges, fellowship programmes and conferences.

Under his stewardship, Singapore LIVE Course (previously known as Live Demonstration Course in Basic and Advanced Techniques), the flagship event of NHCS, has achieved successful momentum for the last 29 years. As course director to this reputed international live interventions course in vascular therapy, Prof Koh said that the journey had been testing and challenging, "Organising Singapore LIVE has taught me that

details and openness to new ideas have been the catalyst to ground breaking innovations in medicine. Even as much great progress has been made towards advancement in heart care and treatment options, the interventional cardiologist feels strongly that more can be done in preventive cardiovascular care. "To a significant extent, many are still not cognisant of the need to lead a healthy lifestyle in terms of exercise and dietary preventive measures, that are vital to improve Singapore's heart health."

His tireless efforts to raise the standards of cardiovascular care in the region has won him the National Outstanding Clinician Mentor Award in 2015. For his contributions to education in Asia Pacific, he was awarded the Chien Foundation Award in 2012.



### Winning the National Outstanding Clinician Award - Assoc Prof Chua Yeow Leng

A cardiothoracic surgeon by training, Assoc Prof Chua Yeow Leng has treated countless patients with debilitating heart

### Congratulations to both Prof Koh and Assoc Prof Chua in receiving the highest honour!



# RESEARCH PUBLICATIONS

August 2019 – December 2019

## AUGUST 2019

**High-sensitivity troponin T and long-term adverse cardiac events among patients presenting with suspected acute coronary syndrome in Singapore** *Singapore Med J*. 2019 Aug;60(8):418-426. doi: 10.11622/smedj.2019013

**The clinical significance of interleukin-6 in heart failure: results from the BIOSAT-CHF study** *Eur J Heart Fail*. 2019 Aug;21(8):965-973. doi: 10.1002/ehf.1482

**20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study** *Lancet Public Health*. 2019 Aug;4(8):e406-e420. doi: 10.1016/S2468-2667(19)30108-2

**WWP2 regulates pathological cardiac fibrosis by modulating SMAD2 signaling** *Nat Commun*. 2019 Aug 9;10(1):3616. doi: 10.1038/s41467-019-11551-9

**Targeting Mitochondrial Fission Using Mdivi-1 in A Clinically Relevant Large Animal Model of Acute Myocardial Infarction: A Pilot Study** *Int J Mol Sci*. 2019 Aug 15;20(16). pii: E3972. doi: 10.3390/ijms20163972

**Semaphorin 3E/PlexinD1 signaling is required for cardiac ventricular compaction** *JCI Insight*. 2019 Aug 22;4(16). pii: 125908. doi: 10.1172/jci.insight.125908

**Myocardial Viability and Long-Term Outcomes in Ischemic Cardiomyopathy** *N Engl J Med*. 2019 Aug 22;381(8):739-748. doi: 10.1056/NEJMoa1807365

**Low Mir-19B-1-5P Expression In Acs Patients Is Related To Aspirin Resistance And Major Adverse Cardio-Cerebrovascular Event (Macce)** *Atherosclerosis*. August 2019 Volume 287, Page e142, DOI: <https://doi.org/10.1016/j.atherosclerosis.2019.06.e142>

**Left Atrial Myopathy in Heart Failure with Preserved Ejection Fraction: Insights from the PROMIS-HFpEF Study** *Journal of Cardiac Failure, Volume 25, Issue 8, Supplement, August 2019, Page S43*. DOI: <https://doi.org/10.1016/j.cardfail.2019.07.119>

## SEPTEMBER 2019

**Outcome in Dilated Cardiomyopathy Related to the Extent, Location, and Pattern of Late Gadolinium Enhancement** *JACC Cardiovasc Imaging*. 2019 Aug;12(8 Pt 2):1645-1655. doi: 10.1016/j.jcmg.2018.07.015

**Cholesterol goal achievement and lipid-lowering therapy in patients with stable or acute coronary heart disease in Singapore: results from the Dyslipidemia International Study II** *Singapore Med J*. 2019 Sep;60(9):454-462. doi: 10.11622/smedj.2019021

**Supporting the Management of Patients with Heart Failure within Asia-Pacific, middle East, and African Countries: A Toolbox for Healthcare Providers** *Cardiology*. 2019;142 Suppl 1:1-10. doi: 10.1159/000496663

**Melatonin Stabilizes Rupture-Prone Vulnerable Plaques via Regulating Macrophage Polarization in a Nuclear Circadian Receptor ROR  $\alpha$ -Dependent Manner** *J Pineal Res*. 2019 Sep;67(2):e12581. doi: 10.1111/jpi.12581

**Inhibiting Interleukin 11 Signaling Reduces Hepatocyte Death and Liver Fibrosis, Inflammation, and Steatosis in Mouse Models of Non-Alcoholic Steatohepatitis** *Gastroenterology*. 2019 Sep;157(3):777-792.e14. doi: 10.1053/j.gastro.2019.05.002

**ST-segment elevation myocardial infarction with non-chest pain presentation at the Emergency Department: Insights from the Singapore Myocardial Infarction Registry** *Intern Emerg Med*. 2019 Sep;14(6):989-997. doi: 10.1007/s11739-019-02122-3

**Widespread Translational Control of Fibrosis in the Human Heart by RNA-Binding Proteins** *Circulation*. 2019 Sep 10;140(11):937-951. doi: 10.1161/CIRCULATIONAHA.119.039596

**Intracardiac 4D Flow MRI in Congenital Heart Disease: Recommendations on Behalf of the ISMRM Flow & Motion Study Group** *J Magn Reson Imaging*. 2019 Sep;50(3):677-681. doi: 10.1002/jmri.26898

**Association of Diabetes Mellitus on Cardiac Remodeling, Quality of Life, and Clinical Outcomes in Heart Failure With Reduced and Preserved Ejection Fraction** *J Am Heart Assoc*. 2019 Sep 3;8(17):e013114. doi: 10.1161/JAHA.119.013114

**World Heart Federation Roadmap for Heart Failure** *Glob Heart*. 2019 Sep;14(3):197-214. doi: 10.1016/j.gheart.2019.07.004

**Can Lightning Strike Twice? Tackling Complications From Transcatheter Aortic Valve Implantation** *J Invasive Cardiol*. 2019 Sep;31(9):E277

**In-Hospital Coronary Revascularization Rates and Post-Discharge Mortality Risk in Non-ST-Segment Elevation Acute Coronary Syndrome** *J Am Coll Cardiol*. 2019 Sep 17;74(11):1454-1461. doi: 10.1016/j.jacc.2019.06.068

**Interleukin-11 is a therapeutic target in idiopathic pulmonary fibrosis** *Sci Transl Med*. 2019 Sep 25;11(511). pii: eaaw1237. doi: 10.1126/scitranslmed.aaw1237

**Association of obesity with heart failure outcomes in 11 Asian regions: A cohort study** *PLoS Med*. 2019 Sep 24;16(9):e1002916. doi: 10.1371/journal.pmed.1002916

## OCTOBER 2019

**An East-West comparison of self-care barriers in heart failure** *Eur Heart J Acute Cardiovasc Care*. 2019 Oct;8(7):615-622. doi: 10.1177/2048872617744352

**Toil-like Receptor 7 Deficiency Promotes Survival and Reduces Adverse Left Ventricular Remodeling After Myocardial Infarction** *Cardiovasc Res*. 2019 Oct 1;115(12):1791-1803. doi: 10.1093/cvr/cvz057

**Time course of left ventricular remodelling and mechanics after aortic valve surgery: aortic stenosis vs. aortic regurgitation** *Eur Heart J Cardiovasc Imaging*. 2019 Oct 1;20(10):1105-1111. doi: 10.1093/ehjci/jez049

**Chronic Total Occlusion Wiring: A State-of-the-Art Guide From The Asia Pacific Chronic Total Occlusion Club** *Heart Lung Circ*. 2019 Oct;28(10):1490-1500. doi: 10.1016/j.hlc.2019.04.004

**Homemade Candy Plug Using a Zenith Alpha Thoracic Stent-Graft for False Lumen Distal Occlusion in Acute-on-Chronic Type B Aortic Dissection** *J Endovasc Ther*. 2019 Oct;26(5):732-735. doi: 10.1177/1526602819860801

**Motivation, Challenges and Self-Regulation in Heart Failure Self-Care: a Theory-Driven Qualitative Study** *Int J Behav Med*. 2019 Oct;26(5):474-485. doi: 10.1007/s12529-019-09798-z

**Health-Related Quality of Life in Heart Failure With Preserved Ejection Fraction: The PARAGON-HF Trial** *JACC Heart Fail*. 2019 Oct;7(10):862-874. doi: 10.1016/j.jchf.2019.05.015

**Application of the H2 FPEF score to a global clinical trial of patients with heart failure with preserved ejection fraction: the TOPCAT trial** *Eur J Heart Fail*. 2019 Oct;21(10):1288-1291. doi: 10.1002/ehf.1542

**Galectin-3 as a candidate upstream biomarker for quantifying risks of myocardial ageing** *ESC Heart Fail*. 2019 Oct;6(5):1068-1076. doi: 10.1002/ehf2.12495

**Educational Recommendations on Selected Analytical and Clinical Aspects of Natriuretic Peptides with a Focus on Heart Failure: A Report from the IFCC Committee on Clinical Applications of Cardiac Biomarkers** *Clin Chem*. 2019 Oct;65(10):1221-1227. doi: 10.1373/clinchem.2019.306621

**Heart failure around the world** *Eur J Heart Fail*. 2019 Oct;21(10):1187-1196. doi: 10.1002/ehf.1585

**A new machine learning technique for an accurate diagnosis of coronary artery disease** *Comput Methods Programs Biomed*. 2019 Oct;179:104992. doi: 10.1016/j.cmpb.2019.104992

**Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study** *Lancet*. 2019 Oct 5;394(10205):1254-1263. doi: 10.1016/S0140-6736(19)31792-1

**Angiotensin-Nephrilysin Inhibition in Heart Failure with Preserved Ejection Fraction** *N Engl J Med*. 2019 Oct 24;381(17):1609-1620. doi: 10.1056/NEJMoa1908655

**How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)** *Eur Heart J*. 2019 Oct 21;40(40):3297-3317. doi: 10.1093/eurheartj/ehz641

**Digital phenotyping by consumer wearables identifies sleep-associated markers of cardiovascular disease risk and biological aging** *Commun Biol*. 2019 Oct 4;2:361. doi: 10.1038/s42003-019-0605-1

**Plasma Desmosome and Abdominal Aortic Aneurysm Disease** *J Am Heart Assoc*. 2019 Oct 15;8(20):e013743. doi: 10.1161/JAHA.119.013743

**Non-viral vector based gene transfection with human induced pluripotent stem cells derived cardiomyocytes** *Sci Rep*. 2019 Oct 7;9(1):14404. doi: 10.1038/s41598-019-50980-w

**Large-Scale Whole-Genome Sequencing of Three Diverse Asian Populations in Singapore** *Cell*. 2019 Oct 17;179(3):736-749.e15. doi: 10.1016/j.cell.2019.09.019

**Update on anesthesia management for explanation of veno-arterial extracorporeal membrane oxygenation in adult patients** *Ann Card Anaesth*. 2019 Oct-Dec;22(4):422-429. doi: 10.4103/aca.ACA\_178\_18

**Biomarker Correlates of Coronary Microvascular Dysfunction in Heart Failure With Preserved Ejection Fraction** *Circulation*. 2019 Oct 15;140(16):1359-1361. doi: 10.1161/CIRCULATIONAHA.119.042569

**SGLT-2 Inhibitors in Heart Failure: Current Management, Unmet Needs, and Therapeutic Prospects** *J Am Heart Assoc*. 2019 Oct 15;8(20):e013389. doi: 10.1161/JAHA.119.013389

**Infrared (IR) thermography as a potential screening modality for carotid artery stenosis** *Comput Biol Med*. 2019 Oct;113:103419. doi: 10.1016/j.combiomed.2019.103419

**Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial** *Lancet*. 2019 Oct 19;394(10207):1415-1424. doi: 10.1016/S0140-6736(19)32039-2

## NOVEMBER 2019

**Clinical safety of the ProMRI implantable cardioverter-defibrillator systems during head and lower lumbar magnetic resonance imaging at 3 T: results of the ProMRI 3T ENHANCED Master study** *Europace*. 2019 Nov 1;21(11):1678-1685. doi: 10.1093/europace/euz189

**Physiological Optimization of Robotic Endoscopic Epicardial CRT-D Implantation Using Multielectrode Electroanatomic Mapping** *J Cardiovasc Electrophysiol*. 2019 Nov;30(11):2564-2568. doi: 10.1111/jce.14126

**Hyperkalemia and Treatment With RAAS-Inhibitors During Acute Heart Failure Hospitalizations and Their Association With Mortality** *JACC Heart Fail*. 2019 Nov;7(11):970-979. doi: 10.1016/j.jchf.2019.07.010

**Effects of Interatrial Shunt on Pulmonary Vascular Function in Heart Failure With Preserved Ejection Fraction** *J Am Coll Cardiol*. 2019 Nov 26;74(21):2539-2550. doi: 10.1016/j.jacc.2019.08.1062

**Harnessing technology and molecular analysis to understand the development of cardiovascular diseases in Asia: a prospective cohort study (SingHEART)** *BMC Cardiovasc Disord*. 2019 Nov 21;19(1):259. doi: 10.1186/s12872-019-1248-3

**Dapagliflozin in heart failure: new frontiers** *Eur J Heart Fail*. 2019 Nov;21(11):1412-1414. doi: 10.1002/ehf.1633

**Model uncertainty quantification for diagnosis of each main coronary artery stenosis** *Soft Computing*. pg1-12. DOI: <https://doi.org/10.1007/s00500-019-04531-0>

## DECEMBER 2019

**Predicting two-year mortality from discharge after acute coronary syndrome: An internationally-based risk score** *Eur Heart J Acute Cardiovasc Care*. 2019 Dec;8(8):727-737. doi: 10.1177/204887261719638

**History and Current Status of Cardiac Anesthesia in Singapore** *J Cardiothorac Vasc Anesth*. 2019 Dec;33(12):3394-3401. doi: 10.1053/j.jvca.2018.07.018

**Associations between Skeletal Muscle and Myocardium in Aging: A Syndrome of "Cardio-Sarcopenia"** *J Am Geriatr Soc*. 2019 Dec;67(12):2568-2573. doi: 10.1111/jgs.16132

**Sex differences in left ventricular remodelling, myocardial fibrosis and mortality after aortic valve replacement** *Heart*. 2019 Dec;105(23):1818-1824. doi: 10.1136/heartjnl-2019-314987

**Automated detection of shockable and non-shockable arrhythmia using novel wavelet-based ECG features** *Comput Biol Med*. 2019 Dec;115:103446. doi: 10.1016/j.combiomed.2019.103446

**Why did remote ischaemic conditioning not improve clinical outcomes in acute myocardial infarction in the CONDI-2/ERIC-PPCI trial?** *Cardiovasc Res*. 2019 Dec 1;115(14):e161-e163. doi: 10.1093/cvr/cvz242

**David Garcia-Dorado: a true pioneer in cardiac ischaemia/reperfusion injury** *Cardiovasc Res*. 2019 Dec 1;115(14):e177-e180. doi: 10.1093/cvr/cvz282

**deltaTE: Detection of Translationally Regulated Genes by Integrative Analysis of Ribo-seq and RNA-seq Data** *Curr Protoc Mol Biol*. 2019 Dec;129(1):e108. doi: 10.1002/cpm.108

**Computational quantification of patient specific changes in ventricular dynamics associated with pulmonary hypertension** *Am J Physiol Heart Circ Physiol*. 2019 Dec 1;317(6):H1363-H1375. doi: 10.1152/ajpheart.00094.2019. Epub 2019 Nov 1

**Sex differences in heart failure** *Eur Heart J*. 2019 Dec 14;40(47):3859-3868. doi: 10.1093/eurheartj/ehz835

**Primary cardiac lymphoma** *BMJ Case Rep*. 2019 Dec 2;12(12). pii: e230468. doi: 10.1136/bcr-2019-230468

## PATIENT EDUCATION RESOURCES AVAILABLE ONLINE

It's never too late to change your habits and establish a healthy lifestyle. Scan the codes to access our patient education videos and find out more about cardiovascular diseases' risk factors, early signs and symptoms, and more!



**Do you know that 25% of heart attacks are clinically silent? Some people may suffer a heart attack without having any symptom.**

**Understand more about heart attack:**



**Heart failure happens when the heart loses its ability to pump enough blood, leaving the organs and tissues with insufficient oxygen and nutrients to function properly.**

**Learn how heart failure patients are still able to lead a normal active life:**



**Do you know 1 in 3 women died of cardiovascular disease in Singapore, claiming more lives than breast cancer?**

**Find out more on heart diseases in women:**



## APPOINTMENTS & PROMOTIONS



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Adjunct Associate Professor



**Asst Prof Kang Ning**  
Adjunct Assistant Professor



**Asst Prof Philip Pang Yi Kit**  
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