www.harleystreet.sg
Email **enquiries@harleystreet.sg**

CARDIOVASCULAR EFFECTS

OF ALCOHOL- GOOD, BAD OR NEUTRAL?

Many patients often ask doctors about whether they can continue to consume alcohol, especially if they have heart disease or are on medication. The consumption of alcohol has an important but complex impact on the cardiovascular (CV) system. From a public health perspective, alcohol consumption is regarded as a risk factor for chronic diseases, and globally it contributes to an increase in disease burden. Whilst both irregular binges and chronic heavy drinking can have adverse cardiovascular, biological and social effects, there is also some evidence that light to moderate alcohol consumption, especially in the form of red wine, can be beneficial. This article summarizes the main cardiovascular effects of alcohol and ends with some general recommendations.

How much alcohol is too much?
A "standard drink", consists of an alcohol content of between 10-15g (the WHO definition is 10g). Light alcohol consumption is <7 standard drinks per week (or one drink a day), moderate 7-21 standard drinks per week and excessive > 21 standard drinks per week. One unit of alcohol, as used in the UK, is defined as 10ml (8g) of pure alcohol and is equivalent to one single measure of whisky or a third of a pint of beer or half a standard glass of red wine.

Low-to-moderate daily alcohol consumption (i.e. 1 to 2 standard drinks a day) has been associated with a reduced risk of CV disease and mortality, whereas greater amounts of alcohol consumption (>3 standard drinks a day) and binge drinking (>5 standard drinks in a single sitting) have been linked to an increased risk and should be considered excessive.

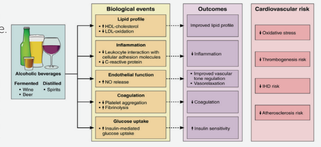
Beneficial effects of light/ moderate amounts alcohol:
The term the "French Paradox" was first coined in 1992, when investigators observed that people living in Southern France had lower rates of ischaemic heart disease (IHD) and associated mortality despite the high intake of saturated fat. The authors attributed the cardioprotective effects of this phenomenon to the moderate consumption of alcoholic beverages, especially red wine, which was highly consumed in the area. The French Paradox started extensive research into wine and led to the identification of many compounds found in wine, namely polyphenols, that are thought to underlie wine's apparent cardioprotective effects. Consequently, scientific advisory committees have labelled moderate amounts of red wine, among other constituents found in the "Mediterranean diet", as having beneficial effects, including improving lipid profile and blood pressure, promoting nitric oxide release, reducing platelet aggregation and improving fibrinolysis.

Detrimental cardiovascular effects of alcohol:
Hypertension- A number of prospective studies and meta- analyses have reported a J-shape relationship between alcohol consumption and the risk of hypertension. The consumption of more than 20 g alcohol/day has been shown to significantly increase the risk of hypertension in women, and higher amounts (31 to 40 g/day) increases the risk in men. However, consumption of <10 g/day in women was associated with a reduced risk of hypertension, whereas in men the alcohol–risk relationship appears to be more linear, highlighting important gender differences in response to alcohol consumption and biological effects [Briasoulis et al 2012]. Consequently, the American Society of Hypertension and the International Society of Hypertension recommend that men limit their alcohol consumption to no more than 2 drinks a day, and women to no more than 1 drink a day.

Ischaemic heart disease (IHD)- The effects of alcohol consumption on IHD also appear to vary in relation to the amount consumed. Investigators have found a U-shaped relationship between alcohol intake and MI risk, with the greatest benefit occurring after up to 2 drinks a day (low/ moderate consumption) and a higher risk after ≥9 drinks a day (heavy consumption) . Within a week after alcohol consumption, there was a lower risk of MI with moderate alcohol consumption but a greater risk with heavy alcohol consumption [Mostofsky et al. 2016]. However, the potential cardioprotective effects of low/ moderate alcohol consumption may not apply in certain racial or ethnic groups, such as in people in South Asia

Heart failure and arrhythmias- Alcohol has a direct acute toxic effect on cardiac muscle that causes in a reduction in systolic contraction which can lead to an alcohol-induced cardiomyopathy if moderate/ high amounts are consumed over a period of time. Alcohol should be consumed with caution in patients with heart failure as they are usually older and are often on numerous medications which can interact with alcohol. Also, the effects of alcohol on diastolic heart failure have not been well investigated.

Cardiac arrhythmias- Alcohol can also cause palpitations due to sinus tachycardia, which can be unpleasant to patients, as well as lead to other cardiac arrhythmias, in particular, atrial fibrillation. One report suggested that binge drinking was associated with an increased risk of new-onset atrial fibrillation.



Biological mechanisms of alcohol (from Haseeb et al. *Circulation* 2017;136: 1434–1448)

Conclusions:
The American Heart Association advisories conclude that a moderate intake of alcohol (1–2 drinks/day) is associated with a reduced CV risk with no clear consensus of wine conferring greater benefits than other alcoholic beverages. For women, however, the general recommendation is that they should not consume more than one drink/day. Mounting evidence suggests that polyphenols within wine can synergistically confer benefits against chronic CV diseases, mostly IHD. To substantially reduce CV disease risk, doctors should still advise patients to focus on having a good balanced and healthy diet, reduce other cardiac risk factors, exercise more and stop smoking. Initiation of drinking should not be recommended as a public health measure because a safe consumption level does not exist.

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

VITAMIN D

AND CARDIAC RISK PREVENTION

Vitamin D deficiency has been estimated to affect 30-50% of adults in developed countries and is largely due to inadequate cutaneous production that results from decreased exposure to sunlight, and to a lesser degree from low dietary intake of vitamin D. Higher risk of deficiency results from increasing age, darker skin pigmentation, clothing, or behaviors that limit sun exposure (for religious, cultural, or health reasons). Those chronically deprived of sun exposure secondary to geography, debilitation or work schedule are also vulnerable.

Human skin synthesizes cholecalciferol, (or vitamin D3) by the photochemical cleavage of cutaneous 7-dehydrocholesterol, which is most efficient at ultraviolet wavelengths. Vitamin D3 is also found naturally in fatty fish, fish oils, and egg yolks (Figure). Vitamin D3 is biologically inert and undergoes sequential hydroxylation steps to generate the 1,25-OH Vitamin D, which is the biologically active metabolite that interacts with the Vitamin D receptor to mediate most of its known functions.

The most suitable metabolite for assessment of vitamin D status is serum 25-hydroxyvitamin D (25-OH D), given its long t½ (weeks v hours for 1,25-OH vitamin D) and its reflection of both dietary intake and cutaneous synthesis. Serum 25-OH D levels >12 ng/ml are generally required to maintain 1,25-OH vitamin D within its narrow physiological range and to suppress parathyroid hormone (PTH), and most current guidelines agree that levels <20ng/ml are inadequate for maintaining bone health and are therefore diagnostic of vitamin D deficiency. Levels >30 ng/mL are considered optimal.

Isolated vitamin D deficiency, confirmed by low serum 25-OH D, commonly manifests as a constellation of vague, local, or diffuse musculoskeletal aches and pains, accompanied by low serum calcium and phosphorus and elevated alkaline phosphatase and PTH levels.

Vitamin D DEFICIENCY AND CARDIOVASCULAR DISEASES: EPIDEMIOLOGY
Vitamin D deficiency has been implicated as an independent risk factor for the prospective development of cardiovascular disease (CVD), including myocardial infarction, congestive cardiac failure and peripheral arterial disease or its risk factors, as well as all-cause and CVD-related morbidity and mortality in several cohort studies that followed hundreds of thousands of subjects for nearly 2 decades. Vitamin D deficiency has been to show upregulation of the renal angiotensin system activation, left ventricular hypertrophy and vascular dysfunction, including exacerbation of atherogenesis and acceleration of arterial calcification.

However, randomized trials examining blood pressure changes with vitamin D supplementation have been generally disappointing. Similarly, a meta-analysis of numerous such trials concluded that vitamin D supplementation is ineffective in lowering blood pressure (BP) and should not be used as an antihypertensive agent. Overall, there were either no changes or only small reductions in BP in most studies. Limited experimental evidence purports to a role of vitamin D in glycaemic control, but again, systematic reviews and meta-analyses of available randomized data demonstrate no beneficial effects of supplementing vitamin D in diabetics. Most randomized vitamin D therapy trials to date were designed to investigate protective skeletal effects; therefore, subjects' mean age exceeded 70 years, they were mostly women (~75%), and many had established CVD or risk factors.

For instance, the Women's Health Initiative (WHI) is the largest randomized trial of vitamin D therapy to date. One year following randomization of 36,282 post-menopausal women to hormonal replacement therapy and/or dietary modifications, participants were asked to participate in a double-blind trial of vitamin D (400 IU/day) in combination with calcium (1 g/day) supplementation. Although designed to investigate skeletal and cancer preventive effects, study investigators pre-specified secondary cardiovascular efficacy endpoints. After 7 years of follow-up, rates of myocardial infarction and coronary disease–related death, revascularization, confirmed angina, strokes, and transient ischemic attacks did not differ between the treatment and placebo groups.

The randomized, placebo-controlled VITAL (VITamin D and Omega-3 triAL) will demonstrate whether cholecalciferol supplementation (2,000 IU/day) over a mean of 5 years, with or without omega-3 fatty acids, affects the incidence of CVD, stroke, and cancer in 25,000 healthy, middle-aged U.S. adults. The results are scheduled to be announced later this year and will provide the much-needed evidence to determine the relationship between vitamin D and CVD.

CURRENT PRACTICE GUIDELINES
There is no disagreement on the importance of recognizing and treating severe vitamin D deficiency (25-OH <10 ng/ml) and most practitioners would consider treating subjects with 25-OH D levels <20 ng.ml. To maintain healthy levels most adults on average probably need 1,000 - 2,000 International Unit (IU)/day. The cardiovascular benefits of vitamin D therapy in patients with chronic kidney disease and hyperparathyroidism have also been long recognized, including BP reduction, improved electrolyte imbalances, and overall reduced cardiovascular mortality rates in patients undergoing hemodialysis. On the basis of the available evidence, routine measurement of 25-OH D levels in cardiac patients is only recommended in patients with risk factors for decreased production, with justification to treat deficiency for improving skeletal health and not yet for lowering long term cardiovascular outcomes. CVD endpoint trials of vitamin D therapy are awaited to support vitamin D therapy for cardiovascular protection, independently of other risk factors.

By **Dr. Rohit Khurana**
Senior Consultant Cardiologist
The Harley Street Heart & Vascular Centre

HORMONE REPLACEMENT

THERAPY AND YOUR HEART

It is a less well known fact that heart disease and stroke combined is the leading cause of death among women in Singapore. While women have a lower risk of heart disease than men do before menopause, after menopause their estrogen levels decline and the risk of heart disease subsequently increases. In the 1980's and 1990's, hormone replacement therapy, now known as menopausal hormonal therapy (MHT) was popularly prescribed for the relief of menopausal symptoms of night sweats, hot flushes, sleep disturbances, psychological and genito-urinary problems, vaginal dryness and for the prevention of osteoporosis. In addition, based on many observational studies showing a striking protective benefit of estrogen on the heart, it was also widely believed that taking MHT would keep their hearts healthy.

After the 1990's however, 2 major studies of MHT users: the randomized controlled women's health initiative (WHI), and the observational million women study (MWS), raised concerns that MHT use may cause more harm than good. Initial reports from WHI suggested that in the overall cohort taking combined estrogen-progestin, there was an increased risk of coronary heart disease (CHD), breast cancer, stroke and venous thromboembolism (VTE) over an average follow-up of 5.2 years. Although there were also significant benefits in reducing the risk of fractures and colon cancer. Unlike the excess overall CHD risk observed in the combined estrogen-progestin trial, the WHI reported no increased risk of CHD in the unopposed estrogen trial. In fact, there was a suggestion of a protective effect in younger women aged 50-59 years. This discrepancy in CHD risk between the unopposed estrogen and combined estrogen-progestin trials suggests that progestin plays a role in the increased CHD risk seen with combination therapy.

As a result of these studies, MHT usage dropped significantly in the following years. More recently however, the sentiment has changed again, with newer observational data and reanalysis of older studies by age or time since menopause, including the WHI, suggesting that for healthy, recently menopausal women, the benefits of MHT (estrogen alone or with a progestogen) outweigh its risks, with fewer CHD events in younger versus older women. It was hypothesized that the timing of exposure to MHT is an important factor in determining subsequent cardiovascular risk. The use of MHT in the early menopausal years (<10years since menopause) does not appear to be associated with an excess risk of CHD when compared with older postmenopausal women. This has been referred to as the "timing hypothesis."

The WHI population was an older population (mean age 63 years) when compared with most observational studies; the older age at the time of MHT initiation would be expected to be associated with more subclinical atherosclerosis at baseline, with advanced or complex atherosclerotic lesions that may be more susceptible to the prothrombotic, proinflammatory effects of estrogen. In contrast, starting MHT soon after menopause may not cause harm (or may possibly be beneficial) because advanced, unstable atherosclerotic plaques have not yet formed.

To date, it is generally accepted that there is an increased risk of stroke with MHT, that did not vary significantly by age or time since menopause. However, the low baseline risk and only modest increase in risk makes this less clinically significant. There was also a definite small but significant increase in the risk of VTE with current MHT. Low doses of transdermal estrogen did not appear to be associated with excess risk in either of these. A further publication in JAMA just this year provides further reassurance. In this study of extended MHT for 5-7 years, and after 18 years of follow-up, MHT was not associated with an increased risk of all-cause mortality compared to placebo.

MHT remains the most effective treatment for menopausal symptoms, and has been show to prevent bone loss and fractures. It can also be life changing for some women with severe symptoms. The risks of MHT differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized to identify the most appropriate MHT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks, with periodic re-evaluation of the benefits and risks of continuing or discontinuing MHT.

By **Dr Peter Ting**
Senior Consultant Cardiologist
The Harley Street Heart & Vascular Centre

CARDIOVASCULAR DISEASE AND NON ALCOHOLIC FATTY LIVER

There are now a number of compelling studies that link Cardiovascular Disease (CAD) with Non- Alcoholic Fatty Liver (NAFLD).

Pais et al (J Hepatol 2016 ; 65:95=102) did a Longitudinal cohort study involving 1732 subjects who went for serial Coronary Artery Calcification (CAC) evaluation using CT calcium score . Half of the participants had NAFLD and the other half did not. The conclusion was that more subjects with NAFLD than without showed coronary artery calcification development or progression. In those without calcification at baseline, NAFLD significantly affected the development of calcification after adjusting for traditional metabolic risk factors. The severity of NAFLD was also dose dependently associated with the development of CAC.

Fracanzani et al (Atherosclerosis 2016; 246:208-213) did a longitudinal cohort study involving 125 NAFLD patients and 250 age and gender matched controls at base line and 10 years later . The main finding is that major cardiovascular events were observed in 19% of NALFD patients, with an estimated cumulative risk significantly higher in NAFLD than in controls. Grade of steatosis, ALT and GGT levels were higher in NAFLDs who developed cardiovascular events.

I would recommend therefore that all patients with NAFLD should be assessed for cardiovascular disease risks – including dyslipidemia , hypertension , diabetes and obesity . Assessment for the metabolic syndrome is crucial in the Cardiovascular Risk Stratification. As defined by the National Cholesterol Education Program (NCEP) – the metabolic syndrome requires the presence of 3 or more of the following components:

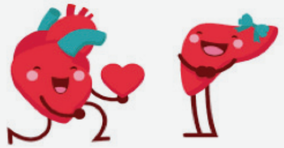
- Increased TG level of >=150mg/dl
- Low HDL level of < 40 mg / dl in men , and < 50 mg/dl in women
- Increased fasting glucose of >= 110 mg / dl
- Hypertension >= 130/85 mmHg or already on anti-hypertensive
- Abdominal obesity (waist circumference of > 102 cm in men and > 88 cm in women)

Patients with NAFLD must be advised lifestyle modifications – including adhering to a low carbohydrate, using low glycemic index carbohydrate and a low fat diet. An exercise regime aimed to achieve a target heart rate of 70% of the maximal heart rate should be done for at least 30 mins 3 times per week. A reduction of weight for those with increased BMI should also be achieved.

For NAFLD patients with increased cardiovascular disease risk, lipid lowering therapy in cases of dyslipidemia should be advised. The use of statins and the incidences of statin hepatotoxicity have not been consistently shown to be of increased risk in NAFLD. The Liver Expert Panel in 2014 (Bays H et al , J Clin Lipidol 2014 ; 8:S47-S57) stated that statins can be safely used in NAFLD but caution that with high dose statins in patients with elevated liver enzymes a more rigorous monitoring of the liver panel would be required – and alternative such as the combination use of Ezetemide should be considered . As for hypertriglyceridemia, first line use of Polyunsaturated Fatty acid (fish oils) can be advocated, failing which use of Fenofibrate can be indicated.

A comprehensive management of Diabetes Mellitus should be done in NALFD patients with hyperglycemia and the use of Metformin, amongst other diabetic medications, has been shown in NAFLD patients to reduce cardiovascular events.

In closing, NAFLD is now considered as a risk factor for unfavourable cardiovascular outcomes. Therefore, NAFLD patients would benefit from more careful cardiovascular surveillance.

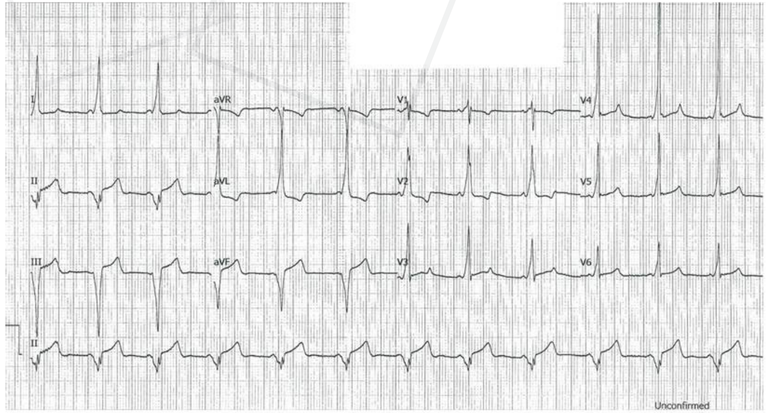


By **Dr Dede S Sutedja**

Senior Consultant Gastroenterologist and Hepatologist
The Singapore Gastroenterology & Liver Internist Centre

ECG QUIZ

Scenario:
The above ECG is that from a 12 year old girl who has had palpitations since the age of 4 and has felt them increase in frequency in the last two months and occur during exercise. She is otherwise fit and well with no other medical history or family history of note.



Questions:

1. What does the ECG show?
2. How would you manage this patient?

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

By **Dr. Reginald Liew**

Senior Consultant Cardiologist
The Harley Street Heart & Vascular Centre

MEDBULLETIN MARCH2018

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 first newsletter of 2018 in which we aim to provide the busy clinician with practical updates in the fields of cardiology and vascular medicine.

The concept of risk factors for cardiovascular disease (CVD) was first introduced through the Framingham Heart Study in 1961 linking the presence of specific antecedent conditions (eg, elevated cholesterol, hypertension, diabetes mellitus, smoking status) to future CVD. Risk factors comprise two major groups, thetraditional and non-traditional. Although traditional risk factors are validated for the diagnosis and management of CVD in many populations, characterizing these attributes does not fully explain incident CVD.

There is an exhaustive and growing list of non-traditional risk factors, which do not have the same weight of evidence validated in prospective studies and which at the current juncture, do not demonstrate independent prediction of vascular events or significantly reclassify CVD risk. The theme of this newsletter is to discuss some of the more commonly observed risks in today's Singaporean lifestyle, and which have the potential to augment clinical CVD risk prediction. Dr Reginald Liew discusses the controversial role of alcohol in cardioprotection, whilst Dr Rohit Khurana focuses on Vitamin D and how deficiency may accelerate CVD risk. Dr Peter Ting shares his thoughts on hormone replacement therapy and finally our guest contributor, Dr Dede Sutedja, a senior gastroenterologist, also based at Gleneagles Hospital writes about a very prevalent condition, fatty liver (hepatosteatosis) and how it relates to increased CV risk.

Please feel free to contact us (enquiries@harleystreet.sg) if you would like to provide any feedback.

From The Harley Street Heart & Vascular Centre

www.harleystreet.sg
Email **enquiries@harleystreet.sg**

LICENSE: MCI (P) 092/01/2018