

# A Review of Coronary Artery Disease Research in Malaysia

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## ABSTRACT

Coronary artery disease is the major cause of mortality and morbidity in Malaysia and worldwide. This paper reviews all research and publications on coronary artery disease in Malaysia published between 2000-2015. 508 papers were identified of which 146 papers were selected and reviewed on the basis of their relevance. The epidemiology, etiology, risk factors, prevention, assessment, treatment, and outcomes of coronary artery disease in the country are reviewed and summarized. The clinical relevance of the studies done in the country are discussed along with recommendations for future research.

## KEY WORDS:

Acute coronary syndrome, myocardial infarction, coronary disease, coronary artery disease, ischaemic heart disease

## INTRODUCTION

Coronary artery disease is the leading cause of mortality worldwide and in Malaysia.<sup>1</sup> Amongst the more developed countries, the highest death rates from coronary heart disease are in the Ukraine and Russian Federation with 718 and 654 deaths per 100,000 population respectively, while the lowest are in South Korea and Japan with 36.5 and 47.0 deaths per 100,000 respectively.<sup>2</sup> Although much research has been done on coronary artery disease worldwide, it is important to review the research done in Malaysia to better understand the disease in the country and how this impacts on clinical practice locally.

This paper reviews all papers published on coronary artery disease (CAD) research done in Malaysia between 2000 and 2015. A literature search of all papers published on coronary artery disease in Malaysia was done as previously described.<sup>3</sup> The PubMed search involved the following medical subject headings (MeSH): acute coronary syndrome, myocardial infarction, coronary disease, and coronary artery disease. 508 articles were found of which 146 were included in this review based on their relevance.

## SECTION 1 – REVIEW OF THE LITERATURE

### ETIOLOGY

The etiology of coronary artery disease involving atherosclerosis is well studied. A fundamental role for

inflammation in atherogenesis has been recently demonstrated. Tiong *et al*<sup>4</sup> examined the role of early inflammatory markers namely interleukin-6 (IL-6), von Willebrand Factor (vWF) and platelet activation marker, P-selectin, in the early phases of acute coronary syndrome (ACS). The authors measured serum levels of these markers in 22 ACS patients and 28 stable CAD controls. They found a significant increase in serum levels of IL-6 and vWF in the ACS group compared to controls. This is consistent with studies showing a prominent role of inflammation and endothelial dysfunction in the early phase of ACS. In another study, Tiong *et al*.<sup>5</sup> demonstrated that serum and peripheral blood levels of CRP and vWF were significantly higher in ACS reflecting an acute phase response due to endothelial dysfunction in early the phase of ACS.

### EPIDEMIOLOGY

According to the World Health Organization, CAD accounted for 98.9 deaths per 100,000 population in Malaysia in 2012, or 29,400 deaths (20.1% of all deaths); it is the most common cause of deaths in the country.<sup>1</sup> The Malaysian burden of disease study<sup>6</sup> conducted in 2000 found CAD to be the biggest cause of death with a total of 22,158 deaths or about one fifth of all deaths. Much information on the burden of disease has also been obtained from death certifications and hospital admission records in Ministry of Health hospitals where circulatory disease accounted for 6.99% of total hospital admissions and 23.34% of all hospital deaths in 2014.

The National Cardiovascular Disease database (NCVD) is another important source of information on the epidemiology of CAD in Malaysia. It provides useful data from 15 public hospitals, 1 university hospital and the National Heart Institute. The acute coronary syndrome (ACS) registry enrolls patients presenting with acute coronary syndrome, ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA), prospectively, while the percutaneous coronary intervention (PCI) registry enrolls patients undergoing PCI in participatory sites.

### Age

The NCVD-ACS registry showed that Malaysians are having ACS at a younger age compared to the developed countries, with a mean age of between 55.9 to 59.1 years compared to mean ages of between 63.4 to 68 years in most developed

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countries.<sup>7</sup> Muda and colleagues<sup>8</sup> retrospectively reviewed the medical records of 165 patients in Hospital Universiti Sains Malaysia with angiographically proven CAD from 2002 to 2004 and found 92 patients (55%) had premature CAD (men less than 55 years old and women less than 65 years). These cases are associated with a positive family history of heart disease and low HDL levels.

More recently, Zuhdi *et al.*<sup>9</sup> looked into the NCVD-PCI registry data between 2007 to 2009 and categorized the patients into young (less than 45 years for men, and less than 55 years for women) and old (45 years and older for men, and 55 years and older for women). There were 1,595 patients of which 16% were categorized into the young CAD group and were significantly associated with more active smoking and obesity compared to the older group. The study also found a preponderance towards single vessel disease in the young CAD group with better clinical outcomes.

#### Gender

CAD generally affects men more than women. Lee *et al.*<sup>10</sup> studied the various aspects of gender differences in 10,554 PCI patients in the NCVD-PCI registry between 2007 to 2009. Women on average were 5 years older than men at presentation and with higher prevalence of risk factors. The in-hospital and six month mortality were also higher in women. In another paper, Lu *et al.*<sup>11</sup> looked into the differences in gender in the NCVD-ACS registry from 2006 to 2010 and found that among 13,591 patients, 24.2% were women and they had more risk factors, were unlikely to undergo intervention, and had higher mortality.

Idris *et al.*<sup>12</sup> studied the NCVD-ACS registry patients between 2006 and 2008 specifically on woman of reproductive age. The authors reported that out of 9,702 patients, 24.2% were females but only 1.9% were at the reproductive age (from 20 to less than 40 years of age) and was associated with Indian ethnicity, diabetes mellitus and hypertension. Young female patients commonly present with STEMI and have poorer prognosis.

Murty *et al.*<sup>13</sup> reviewed 5,579 autopsy reports done at University Malaya Medical Centre from 1996 to 2005 to study the prevalence of cardiac deaths in females and found 83 out of 936 female deaths were due to cardiac causes. The three main causes reported in the study were advanced CAD (14.5%), hypertensive heart disease (13.3%) and coronary atherosclerosis (12.0%). The study reported that hypertension, diabetes and pre-menopausal age were the most significantly associated factors.

#### Ethnicity

Malaysia is a multi-racial country whereby 67.4% are Malays, 24.6% Chinese, 7.3% Indians and 0.7% others. Lu and colleagues<sup>7</sup> examined the ethnic differences in the NCVD-ACS registry between 2006-2010. Indians were over represented in comparison to the general proportion of ethnicities. In terms of risk factor differences, Malays had higher body mass index (BMI), Chinese had higher prevalence of hypertension and hyperlipidemia, while Indians had higher rates of diabetes mellitus and family history of premature CAD. Chiam *et al.*<sup>14</sup> studied the

prevalence of ethnicity and conventional risk factors of diabetes mellitus, hypertension and hyperlipidemia in 302 patients who were admitted for CABG in their centre. Indian patients were associated with a combination of all three risk factors while the Chinese and Malays were mostly associated with hypertension and hyperlipidaemia.

Dhanjal *et al.*<sup>15</sup> compared the cardiovascular risk factors profile of Asian patients admitted with myocardial infarction in a hospital in Kuala Lumpur (42 patients) and in Birmingham, U.K., (28 patients), with Caucasian patients admitted with myocardial infarction in Birmingham (20 patients). The study found a higher prevalence of diabetes amongst Asians in both countries compared to Caucasians which may explain the higher prevalence of CAD in this ethnic group regardless of locality.

#### RISK FACTORS

Much is known about the risk factors for coronary artery disease and its prevalence amongst the population in Malaysia. According to the World Health Organization, 11.6% of adults in the country have raised blood glucose, 28.8% have raised blood pressure, 10.4% are obese, and 43% of adult males are smokers.<sup>1</sup> Much information has also been obtained from the National Health and Morbidity Survey (NHMS), a national household survey of Malaysians. The NHMS is carried out at 4 yearly intervals (4th NHMS in 2011). It is a population-based, cross-sectional epidemiological study using two stage stratified method of sampling. It provides useful and valid data on the prevalence of risk factors for non-communicable diseases (NCD). In the NHMS 2011<sup>16</sup>, 18,231 adults aged 18 years and above were recruited. 32.7% were found to be hypertensive, two thirds of whom were newly diagnosed. The prevalence of diabetes was 15.2%, with more than half of them newly diagnosed. 35.1% had hypercholesterolemia (serum total cholesterol >5.2 mmol/L). The high prevalence of coronary artery disease risk factors hypertension, diabetes mellitus, dyslipidaemia, smoking and obesity are also consistently reported in the NCVD database registry which publishes annual reports. The NCVD-ACS17 annual reports consistently report more than 95% of patients having at least one established cardiovascular risk factor on admission for ACS.

Table I summarizes the studies on coronary artery disease risk factors prevalence in the country. Most of the studies were done in urban populations with specialist cardiology services. In a case-control study done by Suleiman and colleagues<sup>18</sup> in Hospital Kuala Lumpur, out of 102 patients who were admitted to the male medical ward, 44 were diagnosed as CAD and 58 with other diagnosis. Smoking and hypercholesterolemia were significant predictors of CAD diagnosis in this study. In another study, Ahmad and colleagues<sup>19</sup> enrolled 525 patients with unstable angina or NSTEMI in 17 tertiary hospitals between 2004-2005 and found 96.8% with at least one established risk factor. Of the 525 patients, 66.1% of patients had hypertension, 38.9% diabetes mellitus and 40.4% dyslipidaemia, consistent with the NCVD-ACS findings. In another study, Chiam *et al.*<sup>14</sup> retrospectively reviewed the risk factor prevalence in 302 CABG patients. The study found that the prevalence of

diabetes mellitus, hypertension and hyperlipidaemia was 45.7%, 78.8% and 89.1% respectively. Indians had the highest propensity of having all the three risk factors while Chinese and Malays most frequently presented with the combination of hypertension and hyperlipidaemia.

There are a few studies on risk factors prevalence in the rural population. Nawawi *et al.*<sup>20</sup> collected data on the prevalence of CAD risk factors in rural Pahang from 1997-1999. The study recruited 609 subjects and found that the prevalence of CAD risk factors was comparable to that in the urban population: dyslipidemia (67.3%), hypertension (30.3%), smoking (24.4%), diabetes (6.4%), impaired fasting glucose (13.9%), overweight/obesity (44.7%) and increased waist-to-hip ratio (48.5%). Similarly, Yunus and colleagues<sup>21</sup> studied the prevalence of hypertension and smoking in rural Selangor, and found high prevalences of risk factors: 28.6% hypertensive and 21.1% smokers. However, a study by Chang *et al.*<sup>22</sup> in rural Sarawak found lower prevalence of risk factors: 13.5% hypertension, 1.5% diabetes, 15.4% smokers and 22.6% hypercholesterolemia.

### Hypercholesterolemia

Hypercholesterolemia is an established risk factor for CAD. Khoo *et al.*<sup>24</sup> reviewed the patterns of lipid profiles and CAD prevalence in Asia. The authors found that less developed countries had lower levels of serum lipids and ultimately lower CAD prevalence. Serum total cholesterol and therefore CAD rates can be expected to increase as developing countries progress.

Rafidah and colleagues studied the relationship between blood pressure variability (BPV), arterial compliance and hyperlipidemia<sup>23</sup>. Defining hyperlipidemia using TG:HDL ratio, 22 hyperlipidemia patients and 22 normolipidaemia controls were included. There was a significantly higher BPV in the hyperlipidaemic group as compared to the control group but no significant difference in terms of arterial compliance between the two groups.

### Familial Hypercholesterolemia

Khoo and colleagues<sup>25</sup> reported an extensive genetic study on familial hypercholesterolaemia (FH). They studied the genetic mutations of 86 unrelated FH patients and found 23 having LDL receptor gene mutations but none had the APO B-3500 mutation which is commonly reported in the literature. This might explain the lower LDL level and rarer premature coronary events in Asian FH patients. Azian *et al.*<sup>26</sup> reported their DNA mutation screening technique for 72 FH patients in which four different mutations in the LDL receptor gene were detected and again no APO B100 gene mutation was found. Al Khateeb *et al.*<sup>27</sup> screened 154 unrelated FH patients in Kelantan and found a total of 29 gene sequence variants with 8 of the variants reported for the first time in the literature.

Khoo *et al.*<sup>28</sup> reported two different paediatric FH cases to highlight the unique presentation and discussed the management. Junit *et al.*<sup>29</sup> published a case report of the first A519T mutation found in an Asian FH patient.

### Metabolic Syndrome

Yeow *et al.*<sup>30</sup> recruited 4,341 subjects to study the prevalence of metabolic syndrome and its association to CAD risk (using

cardiovascular risk markers of high-sensitivity C-reactive protein, microalbuminuria and HbA1c). They found the prevalence of metabolic syndrome in our population to be high (42.5%) with a significantly higher HbA1c, LDL, albumin:creatinine ratio, and high-sensitivity C-reactive protein levels, putting them at higher risk of CAD.

### Homocysteine

Homocysteine has been associated with cardiovascular diseases but many studies looking into the causality of this relationship have yielded conflicting results. Azizi *et al.*<sup>31</sup> studied the relationship between total plasma homocysteine levels (tHcy) and components of metabolic syndrome and risk factors for CAD (fasting plasma insulin, glucose level, fasting lipid profile). They recruited 44 hypertensive subjects and found only insulin levels to be inversely correlated with homocysteine levels, and no good evidence to associate CAD risk to homocysteine levels.

Choo *et al.*<sup>32</sup> examined the role of gene polymorphism in 5,10-methylenetetrahydrofolate reductase (MTHFR) in the metabolism of folate, B vitamins and homocysteine. The authors recruited 100 subjects and took their folate, B vitamins, and homocysteine levels to detect the presence of MTHFR gene polymorphism. They found folate, vitamin B12 and B6 levels were highest in the wild genotype in all ethnic groups, and subjects with heterozygous and homozygous genotypes showed the highest homocysteine levels. Gene polymorphism was commonest in Chinese and it influenced the folate and homocysteine metabolism.

### Peripheral vascular disease and abdominal aortic aneurysm

Leong *et al.*<sup>33</sup> studied the prevalence of peripheral artery disease (PAD) and abdominal aortic aneurysm (AAA) in CAD patients. The authors recruited 102 patients who were admitted for ACS and found a high prevalence (24.5%) of patients fulfilled the diagnostic criteria of PAD but a low prevalence (2%) of AAA. Most (68.0%) of patients with a diagnosis of PAD were asymptomatic; two factors were significantly associated with PAD namely smoking and age more than 60 years.

### Genetic profiling

The role of ethnicity and family history in CAD suggest that genetic predisposition is an important risk factor. Abdullah *et al.*<sup>34</sup> studied the global gene expression profile of the peripheral blood in CAD patients to look for potential causative gene candidates in our population. The authors analyzed the gene expression of a group of 12 CAD patients (angiographically more than 50% stenosis) and 11 controls, and were able to identify many genetic variants featured prominently in the CAD group. 18 of them were previously known to be involved in CAD and a further 137 new gene variants were identified with no known function.

Normaznah *et al.*<sup>35</sup> studied the -344T/C polymorphism of CYP11B2 gene for an association with CAD. The study sampled bloods from 79 patients with angiographically diagnosed CAD and 84 healthy controls and determined the allele and genotype frequencies of the CYP11B2 gene in them. They found no significant difference between -344T/C polymorphism of CYP11B2 gene in the two groups.

Chu *et al.*<sup>36</sup> studied the relationship between genetic polymorphism of cholesteryl ester transfer protein (CETP) and endothelial nitric oxide synthase (eNOS) and the risk of CAD. They recruited 237 patients with CAD and 101 as controls and sampled their genotype. The study found a significant difference in the CAD group with higher frequency of concomitant presence of both CETP B1 and eNOS 4a alleles in Malays and Indians but not in Chinese.

### **Chlamydomphila pneumonia**

Chronic infection of *Chlamydomphila pneumonia* had been implicated in the development of atherosclerosis. Naidu *et al.*<sup>37</sup> examined the ethnic distribution of *C.Pneumonia* antibodies in our population and a possible correlation with coronary artery disease. They measured the antibody titre in 110 CAD patients and 158 healthy controls. They found Indians had the highest seropositivity (58%) and this was even more evident in the CAD group (Indian positive in 65%, with higher titre). The difference of *C.Pneumonia* seropositivity between the two groups was statistically significant and may explain the higher CAD prevalence among the Indians.

### **Psychological factors**

The association between psychological illnesses and CAD is explained through numerous mechanisms such as higher prevalence of smoking, alcohol intake and sedentary lifestyles. Sidik *et al.*<sup>38</sup> studied prevalence of depression among the elderly in a rural area and found that depression was closely associated with CAD, with 9% of elderly with chronic illnesses especially CAD having depression; 5.6% were depressed without chronic illnesses. In another prospective study conducted by Michael *et al.*<sup>39</sup> in 65 ACS patients, those with depression were ten times more likely to have recurrence of cardiac events. In another study on Type D personality (the distressed personality), Satpal *et al.*<sup>40</sup> validated the Malay version of Type D Personality Scale (DS14) before recruiting 195 CAD patients to determine the prevalence of Type D personality among them. They found 28.2% of the patients with CAD were of Type D personality.

### **Occupation**

Several studies were done on specific occupations. Norazmi *et al.*<sup>41</sup> recruited 176 fishermen and found a very high 76.5% prevalence of smoking. Also, fishermen in general were at high risk of CAD as 91.7% of them had one or more CAD risk factors. In another study, 130 security guards were enrolled by Lua *et al.*<sup>42</sup> and had their risk of CAD stratified. 53% of them were at very high CAD risk according to the Personal Risk Chart. The majority of them had hypercholesterolemia (74.8%) and high BMI (47.8% overweight, 14.8% obese); these may due to unhealthy diet, nature of their job and social class. Separately, Nazri and colleagues<sup>43</sup> investigated the prevalence of hypertension in shift work factory workers. The authors recruited 76 shift workers and 72 day workers and found higher prevalence of hypertension in the shift workers (22.4%) compared to day workers (4.2%).

### **Studies on other possible risk factors**

#### *Non alcoholic fatty liver disease*

Chan *et al.*<sup>44</sup> recruited 399 diabetic patients to investigate the association between ultrasonography-diagnosed non-alcoholic fatty liver disease (NAFLD) and CAD. The authors found 49.6% of the patients fulfilled the diagnostic criteria of

NAFLD on trans-abdominal liver ultrasound but only 26.6% of patients had evidence of CAD based on history, ECG findings and previous medical record review. They found no statistical association between NAFLD and CAD in diabetic patients.

#### *Microalbuminuria*

Some studies in the West found microalbuminuria to be associated with CAD. Yeo *et al.*<sup>45</sup> studied the association of microalbuminuria in diabetic patients and CAD risk (marked by blood sample for highly sensitive C-Reactive Protein (hsCRP), fibrinogen and lipoprotein A levels). The authors recruited a total of 107 patients with and without microalbuminuria and found no significant difference in the levels of all the CAD predictors between the two groups.

#### *Rheumatoid arthritis*

Patients with rheumatoid arthritis (RA) have been reported to have increased risk of cardiovascular events compared to the normal population. Ma *et al.*<sup>46</sup> conducted a pilot study primarily to compare the prevalence of subclinical CAD using CT angiography in 47 RA patients in remission and 47 non-RA patients with atypical chest pain as controls. CT angiography showed evidence of CAD in nine (19.1%) RA patients and three (6.4%) controls. There was no significant association between CAD and RA in this pilot study.

#### *ABO blood group*

Sheikh *et al.*<sup>47</sup> investigated the association between blood group B and myocardial infarction. The authors recruited 170 patients with diagnosis of myocardial infarction and another group of healthy controls. The study found 31.8% of the MI patients were blood group B and 30% of the controls were blood group B. Logistic regression showed no significance to suggest any association between blood group B and myocardial infarction.

### **Case Reports**

There were a few case reports on rare causes of coronary artery disease. These are usually CAD cases in young patients with no common risk factors. Azarisman and colleagues<sup>48</sup> reported two cases of STEMI secondary to commencement on appetite suppressant phentermine and sibutramine. Ngow *et al.*<sup>49</sup> described an extensive STEMI due to congenital anomaly of myocardial bridging and Oteh *et al.*<sup>50</sup> reported another case of congenital anomaly of severe LAD stenosis with proximal arteriovenous malformation. Muthupalaniappen and colleagues<sup>51</sup> described a very rare case of STEMI at the age of 15 years, with aneurysmal dilatation and tortuous LAD on angiogram. Jasmin *et al.*<sup>52</sup> encountered a case of infarcted myocardium due to vasospasm in a 13 year old systemic lupus erythematosus patient. Liew *et al.*<sup>53</sup> reported a case of recurrent coronary artery spasm simulating inferior myocardial infarction who was previously stented. Sulaiman and colleagues<sup>54</sup> described a case of eosinophilic granulomatosis with polyangiitis (Churg Strauss Syndrome) who presented uncommonly with acute myocardial infarction first before other more suggestive symptoms such as asthma, skin manifestations and peripheral neuropathy. Wahab *et al.*<sup>55</sup> reported their experience in using alpha-blockade in an inotropic-dependent hypotensive pheochromocytoma patient secondary to myocardial infarction.

## ASSESSMENT

Cardiac assessment of the patient with known or suspected CAD are performed both in the acute setting to diagnose acute coronary syndromes and in the chronic stable patient to diagnose CAD and evaluate the need for coronary artery revascularization. Several research studies were done to evaluate and improve on the existing cardiac assessment and investigation tools, and also some new ones.

### Risk prediction

Prediction of cardiovascular diseases using scoring systems based on risk factors is useful in patients presenting with symptoms suggestive of CAD to help guide appropriate investigations and treatment. It is also useful in primary preventive treatment of CAD. More recently, it has also been evaluated for the diagnosis of acute coronary syndromes.

Chia *et al.*<sup>56</sup> conducted a validation study on the Pooled Cohort Risk Equation, a scoring system used to estimate the 10-year primary risk of atherosclerotic cardiovascular disease (ASCVD) among patients without pre-existing cardiovascular disease who were between 40-79 years of age. The following parameters are used in the scoring system: gender, age, race, total cholesterol, HDL cholesterol, systolic blood pressure, receiving treatment for high blood pressure, diabetes, and smoking status. The authors reviewed 922 patients' clinical records at baseline and subsequent ASCVD events over 10 years. The study found that the Pooled Cohort Risk Equation score overestimated ASCVD risk; there were less ASCVD events than predicted. However, these observations are retrospective; primary prevention treatment had been instituted in many of the patients and is likely to have influenced the results.

The Rose screening questionnaire (RQ) has been used to detect angina pectoris for epidemiological surveys since 1962. Hassan *et al.*<sup>57</sup> translated the RQ into Bahasa Malaysia and adapted it cross-culturally. The translated Malay version of RQ was shown to have a good inter-rater and intra-rater reliability.

Metabolomics study profile changes in small molecules associated with diseases. Incorporating metabolomics into a prediction model was studied by Muhamed *et al.*<sup>58</sup> to predict CAD risk in Orang Asli. The authors recruited 31 urban patients with myocardial infarction and 23 urban healthy controls to compare the metabolite expressions and form a prediction model. Out of 34 Orang Asli tested using the prediction model, 7 were clustered into the higher risk group. Separate biochemistry tests in these 7 subjects found abnormalities in their lipid profile. The authors suggest this as a useful diagnostic alternative for CAD as compared to the current diagnostic methods.

Bulgiba and colleagues<sup>59</sup> conducted a study on the accuracy of a prediction model using signs and symptoms in diagnosing acute myocardial infarction (AMI). The authors studied 887 patients and found 69 possible variables that could be predictive. 9 variables were significant on multiple logistic regression. The degree of accuracy of this model was 80.5%. The authors concluded the study with a suggestion to incorporate the model with an artificial intelligence method to increase the predictive accuracy. Following that, in a

separate paper, Bulgiba and colleagues<sup>60</sup> incorporated the artificial neural networks (ANN) method in the model. ANN is an artificial intelligence method that arithmetically computes an output from a list of inputs. The results showed that ANN can perform as well as multiple logistic regression models even when using just a selection of 9 clinical symptoms as inputs. The superiority of ANN method was also reported by Purwanto *et al.*<sup>61</sup> in his study with data collected from 929 patients to construct prediction models. Aion *et al.*<sup>62</sup> and Lahsasna *et al.*<sup>63</sup> concurred with the accuracy of ANN in prediction accuracy.

### Electrocardiogram

The electrocardiogram (ECG) is the most readily available and immediate tool to diagnose acute coronary syndromes and myocardial infarctions (MI). Gupta *et al.*<sup>64</sup> recruited 125 patients who were admitted as suspected MI using ECG and cardiac enzyme levels (creatinine kinase-MB and troponin T) at presentation and evaluated the incidence of "false alarm" by capturing the final diagnosis on discharge. The study found revision of the diagnosis in 48 patients (38.4%). The sensitivity and specificity of the initial ECG changes were 54.5% and 70.8%, respectively while raised cardiac enzymes had a sensitivity of 44.3% and specificity of 95.8%. The authors concluded that a significant proportion of patients in Malaysia are admitted with a false alarm, and the efficacy of the ECG was comparable to the West, but cardiac enzymes had a much lower sensitivity.

### Exercise stress ECG

The exercise ECG is an appropriate first line investigation of patients presenting with symptoms suggestive of angina. Ng *et al.*<sup>65</sup> reviewed the benefits of open access exercise stress ECG whereby these were ordered and conducted by the primary care physicians. In 145 tests done, 80.7% was indicated for chest pain. Only 22.1% was found to be positive, 52.8% were negative, 18.1% and 6.9% were uninterpretable and inconclusive respectively. The authors concluded that most of the stress tests had no conclusive diagnosis and most were ordered to rule out CAD in chest pain rather than to diagnose it.

### Biomarkers

An increased cardiac troponin I or T (cTnI or cTnT) level is defined as a measurement above the 99th percentile concentration of a reference population. Sthaneshwar *et al.*<sup>66</sup> established the 99th percentile concentration in our population using ADVIA TnI-Ultra method in 234 healthy men and 208 women. The authors also found no significant difference of cardiac troponin levels between gender and among different ethnic groups. The 99th percentile for ADVIA TnI-Ultra is 0.061 microg/L and a single cut-off value based on this 99th percentile can be used in our population for diagnostic purpose.

### Newer biomarkers

Diabetics are at increased risk of atherosclerosis. Pathogenesis may involve increased production of advanced glycation end products such as Nε-(carboxymethyl) lysine (CML) due to hyperglycaemia. Ahmed *et al.*<sup>67</sup> compared the levels of CML in 60 diabetic patients with CAD, 43 diabetic patients without CAD and 80 matching healthy controls. The authors found significantly higher CML levels in the diabetics and CAD

group compared to the diabetic but non CAD group. This suggests a promising role of CML levels as a biomarker to detect development of IHD in diabetic patients.

The levels of most blood biomarkers are usually obtained from the peripheral circulation. Fong *et al.*<sup>68</sup> studied the levels of C-reactive protein (CRP), myeloperoxidase (MPO), soluble CD40 ligand and placental growth factor (PGF) in both coronary circulation and peripheral circulation among ACS and stable CAD patients. Recruiting 39 ACS patients and 40 stable CAD controls, the authors sampled coronary bloods from occluded coronary arteries during angiogram as well as the peripheral venous blood for comparison. The levels of all the markers was significantly increased in ACS group in both the peripheral and coronary circulation. These markers are potentially useful for the accurate diagnosis of ACS. Interestingly, the level of PGF in coronary blood is much higher than in the systemic circulation suggesting that PGF may be released from the culprit site.

Samsudin and colleagues<sup>69</sup> looked into the usage of Copeptin, a surrogate marker for vasopressin as a combination biomarker with routine troponin. Copeptin increases immediately following an AMI in several studies, and when used in combination with troponin at presentation with AMI, was able to rule out AMI much earlier and with a high negative predictive value. It has diagnostic, prognostic and risk stratifications values but the cost effectiveness of introducing an additional biomarker needs to be determined.

Red cell distribution width (RDW) is a measurement of the variation of red blood cell (RBC) size. It has been suggested that the structural change in RBC of diabetic patients impairs their function and can lead to thrombosis. Ismail and colleagues<sup>70</sup> assessed the association between RDW and CAD by recruiting 472 diabetic patients admitted for coronary angiogram. Defining CAD as significant stenosis of more than 50% in a coronary artery, the authors found no RDW level difference between the CAD and non-CAD group to suggest an association.

### Echocardiography

Echocardiography, particularly stress echocardiography, is a useful investigation in patients at intermediate or high risk of CAD. However, interpretation of the acquired images is subjective and depends on the acoustic windows. Acharya *et al.*<sup>71</sup> studied various grayscale features of echocardiography images from a database of 400 CAD cases and 400 normals, and compiled all the features that had good discriminating capability into a Gaussian mixture model (GMM) classifier. A HeartIndex was generated which could objectively differentiate CAD or normal cases. The authors suggest that this technique could be converted into a simple computer software to produce a HeartIndex from images to assist the operator.

Gunasekaran *et al.*<sup>72</sup> conducted a prospective study to examine the relationship of left atrial volume index (LAVI) and major adverse cardiovascular events (MACE) in ACS patients. The baseline LAVI of 75 ACS patients was measured and the patients were divided into two groups of high LAVI and normal LAVI. At 6 months follow-up, the high LAVI group had significantly more MACE than the normal LAVI group with an odds ratio of 1.229.

### Cardiac computed tomography angiography

Cardiac computed tomography angiography (CCTA) is an appropriate investigation in symptomatic patients with intermediate or high risk of CAD. It is less invasive than coronary angiography. Ong *et al.*<sup>73</sup> published a highly cited study on the accuracy of 64-slice multi detector CT (MDCT) evaluating coronary artery disease in relation to coronary calcifications. The study recruited 134 symptomatic patients scheduled for coronary angiography; a 64-slice MDCT evaluation was done on them within 3 months. The patients were grouped into high or low calcium score groups and their MDCT findings were compared with the coronary angiogram results. The authors reported that the low calcium score group had 97.3% correlation and the high calcium score group 90.5% correlation with results of invasive coronary angiography. This study concluded that the degree of coronary calcification correlates with the extent and severity of CAD.

Ibrahim *et al.*<sup>74</sup> recruited patients attending exercise stress test for CAD screening for CT coronary angiography. Dividing the CAD lesions to obstructive (50% stenosis or more) and non-obstructive (less than 50% stenosis), subjects found to have obstructive lesions then underwent conventional coronary angiograms to confirm the findings. The study found that calcium scoring had 100% sensitivity and 97.5% specificity in detecting obstructive CAD at the optimal cut-off value of 106.5 and above. The positive predictive value (PPV) at score 106 and above was 71.4% and the negative predictive value (NPV) was 100%. Calcium scoring was very useful for patients with inconclusive exercise stress test and low to moderate risk.

Chin *et al.*<sup>75</sup> investigated the feasibility of using MDCT to identify the culprit lesion in ACS which would have low overall vessel lumen and plaque density. The authors suggested the concept of "vessel density ratio" (VDR) which is the ratio of mean density of contrast enhancement within a region of interest to mean density of aortic root. 64 subjects of ACS patients of different stratum and stable CAD were recruited for both angiogram and MDCT. They found that culprit lesions in ACS patients had a lower mean VDR compared to non-culprit lesions and compared to lesions in patients without ACS; thus VDR was a good approach to identify ACS culprit lesions.

Sabarudin *et al.*<sup>76</sup> retrospectively analyzed the radiation dose of prospective ECG triggered cardiac CT angiography (CCTA) with different CT generations in 164 patients. The mean effective doses for 128-slice DSCT, 64-slice DSCT, 64-slice SSCT and 320-slice CT scanners were 6.8±3.2, 4.2±1.9, 4.1±0.6 and 3.8±1.4 mSv respectively. These findings suggest that prospective ECG-triggered CCTA regardless of the scanner generation can achieve low radiation dose, and patient's BMI is the major factor influencing the dose.

### Coronary Angiography

Invasive coronary angiography is the gold standard in diagnosing coronary artery disease and is indicated in symptomatic patients at high risk of CAD. Coronary angiography gives information on the anatomy of the coronary arteries and the lesions present in them. However, it does not give information on the viability of the myocardium if it is akinetic i.e. if the myocardium is still alive and would

benefit from coronary artery revascularization. Such information is usually obtained by stress echocardiography or cardiovascular magnetic resonance imaging with gadolinium enhancement. Ismail *et al.*<sup>77</sup> investigated the accuracy of using myocardial blush grade (MBG) in assessing myocardial viability during coronary angiography. The authors analysed a total of 135 coronary arteries on coronary angiography done on stable post ACS patients. MBG was scored during angiogram and subsequently dobutamine stress echocardiography was performed with blinding of the angiography results. The authors found 22 coronary arteries with non-viable score (MBG 0). When using dobutamine stress echocardiogram, 17 of the MBG 0 arteries were still viable. The study concluded that using MBG alone in stable post ACS was not sufficient to demonstrate myocardial viability.

One of the known complications of coronary angiogram is contrast-induced nephropathy (CIN) and patients with underlying chronic kidney disease (CKD) are at higher risk. However, it is often detected late as serum creatinine (SCr) rises 2-3 days post contrast administration. Alharazy and colleagues<sup>78</sup> investigated the accuracy of using serum neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C (CysC) as an early biomarker of CIN. They recruited 100 patients with underlying CKD who were scheduled for coronary angiogram and measured their levels of serum NGAL, CysC and SCr at baseline and at various time points post procedure. The analysis of the ROC curves of the changes in serum NGAL and CysC at 24 hours post procedure from baseline values showed that both can be used for the early diagnosis of CIN.

#### Fractional flow reserve

Fractional flow reserve (FFR) assessment can be used to grade the severity of coronary lesions during coronary angiography in cases of uncertainty or indeterminate lesions. Yew<sup>79</sup> highlighted the role of FFR in risk stratification of a complex and high risk case of concomitant triple vessel disease and colon carcinoma requiring early surgery; the team integrated FFR findings to the Syntax score to enable accurate cardiac risk stratification.

#### Arterial stiffness

Arterial stiffness has been suggested as a marker of atherosclerosis and can be measured in pulse wave velocity (PWV) non-invasively. Alarhabi *et al.*<sup>80</sup> measured the PWV of 92 patients who were undergoing coronary angiogram. He found the mean PWV was higher in patients with CAD than those without CAD. There was also a significant association between the severity of CAD (number of vessels).

### TREATMENT OF STABLE CORONARY ARTERY DISEASE

The aim of treatment in stable CAD is to improve symptoms and survival. This primarily involves advice on lifestyle changes and optimal medical therapy with antiplatelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, and statins. In symptomatic patients, anti-angina medications such as nitrates and calcium antagonists should be started. Patients who continue to be symptomatic or have lesions involving

the left main stem or proximal left anterior descending coronary artery should be considered for percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery (CABG). A survival advantage has been demonstrated with CABG over PCI in patients with left main stem stenosis, or complex 3 or more vessel coronary artery disease particularly in diabetic patients.<sup>81-82</sup>

### Medical treatment

#### Anti-platelets

Despite the well documented benefit of anti-platelets in CAD, there is a growing concern that the individual's response to anti-platelet therapy varies. Ibrahim *et al.*<sup>83</sup> investigated the prevalence of anti-platelet resistance in 64 CAD patients and found the proportion of laboratory determined aspirin and clopidogrel resistance was 4.69% and 21.9% respectively. Ibrahim *et al.*<sup>84</sup> measured aspirin resistance in 74 patients with stable CAD on aspirin (52 presented with their first-ever acute event and 22 patients with recurrence). Aspirin resistance was observed in 12 patients (16%) out of the entire cohort, and all but one resistant patient were in the first-ever coronary event group. There were significant correlations between aspirin resistance and age, total cholesterol and LDL levels. The study found no association between aspirin resistance and recurrent coronary events.

The ABCB1 and CYP P450 genes are highly polymorphic and may contribute to the wide inter-individual variability in clopidogrel response. Chua *et al.*<sup>85</sup> reported that in a cohort of 237 patients scheduled for angiogram and possible PCI, the prevalence of ABCB1 3435CT and CYP2C19\*2 carriers are high in Chinese ethnicity. However, there was no significant association of the genotypic polymorphisms and platelet activity and one month clinical outcomes.

Tiong *et al.*<sup>86</sup> recruited 237 PCI patients and studied the different pre-PCI clopidogrel regime, genetic prevalence of CYP2C19 polymorphisms, platelet inhibition and 12 month outcomes. They found considerable variations in the loading patterns but regardless of the regime, and even in the presence of CYP2C19 lost-of-function allele carriers, there were no significant difference in platelet inhibition and 12 month outcomes. Further, Mejin *et al.*<sup>87</sup> reported the prevalence and impact of CYP2C19\*2, \*3 and \*17 genotypes on clopidogrel responsiveness among 118 PCI patients who were given dual antiplatelets prior to procedure. There was a diverse inter-ethnic difference in the distribution of CYP2C19 polymorphism which appeared to have a limited impact on clopidogrel responsiveness and clinical outcomes in low-risk patients.

Some studies have shown that proton pump inhibitors and clopidogrel co-prescription increases the incidence of cardiovascular events and mortality. Tan *et al.*<sup>88</sup> reviewed the available data regarding this controversy and concluded that the available data at the time of writing (2010) was too weak to prove causality.

#### Beta Blockers

There is good evidence for the use of beta blockers to improve outcomes in CAD patients. Ong *et al.*<sup>89</sup> conducted a retrospective study to assess their centre's usage of beta

blockers in post MI patients. A total of 315 patient notes were reviewed; a good percentage of patients (77.5%) were prescribed beta blockers as indicated but doses were optimized only in 39.3% of these patients.

#### *Anti-cholesterol medications*

Thuraisingham *et al.*<sup>90</sup> randomised 60 patients with hypercholesterolemia treated with simvastatin to either a normal diet or a dietitian guided low cholesterol diet. The authors assessed the effects after 24 weeks and found that a low cholesterol diet did not confer additional advantage on lipid-profile once simvastatin therapy had been instituted.

The REALITY-Asia study<sup>91</sup> enrolled 2622 new hypercholesterolemic patients in 6 countries including Malaysia and risk stratified them accordingly. The study found that 48% of patients attained their LDL targets and most patients did so within the first 3 months. Increasing age and initial statin potency were associated with success. Al-Khateeb *et al.*<sup>92</sup> retrospectively reviewed the lipid target attainment of 890 patients and found only 64.2% of patients achieved their respective LDL targets. Similar with REALITY-Asia study, both the studies showed that patients of higher risk were less likely to achieve their LDL targets.

It is known that muscular adverse events occur more frequently with concomitant usage of fibrates and statins. However, switching from one type of fibric acid derivative to another (gemfibrozil to bezafibrate) had not seen any adverse effects prior to the case report of rhabdomyolysis and acute renal failure by Kamaliah *et al.*<sup>93</sup> in two patients with underlying renal impairment.

#### *Dietary supplements*

Yusoff<sup>94</sup> reviewed the available clinical trial evidence in 2002 on the role of Vitamin E supplementation in CAD patients. There were many positive results from various observational studies, dietary studies and animal studies but evidence from good quality, large clinical trials were lacking.

Ong and colleagues<sup>95</sup> examined the clinical trial evidences of dietary supplement omega-3, red yeast rice and garlic in preventing clinical cardiovascular events. The authors found the GISSI-P and JELIS trials, which were using modest and high dose of omega-3 fatty acids respectively, had convincing evidence. The CCSPS trial studying red yeast rice was reported to have 46% reduction in nonfatal myocardial infarction and coronary death but needed a bigger sample. Garlic products, however, did not reduce cardiac outcomes.

There have been studies on heart failure using a single nutrient or a combination of multiple nutrients but results were inconclusive. Wong and colleagues<sup>96</sup> recruited 12 heart failure patients with routine medications to study the effect of high dose multiple micronutrient supplementations on their quality of life. The authors followed these cases for a period of 3 to 8 months and administered the Minnesota Living with Heart Failure Questionnaire (MLHFQ). The study found a significant difference between baseline and endpoint of treatments but recommended a further larger, longer term randomized study.

#### **Percutaneous Coronary Intervention**

Much advances have been made in the treatment of CAD by percutaneous coronary intervention (PCI). Advances in guide wire, balloon and stent technology has made it technically feasible to treat most coronary stenosis by PCI. It should be noted that the aim of PCI is to improve symptoms; no study has demonstrated a survival benefit with PCI in stable CAD. Ahmad *et al.*<sup>97</sup> reviewed NCVD-PCI data from 2007 to 2009. 10,620 patients underwent 11,498 PCI procedures with 18,116 stents for 15,538 lesions with a 97% procedural success rate. The femoral artery was the commonest percutaneous approach, with the radial artery approach becoming more popular (36% in 2007 to 40% in 2009). 58% of all cardiac lesions had high risk characteristics; post-procedure TIMI grade-3 flow was achieved in 97% of all lesions and the incidence of stent thrombosis was 1%.

Ho and colleagues<sup>98</sup> examined the patient's anxiety and depression before and after the PCI procedure in their centre using the Hospital Anxiety and Depression Scale. They recruited 61 patients and found that the level of anxiety and depression before and after PCI was low and not significantly correlated with demographic factors.

Ponniah *et al.*<sup>99</sup> looked into the predictors of 3 year mortality in 630 PCI patients as captured in NCVD-PCI in 2007. Mortality records were tracked from the National Registration Department from the year 2007 to 2009 and non-cardiac causes of death were excluded. The authors found only renal failure and age group as significant predictors on multivariate analysis. The authors suggested careful evaluation especially for the higher risk older patient and those with renal failure.

#### *Case reports*

Yew published a few reports on experiences with various new stent technologies, bioreabsorbable vascular stents (BVS) and STENTYS platform, and difficult cases of CAD. He described his experience in treating a coronary ectasia case which had atypical coronary anatomy with the STENTYS platform and BVS.<sup>100-101</sup> This new platform had novel self expanding properties, ideal for such lesions but with more challenging technicalities. He also reported his various innovative approaches in deploying a hybrid of overlapping BVS-DES in a long lesion case,<sup>102-103</sup> application of BVS and STENTYS self apposing stent for complex vein grafts occlusion case,<sup>101</sup> and successful treatment of iatrogenic coronary dissection with paclitaxel coated balloon.<sup>104</sup> In all his reports, he discussed the various issues of choice of stents in the cases, technical deployment and difficulty considerations during the procedures. Sadiq and colleagues<sup>105</sup> reported a rare complication of permanent complete heart block secondary to the loss of first septal perforator after PCI of the LAD and highlight the importance of careful patient monitoring in such cases.

#### *Multi-national studies involving Malaysia*

A number of multinational industry sponsored research trials included investigators and patients from Malaysia. Nakamura and colleagues<sup>106</sup> demonstrated the benefit of sirolimus eluting stents (SES) in chronic total coronary occlusion (CTO) over BMS. The study recruited 240 subjects

and found SES implantation after recanalisation of CTO resulted in better outcomes. Chan *et al.*<sup>107</sup> published the study comparing the SES and BMS in diabetic patients in 2008. The study found the mean 6-month in-stent luminal loss was significantly smaller, and 12-month major adverse cardiac events rate was significantly lower in the SES group.

Kaul *et al.*<sup>108</sup> made an outcome comparison between Asians and non-Asians in the everolimus eluting stent (EES) post-marketing surveillance study. The study found that of the 2,700 subjects, the MACE, myocardial infarction and target lesion revascularization rates were lower in the Asian subgroup than in the non-Asian subgroup. The authors noted that this result was driven by good outcomes reported in many centres in India, despite the high prevalence of risk factors.

In 2013, Lee *et al.*<sup>109</sup> reported on a study on 224 patients with 269 angiographic lesions to study the safety and efficacy of using a long drug-eluting stent (38mm Resolute Zotarolimus-eluting stent) instead of multiple stents. The authors found that the target lesion failure rate using a single-vessel analysis was 4.5% and the rate of stent thrombosis was 0.9%. In patients who are at risk of bleeding, BMS are still widely used to avoid the need for prolonged dual antiplatelet therapy.

Urban *et al.*<sup>110</sup> randomised 2,466 patients who were at increased risk for bleeding to the new polymer-free-drug-coated stent and BMS with only a 1-month course of dual antiplatelets followed by a single agent. The use of a polymer free drug-coated stent achieved better outcomes than BMS.

### Coronary artery bypass grafting surgery

Much has advanced in coronary artery bypass grafting surgery (CABG) in recent years. Better surgical techniques, the use of arterial grafts and optimization of medical therapy post CABG has improved graft patency, while advances in anesthetic techniques, better myocardial protection during surgery and improved post-operative care have made CABG a safe operation with very low morbidity and mortality in most cases. A key difference between CABG and PCI, which explains the better long term outcomes with CABG, is that CABG bypasses entire areas of at-risk myocardium and therefore treats both the local culprit coronary lesion and adjacent at-risk areas, while PCI only treats the targeted local coronary lesion and leaves adjacent areas of at-risk myocardium alone, and is therefore not protective of future progressive CAD.<sup>111</sup>

Ishamuddin *et al.*<sup>112</sup> conducted a cross sectional study on 137 patients with left main stem disease (LMS), 38% of whom underwent CABG without the use of cardiopulmonary bypass. Less bleeding and blood transfusion were reported in those who underwent CABG without cardiopulmonary bypass with no difference in other outcomes. However, it should be noted that this was a non-randomised study and confounding factors may have influenced the results. There is concern with long term patency of the grafts when CABG is done without cardiopulmonary bypass and this was not accessed in this study.

In another small study, Ooi and colleagues<sup>113</sup> compared the outcomes of on-pump (35 patients) and off-pump (29 patients) CABG in patients with pre-existing non-dialysis renal failure. Creatinine clearance worsened in the on-pump group post-operatively but not in the off-pump CABG group. Renal function in both groups were back to baseline at 4 weeks post-operatively.

Park and colleagues<sup>114</sup> randomised 880 multivessel CAD patients in 4 Asian countries to either CABG or PCI (everolimus-eluting stents). The authors reported that at 4.6 years, there were significantly fewer myocardial infarctions and repeat-revascularization procedures in the CABG group.

Sokran *et al.*<sup>115</sup> studied the relationship between hand grip strength (HGS) and myocardial oxygen consumption (MVO2) index before and after CABG surgery. HGS is a good marker of peripheral muscle function while MVO2 is an objective measure of functional capacity. The authors recruited 27 patients prospectively prior to their planned CABG and found significant interactions for both HGS (dominant and non-dominant) and MVO2 before and after CABG. HGS was predictive of functional capacity amongst cardiac patients. There were several limitations with this study particularly the small sample size and short follow-up period.

### Case reports

Rare encounters of patients with dextrocardia and "situs inversus totalis" cases were reported. Ismail and colleagues<sup>116</sup> reported their case which underwent CABG with total arterial revascularization and Abdullah *et al.*<sup>117</sup> described their experience with a high risk dextrocardia patient who underwent urgent off-pump CABG. Both reports discussed the different techniques, positioning and approaches needed for dextrocardia during CABG. Raj *et al.*<sup>118</sup> described a successful CABG in a patient with concomitant diagnosis of asymptomatic Brugada syndrome, highlighting some arrhythmias and precautionary steps taken intra-operatively, and discussing the insertion of ICD for this patient.

Young patients with CAD undergoing CABG were also reported. Ramzisham *et al.*<sup>119</sup> and Lim *et al.*<sup>120</sup> both reported CABG on a 29 year old and 20 year old respectively. Ramzisham's patient was a young gentleman with all the CAD risk factors while Lim's patient was a consequence of Kawasaki disease. Both reports discussed the issue of conduit selection in young patients and the need for aggressive control of risk factors for long term graft patency.

A case report on a rare complication of CABG reported by Rahman and colleagues<sup>121</sup> described a delayed acute Stanford Type A aortic dissection following an off-pump CABG case with pre-existing chronic Type B aortic dissection.

Liew *et al.*<sup>122</sup> reported their experience with creation of vascular access for dialysis in forearms for two patients who had previously underwent radial artery harvest for CABG. The creation of brachiocephalic fistula (BCF) on one patient and a brachio basilic fistula (BBF) on the other was successful and no distal hypoperfusion ischemic syndrome (DHIS) was found at 1 year and 6 months follow up respectively.

### Stem cell therapy

In recent years, stem cells have been used in an effort to regenerate areas of infarcted myocardium or to stimulate angiogenesis in areas which cannot be revascularised by conventional means. In 2004, Hattori *et al.*<sup>123</sup> reviewed recent advancement in bone marrow cell research and autologous bone marrow mononuclear cells (BM-MNC) transplantation in severe ischaemic heart disease at IJN. The authors claimed bone marrow cell transplantation into myocardium is a safe and effective technique to stimulate development of collateral arteries. Bone marrow mesenchymal stromal cells (BM-MSC) has also been researched locally. However, the limitation is the transportation risk with contamination, infection and reduced viability of the stromal cells. Chin *et al.*<sup>124</sup> published a small study of three cases of intramyocardial MSC injection during open heart CABG using a new technique of culture and transportation. The study reported good cell viability (90% viable) and sterility. Patients were reported to have significant improvement in cardiac function, volume and wall thickness at 6 months. More recently, Musa *et al.*<sup>125</sup> reviewed the current stage of research and development on cell therapies for cardiovascular disease and questioned the efficacy of available evidence on the various types of cells currently used in research settings. The authors recommended avoiding overzealous extrapolation of data reporting and that future studies focus on the biological functions of the available cell lines.

### TREATMENT OF ACUTE CORONARY SYNDROMES

Current recommendations for the treatment of ST-elevation myocardial infarction (STEMI) include immediate anti-platelet therapy followed by either primary percutaneous intervention (PCI) or thrombolysis in patients presenting within 12 hours of the onset of symptoms. Primary PCI is recommended over thrombolysis if this can be done within 2 hours of arrival at the hospital as this has been shown to produce higher rates of infarct coronary artery patency, TIMI 3 flow, and lower rates of recurrent ischemia, re-infarction, emergency repeat revascularization procedures, intracranial hemorrhage, and death. Where primary PCI cannot be performed within 2 hours of presentation, thrombolysis should be performed. A time-dependent reduction in both mortality and morbidity rates has been demonstrated with both reperfusion strategies; it is therefore important for patients to present to hospital as soon as possible after symptom onset, and for hospitals to minimize delays in instituting appropriate treatment on arrival.<sup>126</sup>

### Time to presentation

A study was conducted to evaluate if transportation mode affected time to presentation at hospitals. Chew and colleagues<sup>127</sup> conducted a survey on 110 acute coronary syndrome (ACS) patients and found 95.5% used their own transportation, all of whom did not reach hospital within one hour of the onset of symptoms. Only 3 patients (2.7%) used ambulances and all 3 of them made it within one hour. Level of education and past history of ischemic heart disease did not significantly influence the patient's choice of transportation.

### Anti-platelets

ACCORD<sup>19</sup> enrolled 525 patients in Malaysia to evaluate the usage of anti-platelet in unstable angina and NSTEMI patients at discharge and during follow-up visits. During hospitalization and at discharge, aspirin only was used in 86.9%, clopidogrel only in 52.4% and dual anti-platelets in 48.4% of patients. During follow-up visits over one year, the percentage of patients on aspirin only was 62.7–77.6%, on clopidogrel only 5.0–6.8% and on dual antiplatelets 15.6–32.3%.

Huo *et al* conducted the EPICOR Asia,<sup>128</sup> to follow 13,000 Asian patients admitted with ACS and then discharged home, for up to two years. The study captured the antithrombotic management patterns in Asia, clinical outcomes, healthcare resource use, and self-reported health status. Enrolment was completed in May 2012 and the study findings provided data of the standard and outcome of Asia's management of ACS.

### Anti-thrombotics

The rate of bleeding complications secondary to enoxaparin was studied by Mohamed and colleagues.<sup>129</sup> The study recruited 40 patients who were treated with enoxaparin and prospectively followed up for 3 days in the ward. They found bleeding episodes in 18 patients (45.5%), mainly with hematuria (83.3%). In this small study, the gender of women and renal impairment were associated with higher risk of bleeding.

### Reperfusion strategies

Lee *et al.*<sup>130</sup> retrospectively reviewed 192 STEMI cases who received thrombolysis using streptokinase and found reperfusion failure rate using ECG criteria of 56.8% associated with diabetes mellitus, hypertension, anterior MI, longer door-to-needle time and high total white cell.

Azlan and colleagues<sup>131</sup> retrospectively reviewed the incidences and risk factors for bleeding complications post tenecteplase thrombolysis over a 2-year-period. In a total of 100 patients thrombolysed using tenecteplase, 12% developed bleeding complications. No demographic factors (age, gender and ethnicity) or comorbidities (diabetes, hypertension, hyperlipidemia, previous CVA and previous CAD) were found to be significantly associated with bleeding complications but it must be noted that the sample size of this study was very small. A rare bleeding complication was encountered by Peyman and colleagues<sup>132</sup> who described a case report of intraocular hemorrhage post streptokinase administration.

The decision to thrombolyse is usually made by the medical-on-call team. Loch *et al.*<sup>133</sup> assessed the door-to-needle times before and after a change of thrombolysis decision-making, from medical team-led thrombolysis to Emergency Department-led thrombolysis. During the study period of one year for each practice method, 169 patients were thrombolysed by the medical on-call and 128 cases by the ED doctors. Median door-to-needle times were 54 and 48 min respectively. The authors found that the transfer of responsibility for thrombolysis to the ED doctors did not improve door-to-needle times significantly.

Selvarajah *et al.*<sup>134</sup> assessed the impact of variation in cardiac care provision and reperfusion strategies on patient outcomes. They found 75% of all STEMI were treated with thrombolysis, 7.6% underwent primary PCI and the remainder were managed conservatively. Timely reperfusion was low, at 24% in specialized cardiac centers versus 31% in non-cardiologist hospitals and 28% for primary PCI. Cardiac centers had significantly higher use of evidence-based treatments. However, the adjusted 30-day mortality rates for in-hospital thrombolysis and primary PCI were similar at 7%. This was, however, not a randomized study. Similar results were reported by NCVD-ACS 2009-2010<sup>135</sup> where 74% of STEMI were thrombolysed at presentation and only 7% were directly treated with PCI. Most NSTEMI/UA were treated medically. Only 13% of NSTEMI and 6% of UA were treated with PCI on the same admission. Only 2% of NSTEMI and 1% of UA underwent CABG on the same admission.

### Adherence to clinical guidelines

Kassab and colleagues<sup>136</sup> retrospectively reviewed the practice adherence to clinical guidelines in 380 ACS patients focusing on the medical treatment: aspirin ± clopidogrel, beta-blockers, statins and angiotensin-converting enzyme inhibitors (ACEI) / angiotensin II receptor blockers (ARBs). They found 95.7% of the patients received antiplatelets comprising of at least aspirin, 82% received aspirin plus clopidogrel, 80.3% of the patients received a beta-blocker at discharge, 95% received a statin and 69.7% received either an ACEI or ARB. The authors concluded that there was good adherence to guidelines for the secondary prevention of CAD after an ACS.

Hassan *et al.*<sup>137</sup> conducted a study on the role of pharmacists in the secondary prevention therapy in ACS patient management. Using a pre-intervention adherence audit as baseline, they investigated the effect of placing two hospital pharmacists in the ward rounds with physicians. A total of 72 interventions were made by pharmacists of which drug initiation was the most common (59.7%), followed by recommendations to switch drugs (23.6%) and dose optimisation (16.6%). Most recommendations (72.2%) were accepted by clinicians. The intervention also led to a significant increase in the utilization rates of all four drug classes (from 42.6% to 62.6%) underlying the important role of ward pharmacists in improving clinical care.

### Patient adherence

There were a number of studies looking into patient adherence with medications and health recommendations. Leong *et al.*<sup>138</sup> assessed the level of adherence using a semi-structured questionnaire in 52 post MI patients and found all the responders did adhere to medications as prescribed. However, only 80% adhered to healthy diet advice; there was low adherence to weight loss (25%), physical activity (65.4%), social activity (44.2%), smoking cessation (28.8%) and alcohol use (19.2%) advices.

Lee and colleagues<sup>139</sup> surveyed 210 ACS patients using the Medical Outcome Study Specific Adherence Scale (MOSSAS) questionnaire on patients' recalled health recommendations. The study found suboptimal adherence rate of 65.2% and it varied from 22.1% to 95.1%. Kassab *et al.*<sup>140</sup> prospectively

followed up 190 ACS patients' level of adherence to evidence-based therapies at 6 months after discharge using the translated eight-item Morisky Medication Adherence Scale (MMAS). The study found 18.4% reported high adherence, 51.1% medium adherence and 30.5% low adherence. Older, unemployed, multiple comorbidities and polypharmacy are associated with poorer adherence. The same group<sup>141</sup> continued the follow-up for another 2 years and managed to retain 151 patients from the original cohort. There was a significant downward trend in the level of adherence to medications during the 2 years period from a mean MMAS score of 6.39 at 6 months to 5.72 at two years. The authors concluded that long-term adherence to secondary prevention therapies among patients with ACS in Malaysia was suboptimal.

Poor patient adherence is detrimental to the long term outcome and studies looked into ways to improve this. Khonsari *et al.*<sup>142</sup> studied the effect of automated SMS-based reminders on medication adherence in ACS patients after hospital discharge. They randomized 62 patients with ACS into two groups, with one group of patients receiving SMS reminders and the other with usual care as control, for a period of eight weeks after discharge. The study found that the intervention group had higher medication adherence level than the usual care group.

### Outcomes

The NCVD-ACS 2009-2010 reported that in-hospital mortality rates of ACS patients remained consistent between 6-8% over the five-year period from 2006 to 2010, with overall average of 7%. Mortality of STEMI was 9% while NSTEMI was 8%. These were higher compared to several other global and regional ACS registries.

Patients who presented with suspected diagnosis of ACS are triaged to red zone for faster treatment. Ahmad and colleagues<sup>143</sup> examined the diagnosis and one week mortality rate of all red zone patients at Hospital University Sains Malaysia and found that out of a total of 440 red tag patients, 54% of them were cardiac related cases. At one week follow-up of these cases, 6.1% died within a week and 44% of their deaths were due to ACS.

Ho *et al.*<sup>144</sup> studied the quality of life of 108 ACS patients using the Medical Outcomes Short Form 36 (SF-36). The study found that respondents had a good quality of life (mean total score 59±22); the general health components was associated with education level while physical components were associated with income level.

Selvarajah and colleagues<sup>145</sup> examined the Thrombolysis In Myocardial Infarction (TIMI) risk score for STEMI. Using the NCVD-ACS 2006-2008 data, the authors found TIMI risk score was strongly associated with 30-day mortality with good discrimination for the overall study population and also the high risk subgroups. Calibration was good for the overall study population and diabetics, but poor for those with renal impairment; it may be due to the small size of the subgroup. The authors concluded that TIMI risk score is valid to be used in our population.

## COMPLICATIONS OF CORONARY ARTERY DISEASE

### Heart failure

Chong *et al.*<sup>146</sup> conducted a prevalence study of heart failure (HF) among all medical admissions and found HF accounting for 6.7% of all medical admissions with an inpatient mortality rate of 11%. CAD was the main etiology (49.5%) followed by hypertension (18.6%). The authors found ACE inhibitors were under-utilized in our HF population.

### Sudden death

Sudden death in chronic heart failure patients is common and can be prevented with implantable cardioverter-defibrillators (ICD). Prophylactic ICD is costly and invasive, often instituted based on several predictors of sudden death such as a very low left ventricular ejection fraction (LVEF). Yap and colleagues<sup>147</sup> pooled available data of 2,828 patients to examine the dichotomy limit of LVEF for ICD treatment. The authors suggest that no single dichotomy limit is satisfactory and patients with too low a LVEF (less than or equal to 10%) would not benefit from ICD treatment; cost effectiveness was maximal in those with LVEF between 16 and 20%.

### Psychological

Ho *et al.*<sup>148</sup> administered Hospital Anxiety and Depression Scale (HADS) questionnaires to 108 ACS patients to determine the prevalence of anxiety and depression. The study found low scores for both anxiety and depression, and significant difference in scores when participants stratified for marital status and comorbidities. Satpal *et al.*<sup>40</sup> recruited 189 CAD patients to establish the factor structure of HADS. The authors found that HADS was good and valid in terms of factor structure and internal consistency to measure the psychological distress among CAD patients and recommended that the cut-off score to screen for psychological distress be re-evaluated.

Sharmini *et al.*<sup>149</sup> examined the relationship between social support, depressive symptoms and quality of life among women with CAD. They interviewed 50 CAD patients in the outpatient clinic using a questionnaire comprised of various scales and interviewed another 10 CAD patients with open-ended questionnaire for qualitative analysis. The study showed that informational support is significantly predictive of depressive symptoms. Qualitative analysis showed that social support improved quality of life and enhanced emotional well being. These factors should be considered in designing cardiac rehabilitation programmes.

Patient's subjective experience and changes in life following myocardial infarction were examined by Sukeri *et al.*<sup>150</sup> using qualitative research. The study interviewed 11 Muslim respondents to investigate the impact of MI from the perspective of Muslim respondents. The respondents commonly reported post-MI stresses such as fear and anxiety. The influence of religion was evident and appeared to be intertwined in many aspects of their feelings on lives and illness.

### HEALTH COST

Aniza and colleagues<sup>151</sup> compared the cost to treat patients with uncomplicated AMI using two different methods,

namely step down costing and activity based costing (ABC) in 2011. They found the cost of treatment (with PCI) using step down costing was RM17,290 and using ABC method RM20,431.39. Cost of treatment calculated by using ABC is higher by 15.3% than the step down costing.

## SECTION 2 - RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Considerable research on CAD has been done in Malaysia. The evidence continues to show that CAD is the major cause of mortality and morbidity in the country. A high prevalence of risk factors for CAD is present in the population. Greater efforts must be made towards education of the public to change dietary habits and other at risk lifestyles such as smoking, and to increase awareness of healthy living such as regular exercise, etc, to reduce the prevalence of CAD in the country. Greater efforts at secondary prevention are also needed to improve outcomes once CAD is diagnosed. However, studies have shown that the adherence of patients in this country to primary and secondary prevention strategies and treatments was not high.<sup>138-142</sup> Steps must be taken to find ways to improve patient adherence, which may necessitate spending a longer time with patients during clinic consultation, setting up specialist CAD clinics for this purpose, and financial incentives or disincentives.

Two studies<sup>134-135</sup> in this review showed that patients presenting with STEMI in this country are typically treated by thrombolysis, contrary to current guidelines which recommend primary PCI as the preferred treatment due to its better outcomes.<sup>126</sup> Much efforts are needed to improve cardiology services in the country with provision of primary PCI facilities in all major cities. Earlier instituting of appropriate treatment has been shown to lead to better outcomes. One study identified mode of transportation as a factor in delayed presentation to hospital following onset of symptoms.<sup>127</sup> Better education of the public on the symptoms and signs of acute coronary syndromes and the urgency and best way to get to hospital is needed, as well as improving our emergency ambulance service.

## SECTION 3 - FUTURE RESEARCH DIRECTION

There is an absence of research on both primary and secondary prevention strategies and treatments in the country. Such studies are needed to determine their feasibility and effectiveness in reducing CAD in the country, and improving its outcome once diagnosed. Studies are also needed to better understand why patient adherence to primary and secondary prevention strategies and treatments are not as good as it can be in this country, and how this can be improved.

There is an absence of data on the long term outcomes following both PCI and CABG in the country. Although such data is available from elsewhere, particularly the western developed countries, it is important that the long term outcomes in this country are also known to ensure that our patients are benefiting from these invasive treatments. To this end, the newly launched National Thoracic and Cardiovascular Surgical Database (NCTSD) Registry should hopefully be able to provide long term outcomes of CABG in

**Table I: Summary of risk factor prevalence studies in Malaysia**

Authors	Study type	Population studied (Location)	Year (of study unless specified)	N	Risk factors findings
Ahmad <i>et al</i> <sup>19</sup>	Prospective	Unstable and NSTEMI patients (17 participating Hospitals)	2004-2005	525	Hypertension (66.1%), Diabetes Mellitus (38.9%), Dyslipidemia (40.4%), Smoking history (Current smoker: 21.7%, ex smoker: 25.3%), previous history of CAD (64.4%), family history of CAD (15%)
Chiam <i>et al</i> <sup>14</sup>	Retrospective	Post CABG patients (HUKM)	1998-2001	302	Hypertension (78.8%), Diabetes Mellitus (45.7%), Hyperlipidemia (89.1%)
Suleiman <i>et al</i> <sup>18</sup>	Case Control	Adult male patients admitted to medical ward (HKL)	1994-1995	102	Smoking >20 sticks/day (OR 9.49 (CI 95% 2.91,40.81), Hypercholesterolemia (OR 21.26 (CI 95% 8.01,125.53).
Nawawi <i>et al</i> <sup>20</sup>	Cross sectional	Adult Malays in rural population in Raub, Pahang (30 to 65 years old)	1997-1999	609	Hypertension (30.3%), Diabetes Mellitus (6.4%) Impaired fasting glucose (13.9%), Dyslipidemia (67.3%), Smoking (24.4%), Overweight/obesity (44.7%), Increased waist hip ratio (48.5%)
Mohd Yunus <i>et al</i> <sup>21</sup>	Cross sectional	Adult Malays in rural population in Dengkil, Selangor (15 years old above)	1999	570	Hypertension (28.6%), Smoking (21.1%)
Chang <i>et al</i> <sup>22</sup>	Cross sectional	Adults in rural Sarawak (20 to 65 years old)	published in 2012	260	Hypertension (13.5%), Diabetes Mellitus (1.5%), Smoking (15.4%), Hypercholesterolemia (22.6%), Overweight (39.6%), Obesity (11.9%)
Norazmi <i>et al</i> <sup>11</sup>	Cross sectional	Fisherman community in Kelantan	1994	223	Hypertension (28.8%), Smoking (76.5%), Low HDL (95.8%)
Lua <i>et al</i> <sup>12</sup>	Cross sectional	Security guards in UM	2003	130	Hypertension (21.7%), Diabetes Mellitus (11.3%), Hypercholesterolemia (74.8%), Smoking (40.5%), Overweight (47.8%), Obesity (14.8%)
Nazri <i>et al</i> <sup>13</sup>	Cross sectional	Adult factory employees in Kota Bahru, Kelantan	2003-2004	148	Hypertension (shift workers group: 22.4%, day workers group: 4.2%).

a few years time. There is also a need for the NCDV-PCI registry to collect and report on long term outcomes following PCI.

There have been very few studies in the country on the mode of coronary artery revascularization in patients who need this. Current evidence demonstrate a survival benefit with CABG over PCI in patients with 3 or more vessel coronary artery disease and complex coronary artery anatomy particularly if the patient is diabetic.<sup>81-82</sup> Studies are needed to evaluate the current practice in the country, and whether current guidelines are being adhered to.

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