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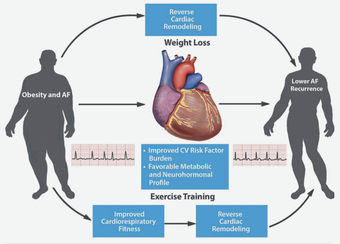
ATRIAL FIBRILLATION

EIGHT LIFESTYLE MODIFICATION APPROACHES TO TREATING AF

Atrial fibrillation (AF) is the most common arrhythmia affecting man and is an independent contributor to mortality, morbidity and impaired quality of life. The prevelance of AF increases with age- it is very unusual in people below the age of 30 but affects as many as 1 in 20 (i.e. 5%) of people over the age of 65. It is estimated that as many as 50,000 people in Singapore have AF with the number in Singapore and worldwide set to double by the year 2050. Although AF is commonly found in patients with other types of heart disease, such as hypertensive heart disease, IHD and heart failure, there are a number of important lifestyle risk factors that also contribute to the development or progression of AF. These should be identified and addressed, especially in younger patients with early onset AF, to try to limit progression of the condition. The following are a list of eight practical lifestyle interventions that can be reinforced in patients with AF to improve their condition.

1) Stopping smoking - smoking can increase the risk of AF due to the inflammatory effect of nicotine and its links with IHD and pulmonary disease. Current smokers are more than twice as likely as non-smokers to develop AF; ex-smokers have 1.3x the risk. Fortunately, quitting smoking can reduce the AF risk by 36% [Heeringa J, et al. Am Heart J. 2008; 156:1163-1169] , so patients with AF or risk factors for AF should be strongly encouraged to stop smoking.

2) Better control of blood pressure - hypertension is a well known contributory factor to AF, as well as other cardiovascular diseases. Hence patients with AF should have their blood pressure carefully controlled. Beta-blockers and ACE-Inhibitors are the anti-hypertensives of choice in patients with AF. There is some evidence that ACE-Inhibitors can have some beneficial effects on the atrial substrate to reduce AF burden.



Link between obesity, weight loss and exercise in AF
(from *Lavie, CJ et al. J Am Coll Cardiol. 2017; 70(16): 2022-35*)

3) Reducing alcohol intake - chronic alcohol consumption as well as alcoholic binges can increase the risk of developing AF. One study found that the lifetime risk for AF was 40.9% for those with increased alcohol consumption compared to 35.1% for those who did not take any alcohol. [Staerk L, Framingham Heart Study. BMJ. 2018, 361:k1453]

4) Avoiding stimulants - Contrary to popular belief, there is no good evidence of a link between increased caffeine intake and the development of AF. Most studies studies looking into this area have been negative. However, artificial stimulants, such as energy drinks have been linked to the development of AF and should be avoided in patients at risk or AF or who have palpitations.

5) Maintaining a healthy diet - a good, healthy and balanced diet is important to lower the risk of AF as well as other cardiovascular diseases. For example, there is some evidence that Mediterranean diet, which is primarily plant- and fish-based with little added or processed food may reduce the risk of AF. [Geisler BP. Am J Med. 2016; 129:11] One reason for this benefit may be related to the polyunsaturated fatty acids in these diets which can help stabilize the cell membranes of the cardiac myocytes.

6) Reducing obesity - There is a strong link between obesity and an increased burden of AF. Importantly, the AF burden and need for medication in patients with AF who are obese, can be significantly reduced if they can successfully lose weight. This was demonstrated in the LEGACY study in which a total of 355 AF overweight patients an an average BMI of 27 were studied prior to undergoing AF ablation. The 38% who managed to significantly lose weight showed significant AF reduction, with some no longer requiring the AF ablation procedure. [Pathak RK, et al. J Am Coll Cardiol. 2015, 65:2159-2169.] Weight reduction and increasing exercise can help reverse the adverse cardiac remodeling and neurohormonal changes that occur in patients with AF [see diagram]. Thus, obese patients with AF should be strongly encouraged to lose weight, espeicailly if they are due to undergo an AF ablation procedure.

7) Addressing sleep problems - Sleep issues, including sleep deprivation and obstructive sleep apnoea (OSA), are additional modifiable risk factors that have been linked with AF. For example, one study showed that acute sleep deprivation increases AF risk by 3.36 times. [Kayrak M, et al. Pacing Clin Electrophysiol. 2013, 36:823-829] This is an important factor to consider as more and more people with busy and hectic working lives are sleeping fewer hours than in previous decades and not achieveing the recommended 7-8 hours a night. The risk of AF is four times higher in patients with OSA independent of obesity, age, hypertension, heart failure or other confounding variables. In addition, 49% of pateints with AF have OSA and furthermore, treatment of OSA prior to AF ablation can improve outcomes.

8) Stress reduction - A healthy mindset and reduction of stress can reduce the chances of developing AF as well as promote general well being. One interesting study found that negative emotions including anger, anxiety, sadness, and stress, trigger symptomatic AF, whereas happiness was protective. [Lampert R, et al. J Am Coll Cardiol. 2014; 64:1533-1534]. Patients with AF who lead stressful lives should be encouraged to reduce their work stress through activities such as yoga and other relaxation techniques.

Summary: AF is very common in Singapore and worldwide and appears to be on the rise. In addition to the need for careful medical evaluation and consideration of the optimal treatment of AF, including anticoagulation if required, lifestyle issues should also be identified and addressed as these can have an important impact on the condition.

By **Dr. Reginald Liew**
Senior Consultant Cardiologist
The Harley Street Heart & Vascular Centre

ISCHAEMIC HEART DISEASE

RISK REDUCTION IN ISCHAEMIC HEART DISEASE: LOWERING CHOLESTEROL TO NEW DEPTHS

Low density lipoprotein (LDL)-cholesterol is an extensively researched modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD). Decades of prospective cohort and randomized control trial data confirm a significant absolute reduction in cardiovascular events with lower serum LDL-cholesterol concentrations. LDL-cholesterol (LDL-C) can be lowered by reductions in saturated fat consumption, caloric intake and several classes of cholesterol lowering medications, of which statins are the most well studied. For every 38.6 mg/dl (1 mmol/l) reduction in LDL-cholesterol, ASCVD events are reduced by 21% after 1 year of treatment with moderate- or high-intensity statins.

Circulating levels of proprotein convertase subtilisin/kexin 9 (PCSK9) represent the strongest regulator of cholesterol trafficking in the body. The mechanism of action of PCSK9 is via inhibition of LDL-receptor (LDLR) recycling, a process that usually allows the LDLR on the surface of the hepatocyte to internalize hundreds of LDL particles. More recent trials demonstrated that statin therapy combined with PCSK9 inhibitors incrementally reduces ASCVD events in high risk populations.

Therapeutic Inhibition of PCSK9 and Clinical Outcomes
The 2 currently available antibodies (alirocumab, evolocumab) against PCSK9 are fully human IgG subtypes that bind with an approximate 1:1 stoichiometry to circulating PCSK9 and prohibit its binding to the LDLR, thus creating a PCSK9-deficiency state that results in marked accumulation of LDLR on the membrane of hepatocytes, accelerated clearance of LDL particles, and large decreases in plasma LDL-C levels. The subcutaneous injection of either drug introduces a vast excess of antibodies that within just a few hours of administration capture all of the circulating PCSK9 and will capture all the newly secreted PCSK9 for the following several days.

Alirocumab is available in 2 doses: 75 mg or 150 mg subcutaneously (SC) every 2 weeks and 300 mg monthly. With the 75mg dose, LDL-C levels fall by 45%-48%, and by 60% with the 150mg dose. If, after 4 to 8 weeks, the desired level of LDL-Clowering is not achieved, the dose can be titrated to 150 mg. In studies with subjects not taking a statin, the maximal LDL-C reduction was approximately 45%. Evolocumab is available in 2 dosing schedules as well: 140 mg SC every 2 weeks, or 420 mg SC monthly, that achieve the same level of LDL-C reduction, approximately 60%. Monitoring of the effect of this class on LDL-C is recommended, with measurement at the trough level of the dosing interval (i.e., 14 days after the previous dose). [Currently the monthly regimens for both agents are not available for use in Singapore]. Both agents lower triglycerides by 10% - 15%, raise HDL cholesterol by 5% - 10%, and lower Lp(a) by 25% - 30%. High sensitivity C-reactive protein levels are unchanged with PCSK9 inhibition.

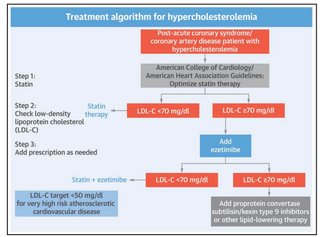
The effects of PCSK9 inhibition on clinical outcomes were reported in 2 large outcomes randomized controlled trials. FOURIER enrolled 27,564 patients with prior ASCVD with an additional high risk feature who were receiving maximally tolerated statin (two-thirds were being treated with a high intensity statin) but who still had an LDL-C ≥70 mg/dl or a non-HDL cholesterol ≥ 100 mg/dl. Patients were randomized to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420mg every month based on patient preference) or matching placebo. Evolocumab reduced LDL-C by 59% from a median of 92 mg/dl to 30 mg/dl. After an average 2 years of follow-up, the composite of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for angina, or revascularization occurred in 11.3% versus 9.8% of the placebo group, a 15% relative risk reduction (p <0.001). The endpoint of cardiovascular death, MI, or stroke was reduced by 20%, from 7.4% to 5.9% (p < 0.001).
An observational analysis from FOURIER found that the rate of ASCVD events fell continuously with lower achieved LDL-C, which suggests that there is no actual limit for the ASCVD benefit of LDL-C lowering, and which raises the issue of whether the current guideline-recommended target/threshold of LDL-C <70 mg/dl should be lowered in these high-risk patients.

Clinical outcomes after treatment with Alirocumab were studied in the ODYSSEY OUTCOMES trial
in patients after acute coronary syndrome treated with maximally tolerated statin therapy. In this trial, 18,924 patients were randomized to treatment with either alirocumab or placebo. All patients were initiated on 75 mg alirocumab every 2 weeks, and the dose was increased to 150 mg every 2 weeks if the LDL-C did not fall <50 mg/dl. A total of 1,955 patients experienced a primary endpoint (CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, or unstable angina requiring hospitalization), 903 (9.5%) and 1,052 (11.1%) in those assigned alirocumab and placebo, respectively, for a relative risk reduction of 15% (p< 0.0003). Secondary efficacy endpoints that were significantly reduced included major CHD event, cardiovascular event, MI, or ischemic stroke. Although it could not be evaluated as part of hierarchical testing, all-cause mortality was lower with alirocumab at 3.5% versus 4.1%, again a relative risk reduction of 15% (nominal p < 0.026).

The 2 clinically available PCSK9 inhibitors were initially approved by the US Food and Drug Administration (FDA) "as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD who require additional lowering of LDL-C". Evolocumab also has an indication for use in homozygous FH. The FDA added an indication for Evolocumab based on the results of the FOURIER trial "to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease."

The safety profile of both agents is excellent. The most common adverse reactions are nasopharyngitis
and mild injection-site reactions. There is no increase in myalgias and importantly no increase in neurocognitive adverse effects, even at very low achieved LDL-C.

Stepwise approach to reduction of LDL-cholesterol in ischaemic heart disease
Adapted from Rosen RS et al. JACC 2018; 72(3): 314-29



By **Dr. Rohit Khurana**
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HEART FAILURE

REDUCING RISK IN HF PATIENTS, NEW AND TRADITIONAL MEASURES

Singaporeans have a higher prevalence of coronary artery disease, hypertension and diabetes, three medical conditions that put them at greater risk of heart failure (HF) than their Asian counterparts. The same study also showed that Singaporean patients suffer from HF at the average age of 61, about 10 years earlier than Americans and Europeans (CS Lam et al, Eur J Heart Fail 2013). The authors put the trend down to the region's social and economic advancement, leading to lifestyle changes that triggered the risk factors. As a result, the management of HF is becoming increasingly important for the general practitioner. So, what's new in the arena of HF management?

Use of Biomarkers for prevention & prognosis in the outpatient
For patients at risk of developing HF (defined as presence of hypertension, diabetes or known vascular disease (Stage A HF), without established LV systolic dysfunction or symptomatic HF, Natriuretic peptide (NP) biomarker screening followed by team based care, including a cardiovascular specialist optimizing guideline directed medical therapy, is useful to prevent the development of LV dysfunction or new-onset HF (Ledwidge M, JAMA 2013). In patients presenting with shortness of breath at the outpatient clinic, measuring NP biomarkers is useful to support a diagnosis or exclusion of HF. In the case of known chronic HF, measuring either the BNP or NT-proBNP is useful for establishing prognosis or disease severity in Chronic HF.

Medical therapy for heart failure with reduced ejection fraction (HFrEF)
All heart failure patients with HFrEF should have inhibition of the renin-angiotensin system with ACEI or ARBs or ARNI in conjunction with evidence based beta blockers, and aldosterone antagonist in selected patients. ACEI and ARBS have already demonstrated their benefits in reducing morbidity and mortality in HFrEF. ARNI is an ARB combined with Neprilysin. In an RCT Valsartan/Sacubitril compared with Enalapril, ARNI further reduced the composite endpoint of death or HF hospitalization significantly by 20% (McMurrya JJV et al, NEJM 2014). The benefit was seen in both death and HF hospitalization and was consistent across subgroups. But take caution, the use of ARNI is associated with the risk of hypotension and renal insufficient and may lead to angioedema as well, just like ACEI. In chronic HFrEF, NYHA II or III who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. To facilitate initiation and titration, the approved ARNI is available in 3 doses. The target dose used in the trial was 200mg bd. More experience in the use of this class will provide further information on optimal titration and tolerability of ARNI with regards to blood pressure reduction, adjustment of concomitant HF meds and rare complication of angioedema. Ivabradine is a new therapeutic agent that selectively inhibits the If current in the sinoatrial node, leading to heart rate reduction. One RCT demonstrated its efficacy in reducing HF hospitalization in NYHA II-IV with EF<=35%, in sinus rhythm with resting HR >=70/min (Swedberg et al, Lancet 2010). But it is recommended to initiate and titrate up guideline proven beta-blockers to target doses as tolerated first, before assessing the resting HR for consideration of Ivabradine.

Medical therapy for heart failure with preserved ejection fraction (HFpEF)
It is believed that in the community, approximately 50% of patients with HF have HFpEF (Dunlay SM, Nat Rev Cardiol 2017). For this group, systolic and diastolic pressure should be controlled in accordance to published clinical practice guidelines to prevent morbidity. Diuretics can be used for relief in the presence of volume overload. Management of atrial fibrillation according to clinical practice guidelines is reasonable to improve symptomatic HF. In terms of drugs therapy BB, ACE and ARBs can be used to in HFpEF to control hypertension. In selected HFpEF with EF>45% elevated BNP or HF admission within 1 year, eGFR > 30ml/Min Cr<2.5mg/dL, K<5.0, aldosterone receptor antagonist might be considered to decrease hospitalizations. One might consider use of ARBs to decrease hospitalizations for patients with HFpEF.

Recommendations for Anemia
In patients with NYHA II, and III HF with Fe deficiency (ferritin < 100ng/mL or 100 to 300 ng/ml if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and quality of life. In patients with HF and anemia, Erythropoietin stimulating agents should not be used to improve morbidity and mortality used to absence of benefit in recent studies (Yancy et al, JACC 2017).

Prevention
Prevention of worsening HF in Stage A HF. The recommendation for optimal BP in those with hypertension should be <130/80mmHg. Targeting a significant reduction in systolic BP in those at increased risk for CV disease is a novel strategy to prevent HF. (Age >75, established vascular disease, chronic renal disease or Framingham risk score>15%) (Wright JT et al, NEJM 2015).

By **Dr Peter Ting**
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CAROTID ARTERY DISEASE

INTENSIVE MEDICAL THERAPY OR INTERVENTION IN CAROTID ARTERY DISEASE?

The management of carotid artery disease, be it symptomatic or asymptomatic, is driven by the fear of embolic stroke and its potential consequences on the quality of life and mortality. Atherosclerotic carotid artery disease accounts for approximately 15% of all focal ischemic lesions. The clinical weight of carotid stroke, however, goes beyond this rather small proportion. Territorial infarction embolism, the most frequent mechanism of symptomatic carotid stroke, carries a worse prognosis regarding disability than lacunar infarction, including the risk of progressive stroke and secondary brain swelling.

The clinical management of symptomatic carotid disease with recurrent transient ischemic attack (TIA) and early recurrence of stroke is among the most challenging in stroke treatment. Patients with carotid disease—frequently smokers with complication-prone concomitant cardiac macro-angiopathy, are often younger than the average stroke population. Furthermore, decisions on the indication and the timing of invasive measures (e.g., carotid endarterectomy or stenting) pose additional challenges different from those for lacunar or cardioembolic infarction. Given the high early stroke recurrence rate, the issue of carotid intervention and the use of aggressive medical therapy is discussed below.

Medical therapy in asymptomatic carotid stenosis
With modern intensive medical therapy, the annual risk of ipsilateral stroke in patients with asymptomatic carotid stenosis (ACS) is now down to ~0.5%. Despite this, there is a widespread practice of routine intervention in ACS with carotid endarterectomy (CEA) and stenting (CAS). This is being justified on the basis of much higher risks with medical therapy in trials conducted decades ago, compared with lower risks of intervention in recent trials with no medical arm. Such extrapolations are invalid.

Although recent trials have shown that after subtracting peri-procedural risks the outcomes with CEA and CAS are now comparable to medical therapy, the peri-procedural risks still far outweigh the risks with medical therapy. In the asymptomatic carotid trial (ACT) 1 trial, the 30-day risk of stroke or death was 2.9% with CAS and 1.7% with CEA. In the Carotid Revascularisation Endarterectomy versus Stenting Trial (CREST) trial, the 30-day risk of stroke or death among asymptomatic patients was 2.5% for stenting and 1.4% for endarterectomy. Thus, intensive medical therapy is much safer than either CAS or CEA.

It is important to understand that patients with ACS have severe atherosclerosis and, besides a moderate risk of stroke, are at high risk of myocardial infarction. Screening for asymptomatic stenosis is justified not just for the purpose of identifying patients for intervention. Ultrasound assessments of atherosclerosis severity may be useful in identifying patients at high risk of coronary events, in whom intensive medical therapy would markedly reduce risk. Indeed, the risk of myocardial infarction in ACS is higher than the risk of stroke. It is thus immaterial that randomised controlled trials have not been carried out to test the efficacy of interventions such as antiplatelet therapy solely for stroke prevention. In the Veteran's Administration trial of ACS, patients with no prior history of coronary disease had a 33% 4-year risk of myocardial infarction. Among patients with diabetes, intracranial stenosis and peripheral vascular disease, the 4-year risk of a coronary event was 69%. It is axiomatic, therefore, that all patients with ACS should receive intensive medical therapy. However, despite widespread belief that carotid endarterectomy (CEA) and stenting (CAS) are justified in ACS, most patients (~90%) with ACS would be better treated with intensive medical therapy than with either stenting or endarterectomy.

The only patients with ACS who should receive surgical or endovascular carotid intervention are those who can be identified as being at high risk of ipsilateral ischemic stroke. Validated methods are transcranial Doppler embolus detection or identification of high risk vulnerable plaques including intra-plaque haemorrhage on MRI, ulceration and plaque lucency on ultrasound, and plaque inflammation on positron emission tomography/CT.

Intensive medical therapy for ACS includes smoking cessation, a Mediterranean diet, effective blood pressure control, antiplatelet therapy, intensive lipid-lowering therapy and treatment with B vitamins (with methylcobalamin instead of cyanocobalamin), particularly in patients with metabolic B12 deficiency. A new strategy called 'treating arteries instead of risk factors', based on measurement of carotid plaque volume, is promising but requires validation in randomised trials.

Carotid intervention – Endarterectomy or Stenting?
The long-term results of CREST may help guide the treatment of patients with carotid artery disease. Emphasis should be given to reducing per-iprocedural risk with both stenting and endarterectomy. In the case of stenting, more than half the ipsilateral-vessel strokes over a 10-year period occurred within the first month. Nonetheless, at centres with experienced interventionists and surgeons who have verifiable good outcomes, as verified during certification in CREST, the rates of per-iprocedural complications were relatively low with stenting and with endarterectomy. Both procedures were associated with rates of stroke that were less than 7% over a 10-year period

Published in October 2006 in the Lancet, the results of a randomized trial of carotid stenting vs endarterectomy in symptomatic patients has failed to demonstrate non-inferiority of the stenting procedure. The trial, called the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) study, actually showed a slightly higher rate of ipsilateral ischemic stroke and death at 30 days in the patients undergoing carotid stenting. "The results of this trial do not justify the widespread use in the short term of carotid-artery stenting for treatment of carotid-artery stenoses," the SPACE investigators conclude in their report. "Patients should be informed that there are insufficient data available for long-term comparison of the 2 treatments."

Our opinion
Despite extensive surgical experience in the vascular team at The Harley Street Heart and Vascular Centre, we are of the opinion that aggressive medical therapy forms the mainstay of stroke and cardiac event prevention in patients with carotid artery disease. Screening for asymptomatic carotid disease and for characterisation of high risk plaque morphology in symptomatic and asymptomatic patients requires a standardised, thorough and validated Duplex ultra-sound technique performed by trained personnel.

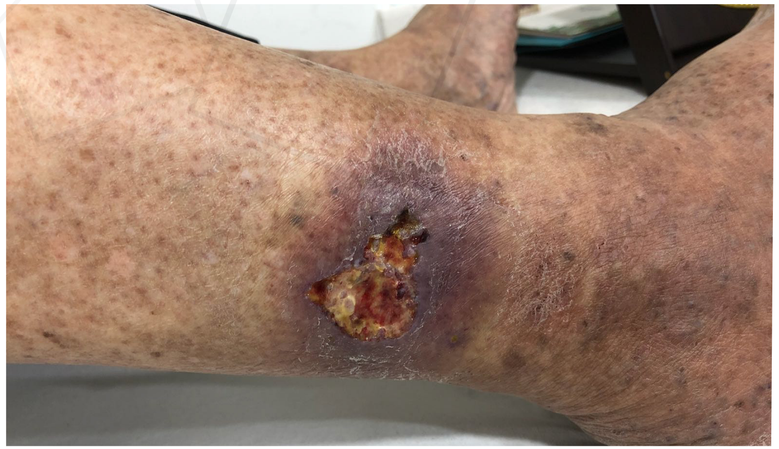
Intervention, if required, should be a carotid endarterectomy in most cases until trial data and verifiable results of an individual endovascular interventionist are available to justify otherwise. Carotid stenting should be reserved for the few symptomatic patients with high risk plaque morphology, hostile surgical necks (previous surgery or radiotherapy to the neck) and angiographically proven (relatively) easy aortic arch anatomy for endovascular intervention.

By **Dr Sriram Narayanan**

Senior Consultant Vascular Surgeon
The Harley Street Heart & Vascular Centre

VASCULAR QUIZ

Please see the clinical picture below and answer the questions that follow:



Questions:

1. What is the likely cause of this ulcer?
2. What non-invasive test would be needed to confirm this as the cause?
3. What non-interventional treatment would be appropriate to heal this ulcer?
4. Is there a role for surgical or minimally invasive intervention to assist in the healing of this ulcer?

Answer is available on our website:
http://www.harleystreet.sg/quiz-answers/medbulletin-sept-2018/

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THE HARLEY STREET HEART & VASCULAR CENTRE

MEDBULLETIN SEPTEMBER2018

THE HARLEY STREET HEART & VASCULAR CENTRE

From left to right:
Dr. Sriram Narayanan, Dr. Peter Ting,
Dr. Rohit Khurana, Dr. Reginald Liew

INTRODUCTION

Greetings from the Harley Street Heart and Vascular Centre! We are pleased to present our second newsletter of 2018 in which we aim to provide the busy clinician with practical updates on the latest advances in the fields of cardiovascular medicine.

In this edition, our cardiologists provide succinct articles shedding new light on how we can best manage both traditional and non-traditional cardiovascular risk factors in our patients with cardiovascular disease. Dr. Reginald Liew addresses the often overlooked lifestyle factors that are important to identify in patients with atrial fibrillation, which can have a significant impact on their overall wellbeing and AF management if successfully implemented. Dr. Rohit Khurana revisits the question of how low we should target cholesterol levels in view of new evidence and treatments available, including the recently introduced PCSK9 inhibitors. Dr. Peter Ting discusses how we can further reduce cardiovascular risk in heart failure patients using a combination of new and traditional measures. Finally, Dr. Sriram Narayanan, our Harley Street vascular specialist, provides an update on how we can best manage patients with carotid disease and decide between medical and interventional therapies.

As usual, the article finishes with an interesting and challenging medical quiz- the answer to the quiz will be posted on our website (www.harleystreet.sg) within a week of the newsletter being sent out.

We hope these articles stimulate and challenge your views on the latest ideas in the treatment of cardiovascular disease. Please feel free to contact us (at enquiries@harleystreet.sg) if you would like to provide any feedback or request a specific topic in future editions.

From The Harley Street Heart & Vascular Centre

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