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High-sensitivity troponin I for cardiovascular risk stratification in the general asymptomatic population: Perspectives from Asia-Pacific

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ABSTRACT

Cardiac troponin is a sensitive and specific biomarker for acute myocardial injury and has been used in the diagnosis of acute coronary syndromes, and has emerged as a tool for identifying high risk individuals for primary preventive therapy. Recent evidence has emerged indicating that high-sensitivity cardiac troponin assays, which allow robust detection of very low troponin concentrations, could detect subclinical injury in asymptomatic patients. On 24 March 2018, a group of cardiologists from the Asia Pacific region convened to review the data and discuss the potential utility of high-sensitivity troponin I (hsTnI) in the risk assessment of cardiovascular disease in the general population. The group recognized the immense burden of cardiovascular disease in the Asia-Pacific region, and the limitations of current risk stratification strategies. Data demonstrates that cardiac biomarkers like hsTnI could improve risk stratification, and thresholds for hsTnI in cardiovascular disease risk classification have been developed in Caucasian populations but not validated in Asian populations. There is an urgent need to improve cardiovascular risk assessment in the Asia Pacific general population, validate the Asian threshold of high risk and prove the utility of targeting these high-risk individuals for primary preventive strategies.

1. Introduction

Currently, decisions regarding the initiation and optimization of therapy for the prevention of cardiovascular disease (CVD) are made through the assessment of traditional risk factors, including non-modifiable (e.g. age, sex) and potentially modifiable factors (e.g. smoking status, LDL-cholesterol, blood pressure levels, blood glucose levels). Though current risk scoring systems for CVD prevention are widely available and easy to use, they were largely derived in white populations and may over- or under- estimate risk in other ethnic groups. In addition, risk scoring systems may not be discriminating enough as patients classified as low risk still experience cardiovascular events. Newer risk assessment tools may permit earlier and more targeted intervention.

Circulating biomarkers have emerged as potentially powerful tools to improve cardiovascular risk stratification in the general population and identify high risk individuals for primary preventive therapy. The assessment of certain novel cardiac biomarkers can reveal subclinical myocardial damage that may elevate the risk of future adverse events. For example, the 2017 ACC/AHA Heart Failure Guidelines recognized the role of natriuretic peptides in screening and prevention of heart

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failure. Recent research has also found that high-sensitivity troponin I (hsTnI) independently predicts cardiovascular events in asymptomatic individuals [1–3].

Troponin I, measured by a high-sensitivity assay, can be reliably detected in the vast majority (80–90%) of the general adult population [1–3]. Recent studies show a link between detectable troponin levels and cardiac abnormalities such as silent ischemia, left ventricular hypertrophy, left ventricular dysfunction, and left atrial enlargement [4].

The use of hsTnI for cardiovascular risk stratification of the general population is a relatively new concept which is yet to be fully elucidated in Asia Pacific populations. In view of this, on 24 March 2018, cardiologists from the Asia Pacific region including Australia, China (Hong Kong), India, Indonesia, the Philippines, Singapore, Thailand and Vietnam, convened to review the data and its potential applicability to local populations. We summarize the findings of the meeting in four consensus statements below.

2. Statement 1: the global burden of CVD is enormous and is burgeoning in Asia Pacific

According to WHO, cardiovascular disease remains the most frequent cause of death globally, and are projected to rise further [5]. In recent decades, deaths from CVDs have declined in developed countries, but have exponentially increased in developing countries [5]. The Asia-Pacific region, which includes East Asia, South Asia, Southeast Asia, and Oceania, has experienced an upward trend in mortality from 1980 to 2016 (Fig. 1) [6]. CVD accounted for an estimated 9.1 million deaths in 2012, with wide variation in mortality rates among Asia Pacific countries; Mongolia exceeded 500 deaths per 100,000 population while more developed countries such as Korea, Japan and Singapore had rates below 120 per 100,000 population [7].

CVD encompasses a range of circulatory-related disorders, including ischemic heart disease (IHD) and cerebrovascular disease [7]. In 2016, IHD was the top cause of death in Australia, India, Indonesia, Philippines, Singapore and Thailand, while cerebrovascular disease was the leading cause in China and Vietnam [8].

Worrying aspects of CVD epidemic in Asia include accelerated progression, early onset of disease and high fatality rates. For example, the onset of CVD in the Indian population is approximately a decade earlier than the West, which results in high premature mortality – 52% of CVD deaths occur before the age of 70 in India compared with 23% in Western populations [9]. China, India, Indonesia, Philippines have an age-standardized death rate of 307.9, 344.3, 384.9 and 427.9 per 100,000 population, which is considerably higher than the global average of 277.9 (Table 1) [10]. This burden is also reflected in years of life lost (YLLs) and disability-adjusted life years [10].

3. Statement 2: current CVD risk stratification strategies are inadequate, and there is a need for improvement

Millions of CVD deaths can be prevented by implementing high-impact interventions, such as reinforcing smoking cessation, healthier diets and physical activity, as well as improving access to essential health care [5]. Identifying members of the general population who are at increased risk would help to allow more effective targeting of counselling measures, and potentially facilitate early treatments to mitigate the risks.

Table 1
Prevalence, deaths, years of life lost (YLLs) and disability-adjusted life years (DALYs) due to CVDs in 2016 [10].

Country	Prevalence	Deaths	YLLs	DALYs
Global	6877.9	277.9	4683.9	5178.4
Australia	5960.0	128.7	1613.9	1972.9
China	6037.0	**307.9**	4615.4	**5217.2**
India	5681.3	**344.3**	**6353.4**	**6880.1**
Indonesia	**7253.3**	**384.9**	**6770.9**	**7302.0**
Philippines	6022.4	**427.9**	**7400.6**	**7820.0**
Singapore	5611.0	111.1	1881.6	2295.4
Thailand	5973.7	132.2	2334.2	2734.9
Vietnam	5663.3	277.9	4448.0	4867.7

Age-standardized rate per 100,000 per year. Values above the global value are in bold.
Source: Global Burden of Disease Study, 2016.

Current CVD risk stratification strategies cited by group members include risk factor counting and estimation based on experience, the American College of Cardiology/American Heart Association (ACC/AHA) risk calculator [11], the Framingham risk score [12,13], SCORE (Systematic Coronary Risk Evaluation) risk charts [14,15], and the Q2Risk score [16]. A comparison of the variables measured by these scores is outlined in Table 2. Moreover, some countries have developed their own risk calculators, e.g. Thailand (Thai CV risk score) [17] while others have issued local guidelines on risk stratification methods, such as Vietnam (Vietnam National Heart Association guidelines), and Australia (National Vascular Disease Prevention Alliance) [18]. Indonesia has been using the Jakarta Cardiovascular Risk Score (JAKVAS Risk Score) since 2002, a modified Framingham Risk Score focusing on level of physical activity and smoking cessation instead of other traditional risk factors [19]. However in 2016, the RISKESDAS risk score was introduced with more simple and applicable use by measuring abdominal circumferential and certain targeted blood pressure. Reliability testing found that the RISKESDAS has a kappa value of 0.6 compared with JAKVAS and Framingham score [20].

The diversity and profusion of strategies underlie the fact that there is no single score that performs optimally for all populations. A study in India examined if CV risk scores were able to correctly classify risk in acute myocardial infarction (MI) patients if they had presented just prior to suffering the acute MI [21]. The study demonstrated that as compared with the World Health Organization (WHO) risk prediction charts, Framingham Risk Score (FRS) and (ACC/AHA) risk calculator, the 3rd Joint British Societies' risk calculator detected the largest proportion of the patients at 'high-risk' [21]. However, another group preforming a similar study in India concluded that FRS was the most useful for CVD risk assessment, while the JBS3 and QRisk2 performed only moderately well [22]. A study in Malaysia found that the FRS and SCORE (high CV risk region) models showed acceptable discrimination for estimating CV risk in its multiethnic population, but the WHO model did not [23]. Interestingly, the SCORE model, though relatively

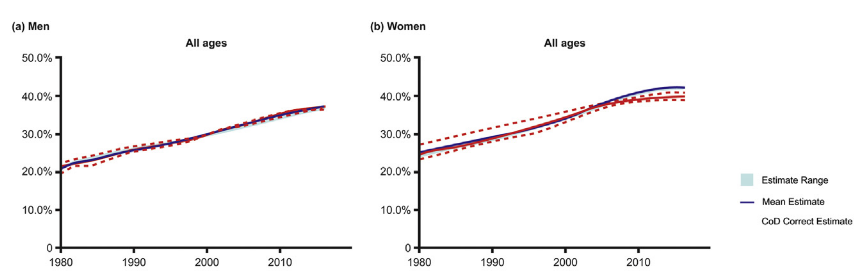

Fig. 1. Rate of mortality due to cardiovascular disease in Southeast Asia, East Asia and Oceania from 1980 to 2016. CoD: causes of death.

Table 2
Clinical and biochemical variables included in commonly used CV risk assessment models.

Variable	ACC/AHA	Framingham	SCORE	Q2Risk
Age	Y (20–79 years)	Y (30–74 years)	Y (40–65 years)	Y (35–74 years)
Gender	Y	Y	Y	Y
Ethnicity	Y	N	N	Y
History of diabetes	Y	Y	N	Y
Smoking history	Y	Y	Y	Y
History of blood pressure treatment	Y	Y	N	Y
Systolic blood pressure	Y (90–200 mm Hg)	Y (90–200 mm Hg)	Y (120–180 mm Hg)	Y (continuous)
Total cholesterol	Y (130–320 mg/dL)	Y (100–405 mg/dL)	Y (154–308 mg/dL)	Y (continuous)
HDL-cholesterol	Y	Y	Y	Y (continuous)
Family history of premature CVD	N	N	N	Y (first degree relative under 60 years)
Body-mass index	N	N	N	Y
Rheumatoid arthritis	N	N	N	Y
Chronic renal disease	N	N	N	Y
Atrial fibrillation	N	N	N	Y
Townsend deprivation score	N	N	N	Y

ACC/AHA. American College of Cardiology/American Heart Association; HDL, highdensity lipoprotein; SCORE, Systematic Coronary Risk Evaluation.

accurate for men, underestimated risk in women [23]. Yet another study in a multiethnic cohort in the US found that the AHA-ACC-ASCVD and 3 Framingham-based scored overestimates CV events by as much as 154% in men and 67% in women [24].

In order to balance risks and benefits of preventive therapies, accurate cardiac risk estimation is paramount. Whereas overestimation of risk may result in inappropriate use of preventive medications, which expose patients to unnecessary risks of these drugs, underestimation of risk may lead to delay in appropriate therapies that may prevent future CVD events. Risk stratification strategies need to improve the identification of young to middle-aged people with a low 10-year risk for CVD, but a moderate to high lifetime risk, so that they can benefit from early interventions that aim to prevent progression to the high-risk group in later life. This is an area where more cardio-specific methods, such as coronary calcium scoring or hsTnI, might be useful. Though extensive literature (MESA Study [25], St Francis Heart Study [26]) support the use of calcium coronary scoring as a CV risk assessment and net reclassification tool, it has limitations such as accessibility, cost and radiation exposure. As our group recognizes the benefits of having a standardized strategy or tool, which may be applied across various populations, we will focus our discussion on hsTnI.

4. Statement 3: including cardiac biomarkers as a risk stratification tool may increase net reclassification improvement

Studies of cardiac troponin I in the general population have shown associations with adverse cardiovascular events (Table 3). While the evidence for prognostic utility of hsTnI in the general population is robust,

Table 3
Summary of selected studies on hsTnI use for risk stratification for primary prevention.

Study	Country	N	Sex (% F)	Mean age (years)	Mean follow-up (years)	Cutoff	HR or OR, (95% CI)	Outcome
					General population			
BiomarCaRE (Blankenberg, 2016) [3]	(Europe-10 populations)	74,738	47.8%	52.2	13.8	≥6.0 ng/L	1.93 for CVD 2.25 for overall mortality	CVD, overall mortality
Busselton Health Study (Zhu, 2017) [28]	Australia	3939	57.1%	52.4	20	≥4.0 ng/L (♀) ≥6.0 ng/L (♂)	♀: HR 1.84 (1.30 to 2.62) ♂: 2.18 (1.42 to 3.37)	CVD event
HUNT (Omland, 2015) [29]	Norway	9712	54.3%	50	13.9	>3.85 ng/L (♀) >5.65 ng/L (♂)	♀: HR 1.44 (1.31–1.58) ♂: HR 1.10 (1.00–1.20)	CV death
HUNT (Sigurdardottir, 2018) [43]	Norway	9005	55.5%	48.5	13.9	>10 ng/L (♀) >12 ng/L (♂)	HR 3.61 (2.89–4.51)	Composite of hospitalization for AMI or HF, or CV death
JUPITER (Everett, 2015) [2]	26 countries	12,956	36.2%	65	2.0	>3.9 ng/L (♀) >4.6 ng/L (♂)	aHR: 2.19 for CV event aHR: 2.61 for all-cause mortality	Major CV event, all-cause mortality
Minnesota Heart Survey (Apple, 2012) [27]	USA	464	39.2%	67.9	8–15	>10.19 ng/L	OR 8.53 (1.68–43)	CV death
MORGAM (Zeller, 2014) [32]	Scotland	15,340	50.5%	49	20	>4.7 ng/L (♀) >7.0 ng/L (♂)	2.5 (1.60–2.61)	CV event Coronary Death MI Stroke
					Elderly			
AGES (Thorsteinsdottir, 2016) [33]	Iceland	5691	57.5%	77	10	>10.6 ng/L	HR 2.27 for all-cause death HR: 2.53 for CV events, HR: 2.88 for coronary heart events	All-cause death CV events Coronary heart events
PIVUS (Eggers, 2013) [34]	Sweden	826	50.0%	70	5	n.a.	HR: 1.44 (1.18–1.77)	All-cause mortality
PIVUS (Barbier, 2014) [35]	Sweden	176	47.2%	70	5	n.a.	OR 1.98 per 1 unit increase (1.17–3.35)	MRI-detected MIs

CV: cardiovascular, HR: hazard ratio; HUNT: Nord-Trøndelag Health; OD: odds ratio.

most of these studies were carried out in Western populations. For example, a nested case-control study from the Minnesota Heart Survey showed that elevations in hsTnI were more common in subjects that died from CVD than in controls (8.7 vs. 1.0%), with an adjusted odds ratio for death of 8.53 (95% CI 1.68–43) [27]. Within the AP region, a study in Australia showed that doubling of baseline hsTnI was a significant predictor of CVD mortality, CVD events, CHD events, HF and stroke, and may help identify at-risk individuals in a general population [28]. Interestingly, data from the Nord-Trøndelag Health (HUNT) Study, a large scale ongoing prospective population-based cohort study in Norway, not only showed that hsTnI was associated with higher incidence of cardiovascular death [adjusted hazard ratio (HR) 1.23 (95% CI 1.15–1.31)], but also that the relative risk in women was significantly higher than men [HR 1.44 (1.31–1.58) vs 1.10 (1.00–1.20); $P_{interaction} < 0.001$]; this implies that the prognostic value of hsTnI in the general population is stronger in women than in men [29]. Furthermore, the West of Scotland Coronary Prevention Study (WOSCOPS) showed that troponin concentration was modifiable by statin therapy and the change in troponin concentration at 1 year was associated with future coronary risk, independent of cholesterol lowering [30]. Specifically, a decrease in troponin concentrations by more than a quarter resulted in a 5-fold greater reduction in coronary events compared with patients whose troponin concentrations increased by more than a quarter [30]. The use of a treatment (pravastatin) reduced troponin concentration by 13% compared with placebo (p < 0.001) and doubled the number of men whose troponin fell more than a quarter (p < 0.001) [30]. Similarly, the JUPITER trial showed that though the risk all-cause mortality was elevated for the highest versus the lowest tertiles of hsTnI (aHR 2.61 (95%CI, 1.81–3.78), P for trend <0.001), rosuvastatin was equally effective in preventing a first cardiovascular event across categories of hsTnI [2].

Several studies with hsTnI have not only shown independent associations with CV outcomes, but also increased net reclassification improvement (NRI) – a quantitative measure of how appropriately a risk model reclassifies subjects compared with a previous model (i.e. individuals who develop events should be classified in a higher risk category whereas those who do not, in a lower risk category) [3,31,32]. An analysis of US county residents found that hsTnI higher than the sex-specific 80th percentile was independently associated with incident heart failure [HR 2.56 (95% CI 1.88–3.5), P < 0.001] and mortality [1.91(1.49–2.46), P < 0.001] beyond conventional risk factors, with significant increases in NRI for heart failure [31]. The MORGAM biomarker project in a large cohort (n = 15,340) also found that the addition of hsTnI levels to clinical variables led to significant increases in risk prediction with significant NRI for CV events (P < 0.0001) [32].

The BiomarCaRE Consortium, which analyzed data from 74,738 participants in 10 prospective population-based studies, showed that in individuals free of CVD, the addition of troponin I to variables of established risk score improves prediction of CV death (NRI 0.048) and CV disease (NRI 0.017) [3].

An ideal biomarker for CVD risk should be cardiac-specific and measurable in the vast majority of the population. Both troponin T and I have cardiac-specific forms which are normally differentiated from those of skeletal origin. However, evidence indicates that diseased skeletal muscle could cause increases in circulating levels of cardiac troponin T (cTnT), and caution is advised when interpreting cTnT levels when skeletal muscle pathology is present [36]. Moreover, high-sensitivity assays can detect troponin I in over 90% of asymptomatic adults [29,37], but the most sensitive cTnT assays can only detect troponin T in <50% of healthy adults [38,39]. This is a significant limitation of cTnT in the context of screening the general asymptomatic population. In addition, compared with cTnT assays, cTnI assays are more robust against supplemental biotin, hemolysis levels and diurnal variations [40–42]. Thus, we chose to focus on cTnI, rather than cTnT.

HsTnI has also been shown to be superior to high sensitivity C-reactive protein (hsCRP) in predicting risk of future cardiac events [43]. In a selected population from the HUNT study, high sensitivity C-reactive protein (hsCRP) and hsTnI were measured in 9005 participants without any cardiovascular disease at baseline, and during a median follow-up period of 13.9 years, 733 participants reached the composite endpoint of CV hospitalization or CV death [43]. Analysis showed that increased hsTnI concentrations were more strongly associated with the incidence of the composite endpoint, compared with increased hsCRP (HR 3.61 vs HR 1.71) [43]. The addition of hsTnI to established cardiovascular risk prediction models led to a NRI of 0.35 (95% CI 0.27 to 0.42), superior to that of hs-CRP (0.21, 95% CI 0.13 to 0.28), and hsTnI also had significantly higher prognostic accuracy than hsCRP, as measured by C-statistics (0.753 vs 0.644) [43].

5. Statement 4: there is an urgent need to improve cardiovascular risk assessment in the Asia Pacific general population, validate the Asian threshold of high risk and prove the utility of targeting these high-risk individuals for primary preventive strategies

Studies have used different methodology to define risk-stratification cutoffs for hsTnI in healthy populations (Table 3). The MORGAM study used receiver operating characteristic curve analysis to determine that a threshold of 4.7 ng/L in women and 7.0 ng/L in men detects individuals at high risk for future cardiovascular events [32], while the JUPITER study used the highest tertile (3.9 ng/L and 4.6 ng/L for women and men, respectively) to define high risk [2].

Notably, the HUNT study prospectively defined 3 risk categories for hsTnI in women and men without a history of cardiovascular disease. The thresholds for low, intermediate and high risk were <4 ng/L, 4–10 ng/L and >10 ng/L for women, and <6 ng/L, 6–12 ng/L and >12 ng/L for men. Thresholds of increased hs-TnI concentrations at >10 ng/L for women and >12 ng/L for men were associated with the incidence of the composite cardiovascular end point (HR 3.61, 95% CI 2.89 to 4.51]) of hospitalization for acute myocardial infarction or heart failure, or cardiovascular death. Moreover, subjects in the highest hsTnI category had a HR of 9.76 (95% CI 7.97 to 11.95) compared with the lowest category [43].

In addition, investigators observed that the prognostic accuracy of hsTnI, measured by C-statistics was 0.753, which is even greater than other traditional risk factors such as total cholesterol (0.652), HDL cholesterol (0.536) and current smoking (0.506), but still less than age (0.862), history of diabetes mellitus (0.823) and treatment for hypertension (0.813) [43]. Based on this, the study authors posited that hsTnI could potentially replace other biomarkers in CVD risk scores, and opined that population screening with hs-TnI may be cost-effective compared with traditional risk factors [43].

However, these studies have been conducted in Western populations, it is not known if the data can be extrapolated to the Asia Pacific context, and if similar gender differences exist in the Asian population. Asia is a very diverse population, and validation needs to factor in the ethnic diversity and lifestyle differences within Asia Pacific. For example, the Asia Pacific Cohort Studies Collaboration (APCSC) found that hypertension, smoking and diabetes are major risk factors for stroke in Asia Pacific countries, but the slope of the relationship between blood pressure (BP) and fatal and nonfatal stroke was steeper in Asian countries than in Australia and New Zealand [44]. Notably, high salt intake, which is common in East Asia, has been associated with elevated BP [44]. In a recent study, the APCSC assessed the relationship between known CV risk factors (elevated BP, cigarette smoking, elevated blood lipids, excess body weight and diabetes) and CVD incidence in 34 population-based cohorts in Asia Pacific [45]. This study found similar relationships between risk factor clusters and risk of CVD events in Australia, New Zealand and Asia, but the varying prevalence of risk factors between sexes and regions led to differences in the burden of CVD attributable to risk factor clusters [45].

An ongoing trial in India, the Apollo Cardiac Registry, aims to explore and validate hsTnI thresholds in the Indian population. Data from propensity-matched scoring analysis of Asian patients taking statins that demonstrate lowering of hsTnI levels and reduction of CV events, independently of LDL-cholesterol, similar to the promising results found in Western populations [2,30], would further validate the use of hsTnI in Asians. More such data is required before hsTnI screening can be recommended for general asymptomatic population.

6. Conclusion

The burgeoning burden of CVD in the Asia Pacific region has made it imperative to accurately stratify risk in patients, so that appropriate interventions may be applied to mitigate the risks in high-risk patients, as well as to avoid inappropriate and expensive treatment of low-risk patients misclassified as high risk. Current risk stratification strategies are inadequate, often over- or underestimating risks. Evidence indicates that measuring circulating sensitive cardiac biomarkers such as hsTnI improves cardiovascular risk stratification in the general population; however the majority of the prior evidence and biomarker thresholds were derived in Western populations. Whether these data are similarly applicable to Asia Pacific populations and may be effectively used to target high risk individuals for primary prevention strategies warrant further study.

Statement of authorship

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Conflict of interest

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