#### UNIT NO. 2

## CARDIOVASCULAR RISK CALCULATORS: BACK TO BASICS

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### ABSTRACT

Cardiovascular disease (CVD) is a leading global cause of mortality and morbidity. Risk assessment of asymptomatic individuals plays an important role in the primary prevention of CVD and its complications by guiding management decisions, in particular the decision to use statins or antiplatelet agents, as well as more controversially, the target level for risk factors such as hypertension and cholesterol. Timely and regular risk assessments also identify the development of physiological disturbances such as pre-hypertension, pre-diabetes, dyslipidaemias, clinical obesity and metabolic syndrome, which can be asymptomatic in the early stages, but may lead to increased risk for many ageing-related degenerative diseases, including CVD. These physiological mal-adaptations are remarkably responsive to behavioural lifestyle interventions at an early stage, and may be stabilised or even reversed without medications. This article describes the why and how of assessing CVD risk and a suggested framework for management, including the appropriate use of behavioural lifestyle interventions as first-line treatment. It also describes the various risk scores available, their differences and limitations and how to best use them in clinical practice. More research is required regarding the use of non-traditional and emerging markers of CVD risk such as carotid intima-media thickness, coronary artery calcium scoring, hsCRP, ankle brachial index, Apo-B, albuminuria, and how they may be incorporated into existing risk models.

#### **Keywords:**

Risk Assessment; Risk Stratification; Risk Scoring; Cardiovascular Disease Prevention;

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## **BURDEN OF CVD IN SINGAPORE**

Atherosclerotic CVD is a common cause of mortality and morbidity globally, and is anticipated to affect a majority of adults past the age of 60 years. Cardiovascular disease includes coronary artery disease [acute myocardial infarction (AMI), angina, and heart failure (HF)]; cerebrovascular disease, including stroke and transient ischemia attacks (TIA); peripheral artery disease; and thoracic or abdominal aortic aneurysms. The burden of CVD in Singapore is sizeable, being responsible for one-fifth of the total disease and injury burden in 2010. Between 2004 and 2010, there was a 10.4-percent

PETER TING Senior Consultant Cardiologist The Harley Street and Cancer Centre Gleneagles Hospital increase in CVD burden: 31.3-percent increase in disability burden and 5.9-percent increase in premature mortality burden. About 80 percent of cardiovascular burden in 2010 was from premature mortality. Ischaemic heart disease (53%) and stroke (34%) were the main contributors of the cardiovascular burden. These two diseases were ranked first and third in overall disability-adjusted life years lost (DALYs) respectively.<sup>1</sup> Coronary artery disease (CAD) and cerebrovascular disease contributed to 16 percent and 8.4 percent of all deaths, respectively, in 2014.<sup>2</sup> Heart disease and stroke also accounted for almost 8 percent of hospital discharges that same year.<sup>3</sup> Given the magnitude of the problem it is crucial that preventive measures be adopted to avoid the late complications of CVD which can be severe and impose a heavy social and financial burden.

## **RISK FACTORS FOR CVD**

Atherosclerotic CVD is a continuum that can begin early in life through the presence of genetic and lifestyle-related risk factors. Atherosclerosis generally progresses with time, often accelerated by these risk factors, eventually causing damage to the organs supplied by these blood vessels (heart, brain, kidney, eye, and distal extremities), and in severe instances causing organ failure or death. Hence early detection of the risk factors and timely intervention and optimisation may alter the trajectory of atherosclerotic disease progression. The risk factors for atherosclerosis have been well defined over the years; these are divided into non-reversible and reversible.

Non-reversible risk factors include age, gender, ethnicity and family history. Age increases one's risk of developing heart disease. According to the American Heart Association, about 80 percent of people who die from cardiovascular disease are 65 years and older. Although heart disease has long been considered to be primarily men's disease, women tend to develop cardiovascular disease about 10 years later in life than men and often have worse outcomes. The risk for developing heart disease also increases if there is a first-degree male relative with heart disease before 55 years old or a female before 65 years.<sup>4</sup> With regards to the different ethnic groups in Singapore, the age-standardised rates (ASR) of AMI for Malays and Indians were about 2 - 2.5 times that of Chinese. In particular, the ASR among Malays has shown an upward trend since 2009.<sup>5</sup>

The landmark INTERHEART study, a large, standardised, case-controlled study of AMI in 52 low- and middle-income countries showed that 9 reversible risk factors account for almost 90 percent of the risk of developing AMI (Table 1).<sup>6</sup> The harmful factors that increase risk in decreasing order are: dyslipidaemia, smoking, diabetes mellitus, hypertension, and abdominal obesity. The protective factors which decrease risk are daily fruit and vegetable consumption, and regular physical activity. Moderate alcohol consumption seemed to have a

modest protective effect, but subsequent analysis by the INTERHEART investigators showed that heavy drinking was associated with an increased risk of myocardial infarction in the subsequent 24 hours.<sup>7</sup> These same factors have also been shown to have similar influence in the development of stroke in the INTERSTROKE study.<sup>8</sup> These are important revelations, as they demonstrate that a majority of heart attacks and strokes can actually be prevented through early detection and correction of these factors.

Table 1: Reversible factors that influence	the risk of acute myocardial infarction
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Harmful Risk Factors	Odds Ratio (95% CI)	
Dyslipidemia (highest vs. lower decile)	3.25(2.81-3.76)	
Smoking (current vs. never)	2.87(2.58-3.19)	
Diabetes	2.37(2.07-2.71)	
Hypertension	1.91(1.74-2.10)	
Abdominal obesity (highest vs. lowest)	1.62(1.45-1.80)	
Psychosocial	2.67(2.21-3.22)	
Protective Risk Factors		
Daily fruit and vegetable consumption	0.70(0.62-0.79)	
Regular exercise	0.86(0.76-0.97)	
Alcohol consumption (moderate)	0.91(0.82-1.02)	

Taken from Yusuf S, et al. Lancet. 2004;364:937.

# RISK ASSESSMENT, RATIONALE, AND STRATEGY

Screening for these modifiable lifestyle risk factors and high-risk metabolic diseases that predispose to atherosclerosis presents an opportunity for timely intervention to disrupt its progression, and alter the vascular health trajectory. Therapeutic lifestyle changes when instituted early and adequately can have a significant impact by treating and even reversing high-risk diseases such as hypertension, diabetes, high cholesterol and obesity. This has been proven in established studies such as the diabetes prevention programme which demonstrated that successful lifestyle intervention administered to 1,079 participants resulted in a 58-percent reduction in the incidence rate of diabetes<sup>9</sup> and the Dietary Approaches to Stop Hypertension (DASH) diet which was shown to be as effective as first-line drug therapy in the treatment of stage 1 hypertension.<sup>10</sup> Appropriate use of pharmacotherapy such as lipid-lowering therapy or antiplatelet agents may also further reduce risk when the benefit-to-risk ratio becomes favourable. This topic is beyond the scope of this article, but is covered by the various lipid guidelines of major international cardiology societies, and the Preventive Services Task Force U.S. (USPSTF) recommendations on aspirin use for primary prevention of cardiovascular diseases.

Risk assessment first takes into account the presence and combination of the various risk factors mentioned earlier to predict future CVD events. Single severe risk factors can have a strong influence on both immediate and longer-term risk, but the combined effect of many low-to-moderately severe risk factors may be just as damaging as a single high-risk factor; hence, the need for a global risk assessment. Persons aged 20 years or older without established CVD should undergo periodic assessment for traditional CVD risk factors every four to six years,<sup>11-13</sup> with some guidelines advocating starting from 18 years.<sup>14</sup> Adults from age 40-79 years free from CVD should have their 10-year CVD risk calculated every 4 to 6 years.<sup>11</sup> It is

unclear at what age periodic risk assessment should no longer be performed, but many of the validated risk models have only included patients up to 79 years of age or less.<sup>12</sup> Decisions regarding the discontinuation of periodic risk assessment should be made in collaboration with each individual patient based on the patient's overall functional status, life expectancy, and values and preferences for risk-factor modification.

# DIFFERENT RISK CALCULATORS AVAILABLE

Several multivariate risk models have been developed for estimating the risk of initial cardiovascular events in apparently healthy, asymptomatic persons. No single risk model is appropriate for all patients,<sup>15,16</sup> and one should individualise based on patient characteristics such as age, gender, ethnicity, geographic location, and disease demographics. In general it is preferable to also use risk models that predict hard CVD events such as death, AMI or stroke, as compared to other endpoints such as revascularisation. The earliest and most well known Framingham risk score was first published in 1998 and was derived largely from a Caucasian population of European descent.<sup>17</sup> This score has since undergone several revisions, once in 2002,<sup>18</sup> which eliminated diabetes from the algorithm since it was considered a coronary artery disease equivalent, broadened the age range, and included hypertension treatment and age-specific points for smoking and total cholesterol. In 2008,19 other important vascular outcomes such as stroke, TIA, claudication, and HF were added, and diabetes was reinstated as a predictor rather than an automatic coronary heart disease risk equivalent.

The Europeans' Systematic COronary Risk Evaluation [(SCORE), 2003] was based on data from more than 200,000 patients pooled from 12 European countries.<sup>11,20</sup> The Systematic COronary Risk Evaluation differed from Framingham in that it estimated the 10-year risk of any first fatal atherosclerotic event (e.g. stroke or ruptured abdominal aneurysm), not just death from CHD, and it estimated CVD mortality. Other risk scores like QRISK and QRISK2 were developed to predict CV risk in different ethnic groups living in England and Wales.<sup>21,22</sup> Additional variables in calculation include ethnicity, socioeconomic status, family history, diabetes, CKD, atrial fibrillation and rheumatoid arthritis. The Reynolds CVD risk score for women (2007) and for men (2008) included family history of AMI and high-sensitivity C-reactive protein (hsCRP) as variables in the risk calculator.<sup>23,24</sup> There was a slight difference in that HbA1C was not taken into account in the Reynolds risk score for men.

A more recent risk-scoring formula to come about was the ACC/AHA pooled cohort hard CVD risk calculator in 2013. This is the first risk model to include data from large populations of both Caucasian and African-American patients.<sup>12</sup> It includes the same parameters as the 2008 Framingham General CVD model, but in contrast includes only hard endpoints (fatal and nonfatal MI and stroke). Other risk scores include the Joint British Societies (JBS) risk calculator in 2014 which is based on the QRISK lifetime cardiovascular risk calculator.<sup>25</sup> This risk calculator extends the assessment of risk beyond the 10-year

window and allows for the estimate of "heart age" and the assessment of risk over longer intervals. The Multi-Ethnic Study of Atherosclerosis (MESA) risk score (2015),<sup>26</sup> also incorporates the coronary artery calcium score if measured, to further classify patients.

While the Framingham criteria are quite commonly used here, several studies have suggested that they tend to over- or under-estimate risk in other non-white populations, as well as in patients older than 85 years.<sup>11,15,20,27-30</sup> The Systematic COronary Risk Evaluation and QRISK2 would have better predictive accuracy in European patients.<sup>11,20-22,27-30</sup> Locally, the Framingham risk score has been modified, taking into account the Singapore cardiovascular epidemiological data. This modification was carried out between investigators at the Singapore Ministry of Health, Singapore General Hospital and National University of Singapore in collaboration with Prof Ralph B D'Agostino from the Framingham Heart Study, USA.<sup>31</sup> However, this version does not consider diabetes as a variable in its risk prediction, but rather a CVD equivalent.

# LIMITATIONS OF CURRENT CVD PREDICTION MODELS

There is no perfect risk score, knowing the limitations allow us to make the most appropriate choice and guide the final interpretation. While useful in stratifying patient risk according to the number of defined risk factors, they tend to falsely reassure persons deemed to be at low risk who may have multiple marginal abnormalities.<sup>31,32</sup> This is especially true in younger individuals who possess risk factors. As age has a strong influence on the overall risk calculation, this may result in a low calculated 10-year risk but in fact mask a substantial longer-term or lifetime risk, which could have been modified through aggressive risk factor reduction.<sup>31,33</sup> ACC/AHA 2013 guidelines do offer lifetime risk calculation, and recommend that assessment of 30-year or lifetime CVD risk on the basis of traditional risk factors may be considered in adults 20 to 59 years of age who are free from CVD and are not at high short-term risk (Class IIb recommendation).<sup>12</sup> Although evidence has not shown the utility of lifetime risk assessment for guiding pharmacological therapy decisions, lifetime risk information may still be useful in motivating therapeutic lifestyle changes in younger individuals. Risk predictions have also been shown to vary significantly between different risk scores when applied to the same population, especially if that population is different from the cohort used to validate that score.<sup>15</sup> Some of the older risk scores may not reflect the changing severity and frequency of the first vascular disease event over the years.<sup>35</sup> The relative effects of traditional risk factors may also differ according to the vascular disease outcome being evaluated.<sup>35</sup> Finally, some risk models do not include patient important CVD outcomes such as stroke, HF, or development of symptomatic peripheral artery disease.

# DIABETES AS A RISK EQUIVALENT

Traditionally, the risk factor of diabetes was considered a CVD risk equivalent. This was based on epidemiological evidence that diabetics, even without prior history of CVD, have higher rates of sudden cardiac death compared to those without diabetes.<sup>36</sup> Furthermore, studies by Haffner<sup>37</sup> also concluded that diabetics had the same risk for future AMI as adults with previous AMI but without diabetes. A meta-analysis by Bulugahapitiya et al,<sup>38</sup> however, did not support the hypothesis that diabetes is a CVD equivalent. This meta-analysis of 45,108 patients showed that patients with diabetes without prior AMI had a 43-percent lower risk of developing total coronary artery disease events compared with patients without diabetes with previous AMI (summary odds ratio 0.56, 95% confidence interval 0.53-0.60). This may be explained by the fact that diabetic patients now receive an optimal aggressive treatment strategy, including the use of statins and antihypertensive agents. Public health decisions to initiate additional investigations to screen for coronary artery disease in patients with diabetes should therefore now be based on the diabetic patient's CAD risk estimate rather than a routine investigations approach. However, diabetes is still an important risk factor and, additionally, diabetics have a greater burden of other atherogenic risk factors than nondiabetics, including hypertension, obesity, increased total-to-HDL-cholesterol ratio, hypertriglyceridaemia, and elevated plasma fibrinogen. The CVD risk in diabetics varies widely with the intensity of these risk factors. Guidelines published by the National Cholesterol Education Program and the sixth Joint National Committee have provided a framework to treat coronary risk factors aggressively in diabetics.<sup>18,39</sup> There is compelling evidence of the value of aggressive therapy for co-existing CVD risk factors in diabetics.40-42

## BEYOND TRADITIONAL RISK-FACTOR ASSESSMENT

There are non-traditional risk factors as well as more recent emerging imaging and biochemical markers. These were considered in the ACC/AHA Risk Assessment report.<sup>12</sup> However, firm evidence of the clinical impact of these factors is lacking, hence a quantitative risk assessment should occur first, and only if a risk-based treatment decision is uncertain, then assessment of family history of CVD, hsCRP, coronary artery calcium (CAC) score, or ankle-brachial index (ABI) may be considered to inform treatment decision-making. These markers may be useful in re-classifying risk in intermediate risk populations determined from traditional factors, and in addition may also help motivate individuals to make more significant and sustained therapeutic lifestyle changes (Table 2). A review by Peters et al43 provides evidence that tends to support the contention that amongst all these factors, measuring CAC score is likely to be the most useful of the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment. Routine measurement of carotid intima-media thickness was not recommended for assessing risk of first atherosclerotic CVD event. The committee also considered the use of Apo-B, chronic kidney disease, albuminuria, or cardiorespiratory fitness evaluation for risk assessment uncertain presently.<sup>12</sup> Future studies that incorporate these additional risk factors into the traditional risk models are needed in order to further elucidate their role in guiding clinicians in the assessment and management of CVD risk.

Table 2: Optional use of screening tests when risk-based decisions about initiation of pharmacological therapy are uncertain after quantitative risk assessment

Measure	Support revising Risk assessment
	upwards
Family history of premature CVD	Male<55 yrs of age, Female<65 yrs of
	age (1 <sup>st</sup> degree relative)
High sensitivity C-reactive protein	<u>&gt;</u> 2mg/L
Coronary artery Calcium score	≥300 Agatston units or ≥75 <sup>th</sup>
	percentile for age, sex and ethnicity
Ankle-brachial index	<0.9

See http://mesa-nhlbi.org/CACReferences.aspx.

## CONCLUSION

Risk assessment plays a key part in prevention of CVD. Early detection of reversible lifestyle risk factors and high-risk metabolic disorders allows implementation of behavioural lifestyle modifications which may alter the progression of disease. Various risk scores exist that stratify patients according to shortand longer-term risk, helping to guide intensity of lifestyle therapies, frequency of monitoring, and addition of preventive medications. However, knowledge of how they work and their limitations is necessary when interpreting the findings. Diabetes should no longer automatically be considered a CVD equivalent, but should be assessed preferably with risk scores that take it into account as a variable. Although evidence on the clinical utility of non-traditional risk factors is weak, expert opinion considers it reasonable to use CAC, ABI, family history, and hsCRP to help support risk estimation when unclear, or in the intermediate-risk group. Finally, all risk assessment is incomplete without a risk discussion with the patients based on their CVD risk, personal preferences, as well as potential benefits and harms with regards to initiation of relevant preventive therapies.

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### LEARNING POINTS

- Reversible CVD risk factors, when detected early, can be managed effectively by behavioural lifestyle interventions, often without the need for additional drugs.
- Nine reversible risk factors exist that, if optimised, can potentially prevent up to 90 percent of AMI and stroke.
- Choice of appropriate risk score and its subsequent interpretation depends on its validated population and the variables assessed in the calculation of risk. Ideally, it should estimate relevant hard CVD endpoints.
- Diabetes should no longer be automatically considered a CVD equivalent, although concurrent CV risk factors in diabetics should still be managed aggressively.
- The utility of non-traditional risk factors has not been well established in current risk assessment, but it is reasonable to use CAC, ABI, family history and hsCRP to help in informing decision-making when uncertain.