WINTER 2019

GP Connect

CARDIOVASCULAR CLINICAL UPDATE

Evaluation of Chest Pain

LIPIDS – A practical update 2019

A/Prof Brown moves consulting to Chatswood

Sydney Cardiology

WELCOME

From the editor – Dr Andrew Terluk

This issue of GP Connect focusses on two subjects which are in some ways interrelated.

The first article offers a great insight into how chest pain (and suspected coronary artery disease) is evaluated from a Cardiologist's perspective. With the rise of contemporary imaging modalities such as CT scan, this article offers clarity regarding the use of various investigations and why certain tests are performed in preference to others.

The second piece reviews what we know about lipids in the setting of cardiovascular disease. While there has been some trepidation in recent years regarding lipid lowering medications, the evidence consistently points to benefit in lipid lowering especially in patients with significant risks. Moreover, we can now stratify risk more accurately than ever before; a coronary calcium score (by way of CT scan) is a modality that can be used in selected cases to arbitrate risk.

Thank you for reading, we hope you enjoy.

MEET OUR TEAM

We have experienced cardiologists in all major sub specialities to provide the highest quality of patient care. Our Sydney Cardiology team includes:

Dr James Wong

Specialising in general cardiology, prevention of coronary artery disease and hypertension.

Dr Bill Petrellis

Specialising in general adult cardiology and electrophysiology, including atrial fibrillation and device implantation.

Dr Fiona Foo

Specialising in general and interventional cardiology with an interest in heart disease effecting women and sports cardiology.

Dr Gunjan Aggarwal

Specialising in general adult cardiology and non-invasive cardiac imaging, particularly echocardiography and cardiac CT.

Dr Abhinav Luhach

Specialising in general adult cardiology, cardiac CT and preventive cardiology.

A/Prof Martin Brown

Specialising in advanced heart failure, pulmonary hypertension and transplant cardiology.

Dr Ru-Dee Ting

Specialising in general and interventional cardiology, including cardiac haemodynamic studies and complex coronary intervention.

Dr Andrew Terluk

Specialising in general cardiology with an interest in cardiomyopathy in the setting of cancer.

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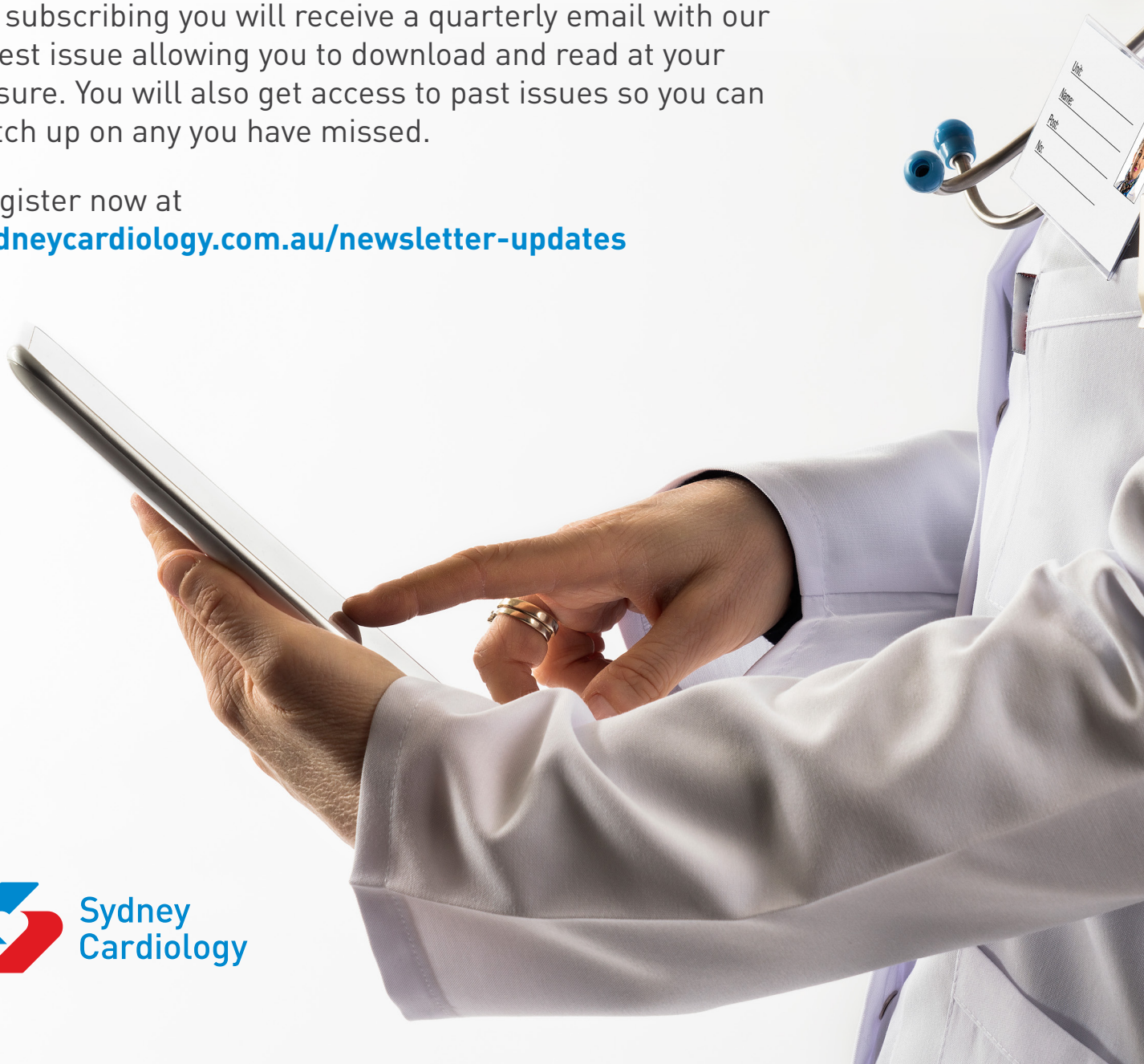


Sydney Cardiology

EVALUATION OF CHEST PAIN

Dr Gunjan Aggarwal

Chest pain is very common in general practice and many patients will present to their general practitioner as the first point of contact. The causes of chest pain can be varied. A careful history, physical examination, resting ECG and appropriate blood tests are required as part of an initial assessment. Cardiovascular investigations are then required to establish the presence of coronary atherosclerosis and obstructive coronary stenosis. The next best non-invasive test will depend upon a number of variables such as availability, cost, radiation exposure, patient's ability to exercise and clinical presentation.

Tests can be divided into functional tests such as exercise stress ECG, exercise stress echocardiography, dobutamine stress echocardiography (for patients that cannot exercise) or myocardial perfusion imaging. Alternatively, newer imaging based anatomical tests such as CT coronary angiography (CTCA) are increasingly being performed for patients with chest pain. The sensitivity and specificity of various test in diagnosing obstructive coronary disease is summarised below in Table 1. CTCA has a very high sensitivity and similar specificity when compared to stress echocardiography which is generally considered a first line diagnostic test in the evaluation of patients with chest pain due to widespread availability and lack of exposure to ionizing radiation.

Table 1: Sensitivity and Specificity of first line tests for evaluation of chest pain

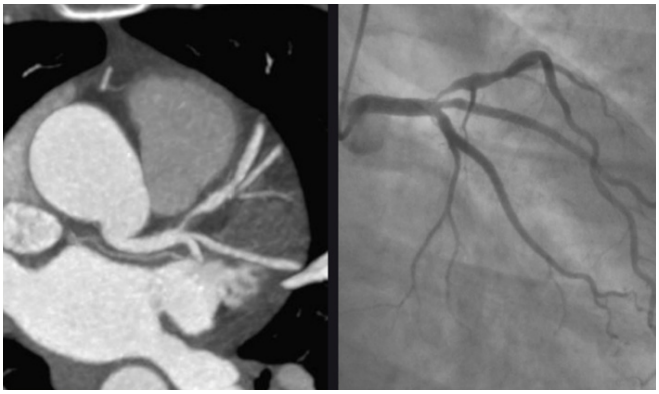
Diagnosis of obstructive CAD		
Test	**Sensitivity**	**Specificity**
Exercise ECG treadmill[1]	68%	77%
Exercise Echo treadmill[2]	86%	81%
Dobutamine Echo[2]	~85%	~85%
Exercise nuclear treadmill[3]	87%	73%
Pharmacologic nuclear[3]	89%	75%
Coronary CTA[4]	**95%**	**83%**

1. ACC/AHA 2002 Guideline Update for Exercise Testing
2. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography
3. ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging
4. ACCURACY study

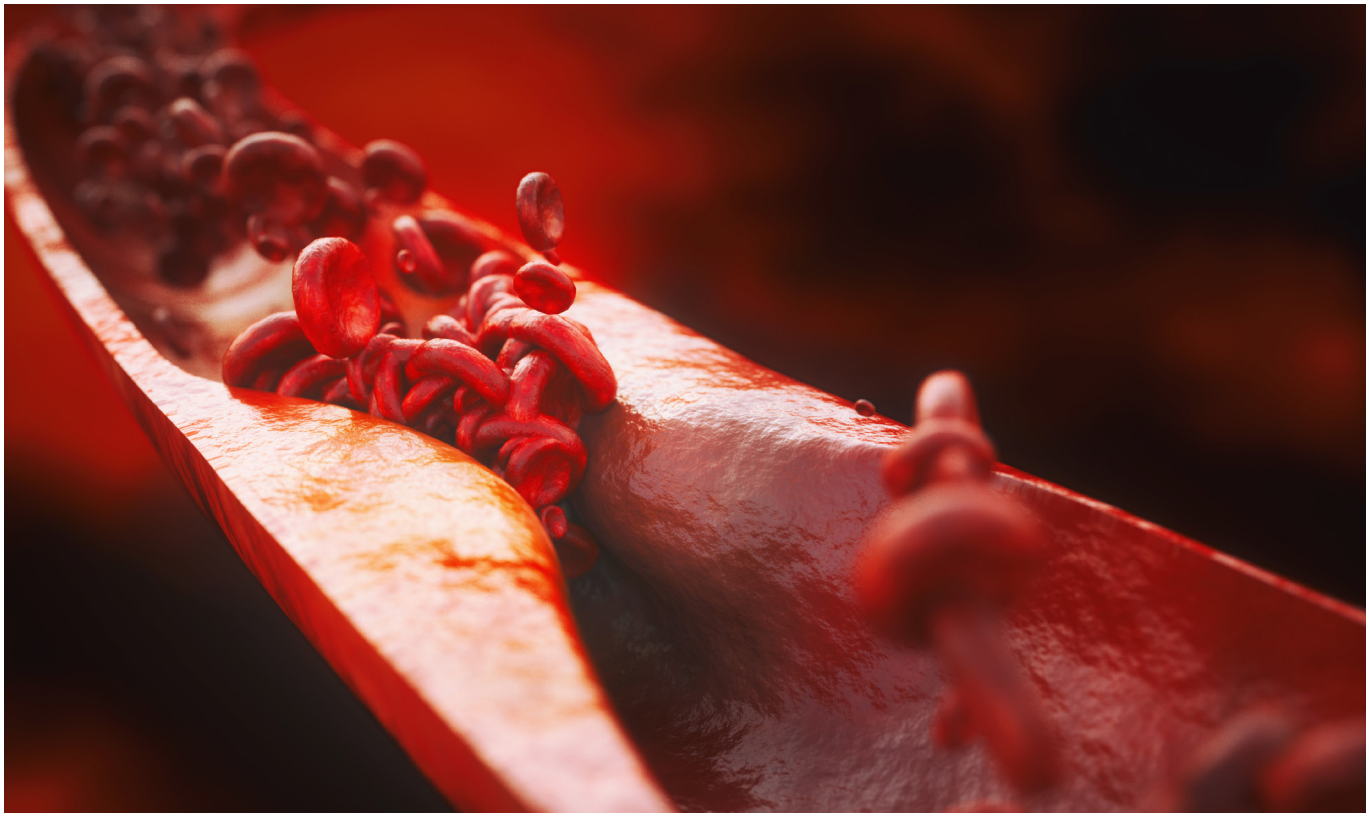
INTRODUCTION TO CT CORONORY

CTCA is a new imaging modality that allows non-invasive evaluation of the coronary arteries. This new technology has advanced rapidly in the last few years and current generation scanners can provide high resolution images of the entire heart at a high speed with very low radiation exposure from as low as around 1mSv (equivalent to a mammogram) to 3 mSv (equivalent to annual background radiation). The ability to provide similar anatomical information such as the presence of atherosclerotic plaque causing coronary artery disease is attractive as it avoids some of the risks associated with invasive coronary angiography (Figure 1). Appropriate use of CTCA allows a reduction in use of invasive coronary angiography which is around five times more expensive making it a more cost effective test that reduces downstream testing, hospital admission and resource utilisation.

FIGURE 1: CTCA and invasive angiogram of a patient with severe stenosis of the proximal Left Anterior Descending artery showing very good correlation



By demonstrating the presence and extent of both non-calcified and calcified plaque, it can also provide very useful prognostic information about the future risk of cardiovascular events such as myocardial infarction. The visualisation of atherosclerotic plaque often provides a strong motivating impetus to the patient to implement preventative strategies such as commencement of aspirin, statins, appropriate lifestyle modification such as dietary change, commencement of an exercise programme, cessation of cigarette smoking and aggressive cardiovascular risk factor management.



SCAN BASICS

Every CTCA performed includes a coronary artery calcium score as routine. Electrocardiogram (ECG) gating allows acquisition of images in diastole when coronary artery motion is minimal. In order to achieve optimal image quality, it is recommended that patients are in sinus rhythm with a heart rate less than 60. This is achieved by premedicating patients with beta blockers such as metoprolol the day before and morning of CTCA. Ectopy, arrythmia such as atrial fibrillation or rapid heart rates can cause malalignment of the images causing step artifact or blurring of the images resulting in difficulty with interpretation. Patients should be able to hold their arms above their head during the scan and also be able to hold their breath for 10 seconds. They should have normal renal function with no previous contrast allergy.

DIAGNOSTIC ACCURACY

CTCA has been shown to be most useful in ruling out significant coronary disease in symptomatic patients presenting with chest pain and a low to intermediate pretest probability of coronary artery disease. This is because it is a highly accurate test with a very high negative predictive value around 98% allowing it to 'rule out' coronary artery disease as a cause for a patient's chest pain. The diagnostic performance of CTCA has been evaluated in multiple prospective randomised trials that are summarised in Table 2.

Table 2: Diagnostic performance of CTCA vs invasive coronary angiography

Diagnostic Performance of CCTA: Three (3) Prospective Multicenter Studies				
	Sensitivity	**Specificity**	**PPV**	**NPV**
ACCURACY	94	83	48	99
	N=230, Stable Chest Pain; No known CAD; No exclusion (CACS, HR, BMI); CAD prevalence 13%			
Meijboom	99	64	85	97
	N=360, Acute and Stable Chest Pain; No known CAD; CAD prevalence 68%			
CorE64	85	90	91	83
	N=291, Stable Chest Pain; No known and Known CAD; Exclusion CACS>600; CAD prevalence 56%			

Source: Budoff et al. JACC 2008; Miller et al. NEJM 2008; Meijboom et al. JACC 2009

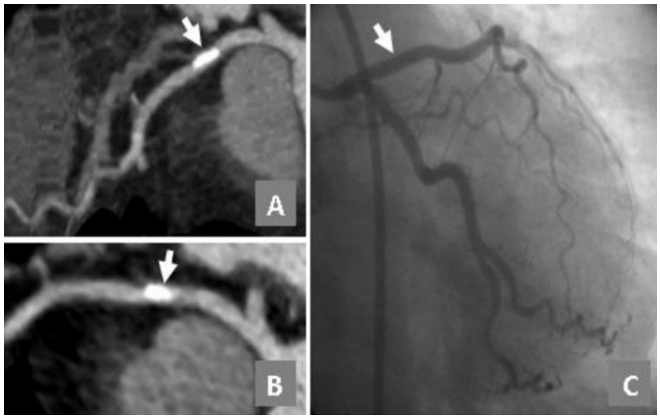
The pretest probability of coronary artery disease can be estimated depending on clinical parameters such as age, sex, characteristics of chest pain and whether it occurs with effort and the presence of other cardiovascular risk factors.

EVALUATION OF CHEST PAIN (CONTINUED)

CTCA can also allow assessment of the aorta, pulmonary vessels, mediastinum and lung thus ruling out other causes of chest pain such as hiatus hernia, pulmonary embolus or aortic dissection.

It is less useful in symptomatic patients with known coronary artery disease or in those with a high pretest probability of coronary artery disease. This is because the percentage of coronary luminal stenosis on CTCA often appears more severe compared with invasive coronary angiography. In these patients the presence of excessive coronary calcification can also hinder assessment of the underlying coronary vessel lumen due to 'blooming artifact' making it difficult to quantify accurately the degree of coronary stenosis at thresholds where it is clinically significant e.g. >70% stenosis vs 50-70% stenosis (Figure 2). In these patients a functional test to assess for the presence of myocardial ischemia such as stress echocardiography is more useful clinically before deciding on the need to proceed to invasive coronary angiography.

Figure 2 A and B: The presence of significant coronary calcification on CTCA is a significant limitation as makes it difficult to ascertain with certainty the degree of underlying coronary stenosis. Figure 2C: Corresponding invasive coronary angiogram however shows no luminal stenosis.



CLINICAL INDICATIONS

Currently appropriate medicare rebateable indications for CTCA in Australia include **patients with stable symptoms such as chest pain or dysnoea** with effort consistent with coronary ischemia due to possible obstructive coronary artery disease and a low – intermediate pretest probability of ischemic heart disease who would have otherwise been considered for invasive coronary angiography. It is also approved to exclude coronary anomalies or fistulae and preoperative evaluation of coronary arteries before non-coronary cardiac surgery.

Other clinical settings where CTCA can be a useful test include:

1. Patients with chest pain and a equivocal or uninterpretable stress echocardiogram (due to left bundle branch block or suboptimal image quality).
2. Patients with a previous negative functional test such as nuclear scintigraphy or stress echocardiography and recurrent chest pain.
3. Evaluation of patency of bypass grafts (because grafts do not move unlike native coronary arteries they can be assessed with ease and a high degree of accuracy).
4. Exclusion of ischemic heart disease as a cause in patients with new onset heart failure or cardiomyopathy.
5. Evaluation of acute chest pain in the emergency department when ECG and cardiac enzymes are normal.
6. Assessment of congenital heart disease, cardiac masses or pericardial conditions (when other more appropriate tests such as echocardiography or cardiac MRI are non-diagnostic, contraindicated or unavailable).
7. Evaluation of pulmonary vein anatomy prior to pulmonary vein isolation for atrial fibrillation.
8. Coronary vein mapping prior to insertion of biventricular pacemaker.

Currently the use of CTCA is considered inappropriate or uncertain as per guidelines for the following groups of patients:

1. Patients with known coronary artery disease or high pretest probability of ischemic heart disease. (A functional test such as stress echocardiography should be considered first line in these patients).
2. Patients with small diameter stents (<3mm) that is not in a proximal coronary artery.
3. Asymptomatic patients. (Coronary artery calcium scoring may be more appropriate for these patients in certain clinical settings).
4. Patients with an acute coronary syndrome with positive serial cardiac enzymes and abnormal resting ECG. (These patients should be referred to an emergency department and will need invasive coronary angiography).

SUMMARY

1. CTCA is a rapidly evolving non-invasive imaging test that is very useful in the evaluation of patients with chest pain.
2. It has a high, negative predictive value allowing clinicians to confidently 'rule out' significant obstructive coronary stenosis.
3. It is an appropriate test in selected symptomatic patients with a low to intermediate pretest probability of coronary artery disease.
4. It has the added benefit of being able to diagnose other causes for the patient's symptoms such as pulmonary, mediastinal or aortic pathology.
5. Its use is generally considered uncertain and it should not routinely be used in asymptomatic patients, patients with known coronary artery disease or patients with a high pretest probability of ischemic heart disease.
6. Careful attention to patient preparation including pretreatment with beta blockers is mandatory to achieve diagnostic image quality and also reduce radiation dose.
7. It has the potential to provide powerful prognostic information about the future risk of cardiovascular events by demonstrating the extent of atherosclerotic plaque therefore allowing introduction of medical therapy such as aspirin and statins in appropriate patients.

A/Prof Martin Brown will now be consulting at Chatswood from mid September 2019.

A/Prof Martin Brown will be moving his patient consulting from Bella Vista to Chatswood. From 16th September patients will be able to consult with A/Prof Martin Brown at our Chatswood location.

The new address is:

Suite 901
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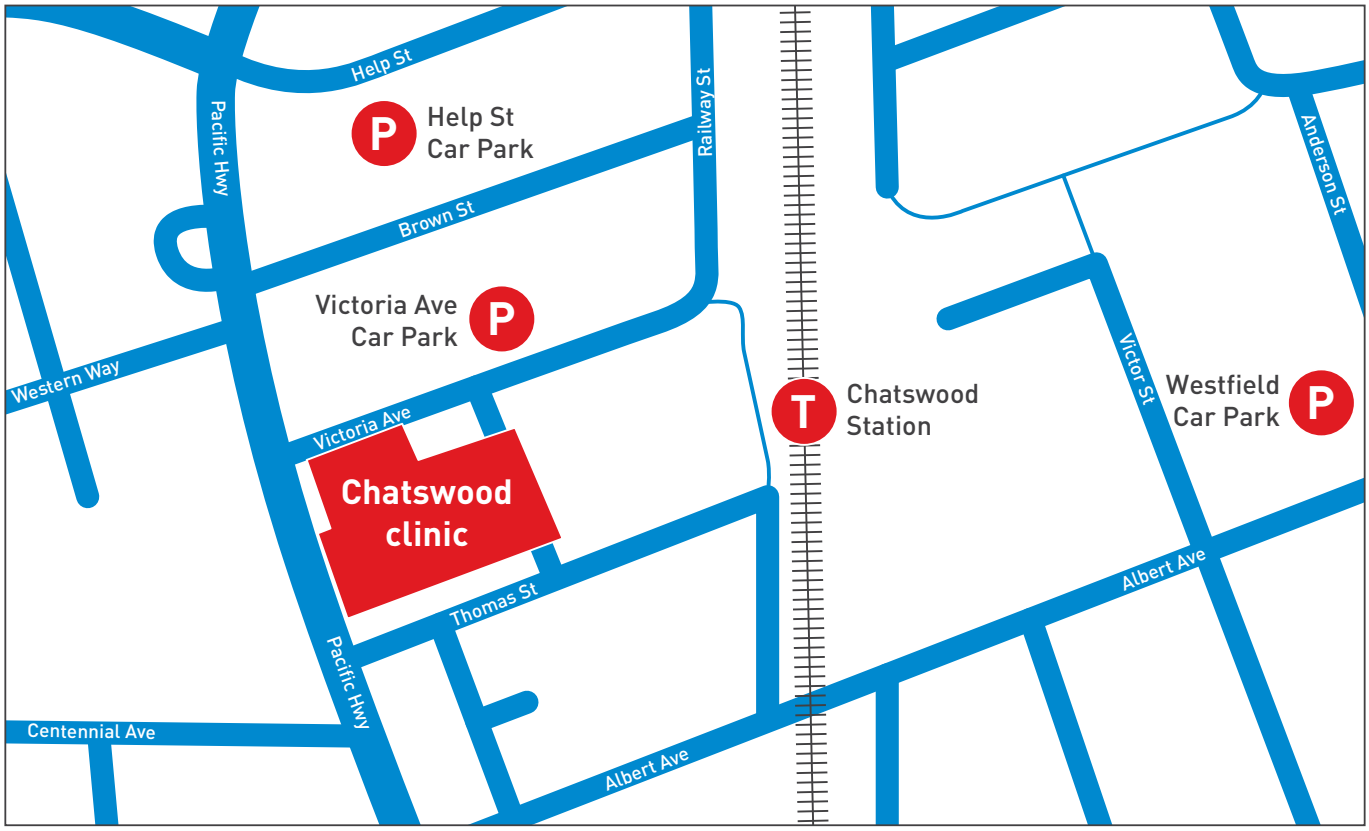

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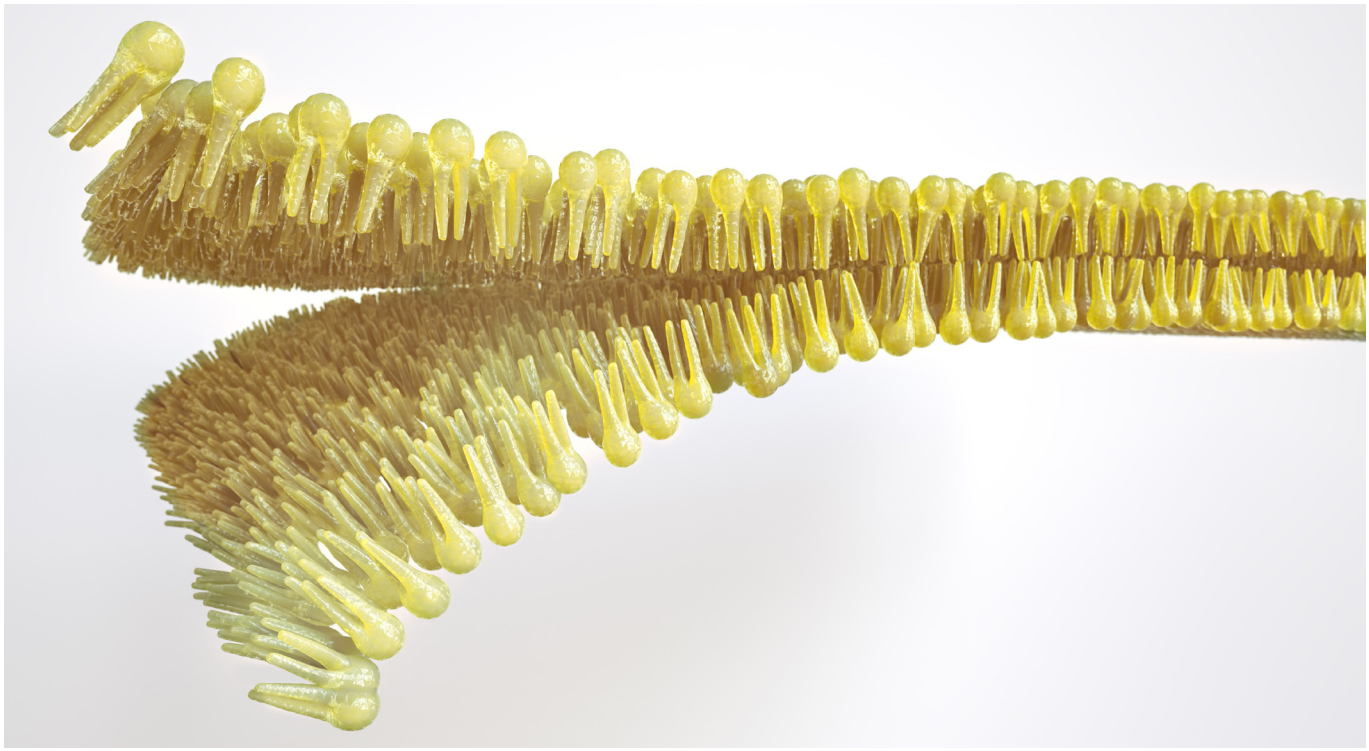
LIPIDS – A PRACTICAL UPDATE 2019

Dr James Wong



'In all individuals, emphasise a heart-healthy lifestyle across the life course'. This is the number one message to reduce cardiovascular risk from the recent US Cholesterol Clinical Practice Guidelines (2018).

In terms of **diet**, it is recommended that:

'patients should consume a dietary pattern that emphasises intake of vegetables, fruits, whole grains, legumes, healthy protein sources (low-fat dairy products, low-fat poultry (without the skin), fish/seafood, and nuts), and nontropical vegetable oils; and limits intake of sweets, sugar-sweetened beverages, and red meats. This dietary pattern should be adjusted to appropriate calorie requirements, personal and cultural food preferences, and nutritional therapy for other medical conditions including diabetes. Caloric intake should be adjusted to avoid weight gain, or in overweight/obese patients, to promote weight loss.'

And for **exercise**:

'In general, adults should be advised to engage in aerobic physical activity 3-4 sessions per week, lasting on average 40 minutes per session and involving moderate-to vigorous-intensity physical activity.'

Also that lifestyle therapy is the primary intervention for the metabolic syndrome.

LDL cholesterol is the dominant form of atherogenic cholesterol and **'the lower the better'** prognostic message has been reinforced by studies using ezetimibe and the PCSK9 inhibitors in addition to statin therapy.

- statins remain the cornerstone of therapy among lipid lowering drugs
- In IMPROVE IT the addition of ezetimibe to moderate intensity statin therapy among patients with ACS and LDL cholesterol levels >1.3mmol/l resulted in significant CVD risk reduction (7% relative risk reduction; 2% absolute risk reduction) at follow-up of 6 years.
- The FOURIER trial evaluated the PCSK9 inhibitor evolocumab in patients with atherosclerotic cardiovascular disease with LDL cholesterol >1.8mmol/l already on maximal statin + ezetimibe. At a median followup of 2.2 years evolocumab significantly reduced composite atherosclerotic cardiovascular disease – 15% relative risk reduction and 1.5% absolute risk reduction. There was incremental benefit down to LDL cholesterol of 0.5mm0l/l with no safety issues.

- The ODYSSEY OUTCOMES trial tested alirocumab, another PCSK9 inhibitor in > 18,000 acute coronary syndrome patients already on maximal statin + ezetimibe over a median of 2.8 years and found a 15% relative risk reduction (1.6% absolute risk reduction) in composite cardiovascular events.

Those with cardiovascular disease are now stratified by risk status.

'In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy. *The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a maximally tolerated statin to lower LDL-C levels by ≥50%.'*

The Guidelines recommend:

'In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy. *Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L). In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices.'*

Those at very high-risk of future ASCVD events include

- recent acute coronary syndrome within past 12 months
- history of myocardial infarction
- history of ischaemic stroke
- symptomatic peripheral arterial disease

High-risk conditions include:

- age > 65 years
- heterozygous familial hypercholesterolaemia
- history of prior coronary bypass surgery or percutaneous coronary intervention
- diabetes mellitus
- hypertension
- CKD (eGFR 15-59ml/min/1.73m2)
- current smoking
- persistently elevated LDL-C > 2.6mmol/l despite maximally tolerated statin therapy and ezetimibe
- history of congestive heart failure

'In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. *If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable. If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is low at mid2018 list prices.'*

For Diabetes:

'In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. *In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.'*

'There is limited information on ASCVD rates among individuals 20 to 39 years of age with diabetes mellitus and no information on whether statin therapy is beneficial in these individuals. Available evidence indicates that although rates of ASCVD are low in those < 30 years of age, they increase with time and may reach intermediate-risk levels by 30 to 39 years of age, especially in individuals with long-standing type 2 diabetes mellitus, who may have more advanced subclinical coronary atherosclerosis than do nondiabetic subjects, and in those with type 1 diabetes mellitus of> 20 years' duration. ASCVD rates will also be influenced by hypertension and diabetic microvascular complications that may be prevalent in these age groups. Thus, it may be reasonable to have a discussion about initiating moderate-intensity statin therapy with patients who have had type 2 diabetes mellitus for at least 10 years or type 1 diabetes mellitus for at least 20 years and with patients with 1 or more major CVD risk factors or complications, such as diabetic retinopathy, neuropathy, nephropathy

(eGFR <60ml/min/1.73m2 or albuminuria > 30mcg albumin/mg creatinine or an ABI < 0.9.'

The intensity of statin therapy is divided into 3 categories ie high-intensity, moderate-intensity and low-intensity:

	High intensity	Moderate intensity	Low intensity
LDL-C lowering	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40mg) 80mg** **Rosuvastatin 20mg (40mg)**	**Atorvastatin 10mg** (20mg) **Rosuvastatin** (5mg) **10mg** **Simvastatin 20-40mg**	Simvastatin 20-40mg
	...	**Pravastatin 40mg** (80mg) **Lovastatin 40mg** (80mg) Fluvastatin XL 80mg **Fluvastatin 80mg BID** Pitavastatin 1-4mg	**Pravastatin 10-20mg** **Lovastatin 20mg** Fluvastatin 20-40mg

PRIMARY PREVENTION

For those without cardiovascular disease, the Guidelines suggest that treatment decisions be tailored to an individual's risk, using a framework of "CPR for prevention" (Calculate the risk, Personalise the risk and Reclassify the risk if needed). The process starts with estimation of the 10-year risk using the Pooled Cohort Equations risk algorithm (we use Australian absolute CVS risk calculator for 5 year risk prediction). Clinicians and patients should then consider risk-enhancing factors, such a inflammatory illnesses, chronic kidney disease, early menopause, and even South Asian ethnicity, that may indicate a higher risk. The guidelines stress that patients should play a central role in the decision-making process.

For those patients who remain unsure whether to initiate therapy after clinical risk assessment, the Guidelines suggest that **coronary calcium scoring is useful to reclassify risk**, specifically recommending that intermediate-risk patients who have a coronary calcium score of 100 should receive a statin, whereas those with a calcium score of 0 may defer statin therapy.

Risk factor algorithms unfortunately have significant limitations in individuals and can misclassify a large number of people, leading to inappropriate and inadequate treatment and are poor at motivating lifestyle changes.

- Subclinical atherosclerosis is common in patients with normal or even optimal LDL cholesterol levels. In the PESA (Progression of Early Subclinical Atherosclerosis) study, investigators found subclinical atherosclerosis in 50% of the participants who had no obvious risks factors.
- Of those with heart attacks, 62% of men and 53% of women have none or only one coronary risk factor.
- A persuasive commentary in Heart, Lung and Circulation journal by Prof Con Aroney recently called for coronary calcium scoring be used as the central tool for cardiac risk assessment and not the CVD risk calculator.

A **CAC score of zero** indicates a low coronary risk for 5-10 years. There are exceptions and CAC scores of zero in persistent cigarette smokers, patients with diabetes mellitus, those with a strong family history of atherosclerotic heart disease and chronic inflammatory illness may still be associated with substantial risk.

Statin safety and statin-associated side effects:

- statin therapy is usually well-tolerated and safe
- the large majority of patients are able to tolerate statin rechallenge with an alternative statin or alternative regimen
- statin associated muscle symptoms an be challenging to assess and manage and the Guideline recommends a comprehensive approach to statin associated muscle symptoms
- it is very concerning that 45% of patients in Australia are not receiving intensive lipid lowering therapy in the 12 months after their acute coronary syndrome (CONCORDANCE ACS registry). An editorial in the February 2019 MJA called for a multidisciplinary patient-focused approach to improve this situation.

NOTES AND REFERENCES

1. Grundy SM, et al. 2018 Cholesterol Practice Guidelines (Accepted Manuscript)
2. Passages in italics are taken from the Guidelines
3. Editorial, Circulation 2019;139:1335
4. Should Coronary Calcium Scoring be used as the Central Tool for Cardiac Risk Assessment. Con Aroney, Heart, Lung and Circulation(2019) 28,207
5. Subclinical atherosclerosis in absence of cardiovascular risk factors JACC March21, 2017,69.
6. David Brieger et al Intensive lipid-lowering therapy in the 12 months after and acute coronary syndrome in Australia: an observational analysis MJA 210(2) 4Feb2019
7. Editorial Karam Kostner MJA 210(2) 4Feb2019

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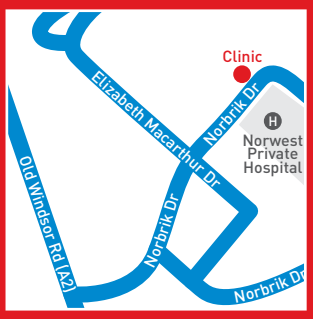

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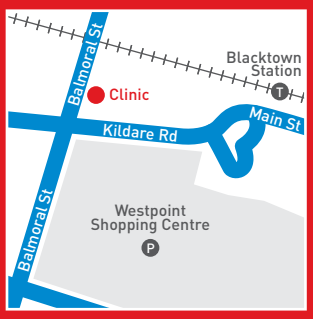

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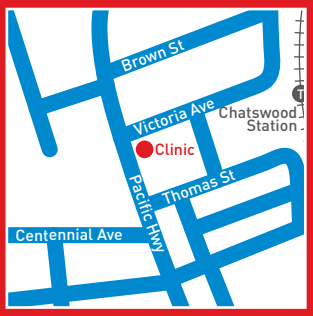

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