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GENETIC

DYSLIPIDEMIAS

Introduction
Dyslipidemia is a common problem that doctors face in daily clinical practice. The causes can be broadly divided into primary (genetic) or secondary. The focus of this article is on primary or genetic dyslipidemias, in particular familial hypercholesterolemia (FH), and why it is important to identify these patients.

Secondary causes must always be considered when managing newly diagnosed dyslipidemia. The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol, and trans-fats. Other common secondary causes include diabetes mellitus, alcohol overuse, chronic kidney disease, hypothyroidism, cholestatic liver diseases and drugs.

Common genetic dyslipidemias
Genetics variants in key genes that are involved in lipid synthesis, transportation or processing have a strong influence on blood lipid levels. The most common form of genetic dyslipidemia is polygenic, involving more than one genetic variation. This is usually less severe than monogenic or familial dyslipidemias. These individuals often have severely abnormal blood lipid levels, which results in early-onset cardiovascular disease. Familial hypercholesterolemia (FH) is a genetic disorder of lipid metabolism that is typified by considerable elevations in levels of low-density lipoprotein cholesterol (LDL-C). The etiology of FH comprises of known mutations in the gene of the LDL receptor (LDLR), the proprotein convertase subtilisin-kexin type 9 (PCSK9) gene, the gene of apolipoprotein B (ApoB) or rare mutations in LDL receptor adapter protein 1 (LDLRAP1) gene.

Familial hypercholesterolemia is an autosomal dominant genetic disorder due to mutation in the LDL receptor gene and has an estimated prevalence of 1 in 200 to 500 for the heterozygous form. Apolipoprotein B mutations which results in a defect in the LDL receptor binding region occur roughly 1 in 1000. Both lead to decreased LDL clearance, and can present with similar clinical signs of tendon xanthomas, corneal arcus, premature coronary artery disease (ages 30-50), and have a total cholesterol of between 250-500mg/dl (7-13mmol/L). PCSK9 gain of function mutations are thought to be rare. Familial combined hyperlipidemia has a prevalence of 1 in 50 to 100. In addition to the above clinical findings, they also have raised triglycerides in the range of 250-750mg/dl (2.8-8.5mmol/L). The genetic mechanism is unknown, but possibly involves multiple gene defects. The homozygous form of FH is thankfully very rare, about 1 in 1 million, but presents with the severest form of the disease. In addition to the above manifestations, they may have planar and tuberous xanthomas, and may get CAD even before the age of 20. Total cholesterol often exceeds 500mg/dl (>13mmol/L).

Diagnosing FH
The diagnosis of FH is based primarily on the finding of severe LDL-C elevations in the absence of secondary causes of hypercholesterolemia. A widely used diagnostic tool is the Simon Broome criteria, which takes into consideration cholesterol concentrations, clinical characteristics, molecular diagnosis, and family history. In general one should suspect FH if there is a family history of diagnosed FH, or an adult with plasma cholesterol of >8mmol/L (>310mg/dL), a child with plasma cholesterol of >6mmol/L (>230mg/dL), premature coronary artery disease, tendon xanthomas, or family history of premature coronary artery disease or sudden cardiac death. A substantial increase in serum triglyceride levels should also raise the possibility of another lipid disorder such as familial combined hyperlipidemia.

Clinical importance and therapeutic strategies
It is essential to consider the possibility of a genetic dyslipidemia because many of them, such as FH have an autosomal dominant genetic transmission and therefore will be present in approximately 50% of other family members. The recognition of the possibility of a genetic disorder will lead to screening family members and early treatment initiation if abnormalities are found, which may prevent the adverse consequences of hyperlipidemia.

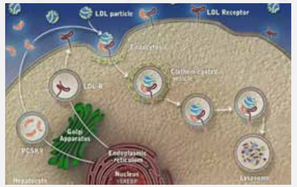

Fig.1) LDL receptor is a key player in the LDL cholesterol metabolism. Abnormalities its function result in more LDL cholesterol remaining in the blood stream. PCSK9 prevents the normal recycling the LDL receptor leading to its destruction.

When considering treatment, contributing secondary factors including lifestyle factors need to be identified and concurrently addressed. Although we cannot change our genetic makeup, there is good evidence that healthy lifestyle habits such as good nutritional choices, physical activity are effective interventions for lowering triglycerides, increasing HDL, as well as reducing LDL cholesterol levels. Obesity, in particular central or visceral adiposity strongly promotesinsulin resistance. Persistent insulin resistance, also known as metabolic syndrome prevents glucose and lipid uptake by the cells, leading to dyslipidemia.

However lifestyle modifications are less likely to reduce cholesterol levels adequately and drug therapy will often be required. This invariably will involve a potent statin, often in combination therapy with ezetimibe, bile acid sequestrants or niacin. In fact ACC/AHA recommend treating adults with LDL-C>4.9mmol/L (>190mmg/dL). PCSK9 monoclonal antibodies delivered as subcutaneous injections once or twice a month may be available soon in Singapore and is an excellent option, but cost may be an issue. They prevent PCSK9 from attaching to LDL receptors, leading to improved function of these receptors and LDL lowering by an impressive 40-70%. Long term clinical trials on cardiovascular outcomes are underway, but initial results are encouraging. In individuals suspected of genetic dyslipidemias, it might also be prudent to consider screening for asymptomatic cardiovascular disease.

By **Dr. Peter Ting**
Senior Consultant Cardiologist
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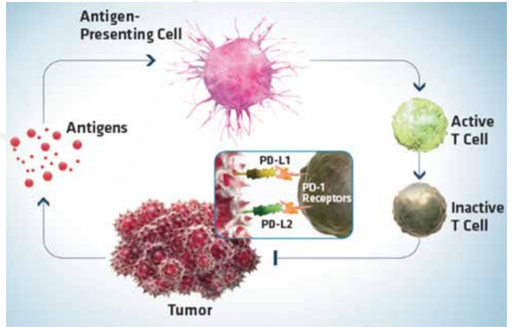
LUNG CANCER

IMMUNOTHERAPY CAN PROLONG SURVIVAL IN LUNG CANCER

One of the most exciting development in the past 12 months in the field of oncology has definitely got to be the approval by the Food and Drug Administration (FDA) in the US of the immunotherapy drugs, Nivolumab and Pembrolizumab, for the treatment of advanced lung cancer. Nivolumab, in particular, had been shown in phase III studies to prolong overall survival in lung cancer patients after failure of first line chemotherapy.



Lung cancer has long been the top cause of cancer deaths worldwide even though other cancers such as breast and colon are more common. The reason being that very often, lung cancers are diagnosed in more advanced stages. Chemotherapy and targeted therapy remain the standard of care for the first line treatment of such cancers which are considered incurable. Subsequent treatment also often involve chemotherapy which may yield low chances of response and pose potential toxicity to patients who already have compromised performance status.

Patients are usually treated with platinum based chemotherapy combination which is the standard of practice. When the cancers progress, other chemotherapeutic agents such as Docetaxel, Gemcitabine or Vinorelbine are used. Immunotherapy now offer another option when this change in treatment is needed. In the phase III study which led to the registration and the approval of the drug, Nivolumab was compared to Docetaxel which is the standard second-line chemotherapy. The median overall survival was 12.2 months for patients in the nivolumab group and 9.4 months among patients in the docetaxel group. This difference was statistically significant. At 1 year, the overall survival rate was 51% with nivolumab versus 39% with docetaxel. There were also fewer adverse events of grade 3 or 4 in the Nivolumab group. The common ones were rashes, fatigue and loss of appetite.

Cancers commonly express the ligands PD-L1 and PD-L2 which when bound to the PD-1 receptor on the T cells in our body, will render the immune system unable to recognize the cancers as foreign. Both Nivolumab and Pembrolizumab are PD-1 inhibitors which are able to disrupt this mechanism, thus restoring the ability of our immune system to recognize the cancers as a threat and kill the cancer cells. The drugs are given as intravenous infusion over a short period with no premedication needed. Therefore they are very convenient to give as they only need to be administered once every 2 or 3 weeks depending on the drug used.

That is not to say that chemotherapy is no longer indicated. On the contrary, it remains an important option as part of the ongoing treatment of advanced cancers. Immunotherapy may have offer double the chance of a response compared to chemotherapy. However, not everyone will benefit to the same extent. The race is on to identify the most suitable patients for these treatment by identifying potential biomarkers such as PD-1 and PD-L1 staining levels on pathology specimens.

There were a number who underwent complete remission with immunotherapy and a significant number of others who had very prolonged control of their cancers without the usual side effects of chemotherapy such as hair loss or risks of infection.

Many other PD-L1 inhibitors are in the pipeline for development and this change in treatment paradigm is rapidly expanding to other tumors such as colon, ovary and liver cancers. They have already been approved for renal cancers and melanoma.

By **Dr. Ooi Wei Seong**
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DIABETES

MANAGEMENT OF DIABETES MELLITUS IN CAD PATIENTS

1 in 9 Singaporeans suffer from diabetes while 1 in 3 deaths in Singapore daily is due to cardiovascular disease. Hence the management of many patients with CAD involves optimal control of their diabetes. With optimisation of HbA1c comes a decrease in the risks of mortality, microvascular and macrovascular diseases, including myocardial infarction, especially if patients are treated earlier on in the disease. Indeed a delay in optimisation of DM control has been found to have substantial impact on mortality rates in the future.

Adoption of an individualized and multi-factorial risk factor approach to management of DM in CAD patients is crucial. Individualization starts right at the first consult from determining the optimal level of diabetes control to the choice of treatment. We have now a panoply of drugs with different mechanisms and each group of drugs come with their inherent side effects and optimal situations for use. Below are some practical tips of management for the patients:

1) Set an appropriate HbA1c goal and amend accordingly if things change in the future. Differing international guidelines would give a goal that is less than 6.5-7%. In general the healthier and younger the patient, the more stringent the goal should be. In patients with established CAD though, one should avoid hypoglycaemia.

2) Metformin is a well established drug that has demonstrated mortality benefits in diabetic patients including cardiac events and unless contraindicated, should usually be the first drug of choice.

3) A second drug choice depends on patient's characteristics. Weight loss and avoidance of hypoglycaemia would be plus points. Hence, drugs such as such as GLP-1 agonists and SGLT2 inhibitors might be a consideration for these patients. Cardiovascular benefit is neutral for GLP-1 but SGLT2 inhibitors such as empaglifozin has recently been proven to have cardiovascular benefit. DPP-4 inhibitors and alpha-glucosidase inhibitors are neutral in terms of weight and most are neutral as well for cardiovascular outcomes. Sulphonylureas have a higher risk of hypoglycaemia and weight gain. Thiazolidinediones are associated with weight gain and may exacerbate heart failure.

4) Manage your patients' expectations. Progression of the disease and hence a worsening HbA1c control in the future is to be expected and not regarded as management failure. HbA1c deterioration occurs around 0.2% per year on stable oral agents.

5) Insulin initiation in patients who need them should not be delayed. In general consider insulin in those with suboptimal control and already on 3 oral drugs or earlier especially if the HbA1c is still high eg over 9%. Basal insulin is usually started as this has a lower risk of hypoglycaemia and also weight gain. Thereafter a step-wise approach to adding on pre-meal insulin might be prudent depending on the patient's blood glucose monitoring profile.

6) The greatest barrier to insulin initiation is the physician's own insulin resistance. If you cannot even try on yourself with a syringe containing saline, how then would you be able to convince your patients to start on insulin?

7)Ultimately, the best drug is the one that the patient takes and continues to take. Hence individualized medication in terms of the side effects, the cost and the frequency of the medications, amongst other barriers to compliance, are issues to think about before prescribing.

By **Dr. Vivien Lim**
Specialist in Endocrinology
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STABLE ANGINA

MANAGEMENT CONCERNS IN STABLE ANGINA

Stable coronary artery disease (CAD) is generally characterized by episodes of reversible myocardial demand/supply mismatch, related to ischaemia, which are usually inducible by exercise, emotion or other stress and reproducible. It also includes the asymptomatic phase following an acute coronary syndrome. Discomfort related to myocardial ischaemia (angina pectoris) has the following characteristics:

- Located in the chest, near the sternum, but may be felt anywhere from the epigastrium to the lower jaw or between the shoulder blades or in either arm to the wrist and finger
- Often described as pressure, tightness or heaviness; sometimes strangling, constricting or burning; maybe accompanied by shortness of breath
- Lasts no more than 10 min in the majority of case; chest pain lasting for seconds is unlikely to be due to angina.

First line testing

Basic testing includes bloodwork, an ECG, ambulatory ECG monitoring (if suspicious that symptoms may be associated with a paroxysmal arrhythmia) and an echocardiogram. Although left ventricular function is often normal, regional wall motion abnormalities may be detected, which increase the likelihood of coronary disease. Furthermore, valvular heart disease (aortic stenosis) or hypertrophic cardiomyopathy, can be ruled out as an alternative / concomitant cause of symptoms. The detection of increased carotid intima-media thickness (CIMT) and/or plaques establishes the presence of atherosclerotic disease, with consequent implications for preventive therapy and increases the pre-test probability of CAD in subsequent diagnostic tests.

Stress Testing

Exercise treadmill testing remains an important test because of its widespread availability. The main diagnostic ECG abnormality consists of a horizontal or down-sloping ST-segment depression ≥0.1mV (or 1m), in >1 ECG leads. In about 15% of patients, diagnostic ST-segment changes appear only during the recovery phase. Additional information, such as heart rate response, blood pressure response, symptoms, and workload achieved, have diagnostic and prognostic relevance. False-positive results are more frequent in patients with abnormal resting ECG in the presence of LVH, electrolyte imbalance, intraventricular conduction abnormalities and atrial fibrillation. Exercise stress testing is also less sensitive and specific in women. Exercise stress testing can also be useful to evaluate the efficacy of medical treatment or after revascularization, or to assist prescription of exercise after control of symptoms. In patients where the exercise test is inconclusive (such as failure to reach 85% of peak maximal predicted heart rate), an alternative non-invasive imaging test with pharmacologic stress should be selected; coronary CT angiography is another option.

The role of angiography

Invasive coronary angiography is rarely necessary in stable patients for the sole purpose of diagnosing stable CAD. I offer coronary angiography to guide treatment strategy for people whose symptoms are not satisfactorily controlled with optimal medical treatment, for those who have a high pre-test probability, in patients with reduced LV function and severe symptoms, or a clinical constellation suggesting high event risk. Tools such as intravascular ultrasound and fractional flow reserve measurements are useful to guide management during angiography.

Treatment options

Lifestyle modification and optimising risk factor reduction- weight loss, smoking cessation, lipid lowering therapy, diabetes and hypertension control – is central to the care of stable patients. Aerobic exercise should be encouraged and may be offered as part of a structured cardiac rehabilitation program, with evidence to support this reduces total and cardiovascular mortality and hospital re-admissions.
Address issues according to the person's needs, which may include:

- self-management skills such as pacing their activities and goal setting
- concerns about the impact of stress, anxiety or depression on angina
- advice about physical exertion including sexual activity

The aim of anti-anginal drug treatment is to prevent episodes of angina, thereby improving quality of life and the aim of secondary prevention treatment is to prevent cardiovascular events (heart attack, stroke). Contemporary data regarding prognosis can be derived from clinical trials (RITA-2, COURAGE) of anti-anginals and preventive therapy and/or revascularization. Estimates for annual mortality rates range from 1.2–2.4% per annum. Reliable identification of those patients with more severe or complex disease, who may have an improvement in outcome with revascularization is important. Conversely, its's also important to identify those patients with a less-severe disease and a good prognosis, thereby avoiding unnecessary invasive and non-invasive tests and revascularization procedures.

Anti-anginal treatment

First-line treatment comprises either a beta-blocker or a calcium channel blocker. Decide which drug to use based on comorbidities, contraindications and the person's preference. For those patients intolerant of these drug classes or both are contra-indicateda a long-acting nitrate, ivabradine or ranolzaine are treatment options. In patients with prior angina, Ivabradine, alone or in combination with beta blockade, reduced the composite primary endpoint of C.V death, hospitalization with MI and HF, and reduced hospitalization for MI (BEAUTIFUL trial). The effect was predominant in patients with a heart rate ≥70 bpm. Ranolazine is a selective inhibitor of late sodium current with anti-ischaemic and metabolic properties. It reduced episodes of stable angina in diabetic patients already receiving one or two anti-anginal drugs and led to less use of sublingual nitroglycerin, and the benefits appeared more prominent in patients with higher rather than lower HbA1c levels (TERISA trial).

Revascularisation, by coronary stenting or bypass surgery, should be recommended *if symptoms are not adequately controlled with optimal medical therapy.*

By **Dr. Rohit Khurana**

Senior Consultant Cardiologist
The Harley Street Heart & Cancer Centre

BREAST CANCER

TREATMENT OF BREAST CANCER IN PREGNANT WOMEN

Breast Cancer is one of the most common cancers in pregnant and non-pregnant women, it is going to become more common as more and more women are delaying pregnancy to a later age. In the 1980's, the incident was 15 in 100,000 deliveries, the number has risen to 35 in 100,000 deliveries in the 2000's.

Breast cancer during pregnancy presents in a similar way to women who are non-pregnant. The most common presentation is a lump. However, it is not easy to detect, this is because the hormonal changes during pregnancy causes the breasts to become larger, lumpy and tender. As a result, most breast cancers during pregnancy are diagnosed at a later stage. So one should have high index of suspicion and rule out breast cancer as early as possible. It is important to diagnose cancer and start treatment early as a delay in treatment by 1 month can increase the risk of nodal involvement by 2%, a delay of 6 months increase the risk of nodal involvement by 10%, and nodal involvement is one of the most important prognostic factors for cancer survival outcome. We should also bear in mind that 80% of breast lumps are benign.

Mammograms can find most breast cancers that start when a woman is pregnant, and it's thought to be fairly safe to have a mammogram during pregnancy. The amount of radiation needed for a mammogram is small. And the radiation is focused on the breasts, so that most of it does not reach other parts of the body. For extra protection, a lead shield is placed over the lower part of the belly to stop radiation from reaching the womb. Still, scientists can't be certain about the effects of even a very small dose of radiation on an unborn baby. Chest x-rays are sometimes needed to help make treatment decisions. They are thought to be safe for pregnant women when the belly is shielded. Other tests, such as PET scans, bone scans, and computed tomography (CT) scans are unsafe to use during pregnancy.

Treating a pregnant woman with breast cancer has the same goal as treating a non-pregnant woman: control the cancer and keep it from spreading. But the extra concern of protecting a growing fetus may make reaching these goals more complex. Surgery for breast cancer is generally safe in pregnancy. Certain chemotherapy can also be safely given after the second trimester. Radiation therapy is unsafe during pregnancy. Treatments should involve close collaboration between the breast surgeons, medical oncologist and obstetricians. With the advances in the management of breast cancer and modern ICU for premature babies, we are able to treat the mother's breast cancer, as well as delivering a healthy baby.

By **Dr. Sue Lo**

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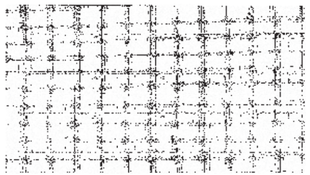
ECG QUIZ

Case Vignette:

The ECG below is that of a 80 year old man who came to clinic for a general cardiac check-up. He was relatively asymptomatic and had no symptoms of chest discomfort, breathlessness or palpitations. He has hypertension which is controlled with medication (amlodipine) and suffered a mini-stroke 2 years ago which caused transient slurred speech.



Questions:

- What is the main abnormality on the ECG?
- What additional tests would you recommend?
- How would you manage the patient?

*Answer is available on our website ***www.harleystreet.sg***

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THE HARLEY STREET HEART & CANCER CENTRE

MEDBULLETIN MARCH2016

THE HARLEY STREET HEART & CANCER CENTRE

From left to right:
Dr. Sue Lo, Dr. Reginald Liew, Dr. Peter Ting, Dr. Ooi Wei Seong, Dr. Rohit Khurana

INTRODUCTION

Greetings from the Harley Street Heart and Cancer Centre. We are pleased to present our first newsletter of 2016 in which we aim to provide the busy clinician with practical updates on the latest advances in the fields of cardiology and oncology.

In this edition, Dr. Rohit Khurana provides a useful overview of the contemporary management of chronic stable angina and discusses the role of newer anti-anginal medication as well as more sophisticated methods for assessing coronary artery disease. Dr. Peter Ting has written an article on primary (genetic) dyslipidaemias, such as familial hypercholesterolaemia, and the use of the novel PCSK9 monoclonal antibodies to treat these conditions. Our guest article, written by endocrinologist Dr. Vivien Lim, is on the management of diabetes in patients with coronary artery disease. She provides some practical tips on the choice of anti-diabetic medication and how best to optimize blood sugar control in our patients.

In the field of medical oncology, immunotherapy has been the buzz word in 2015. At every major international oncology meeting and conference that our oncologists attended last year, the halls were over-filled with keen and eager attendees whenever there was a session on immunotherapy. In this newsletter, Dr. Ooi Wei Seong gives a run down on how and why immunotherapy has stirred up such excitement among oncologists. Dr. Sue Lo has written an article on the less talked about, but nonetheless important subject on the treatment of breast cancer during pregnancy. We hope these articles stimulate and challenge your views on the latest methods for treating heart disease and cancer, and happy reading!

From The Harley Street Group

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