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Review

Consensus Statements on the Use of High–Sensitivity Troponin I as the Assessment of Cardiac Risk in Apparently Healthy Population in Indonesia

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Abstract
Cardiovascular disease (CVD) is a growing burden in Indonesia, making primary prevention of utmost importance. High-sensitivity cardiac troponin I (hsTnI) has been known as one of the biomarkers of choice for diagnosing acute myocardial infarction. Nonetheless, recent studies indicate that hsTnI assay has the potential as a predictor of cardiac risk in asymptomatic individuals. An advisory board consisting of renowned cardiologists from the Indonesian Heart Association was convened in Jakarta in March 2023. The meeting aimed to explore the appropriate use of hsTnI for cardiovascular (CV) risk stratification in apparently healthy adults in Indonesia. The board reviewed relevant literature and developed key consensus statements, including hsTnI cut-off for identifying high-risk asymptomatic patients, the proposed algorithm, and monitoring after aggressive risk factor control. This article presents the resulting consensus statements to provide clinicians with a practical tool for planning primary prevention strategies. Furthermore, it is expected to raise awareness and advocacy among stakeholders in the healthcare infrastructure regarding the use of hsTnI as a guide for assessing CV risk in Indonesia.

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Keywords: Troponin I, high-sensitivity troponin, cardiovascular risk, cardiovascular disease, primary prevention.

Introduction

World Health Organization (WHO) reported in 2019 that cardiovascular diseases (CVD) caused the death of around 17.9 million individuals, accounting for approximately 32% of all global deaths.[1] A similar trend has been seen in Indonesia as well, where CVDs, specifically ischemic heart disease, has consistently held the unfortunate rank of being the second leading cause of death and disability since 2009.[2] According to data from the Indonesian Acute Coronary Syndrome (ACS) Registry involving 11 cardiovascular (CV) centers, around 48.8% of individuals with ACS were diagnosed with ST-elevation myocardial infarction (STEMI). Amongst those with STEMI, 65.2% underwent reperfusion therapy. Additionally, the in-hospital mortality rate was as high as 11.7%.[3] Moreover, when non-communicable diseases (NCDs) are examined collectively, heart problems emerge as the most substantial economic burden on households, totaling Int$1.56 billion in out-of-pocket (OOP) expenses.[4] Hypertension, diabetes, and stroke follow as the subsequent burdens.[4] Considering the high mortality rate as well as its significant impact on public health and the economy, there is an urgent need for effective primary prevention strategies in Indonesia to address the burden of CVD.

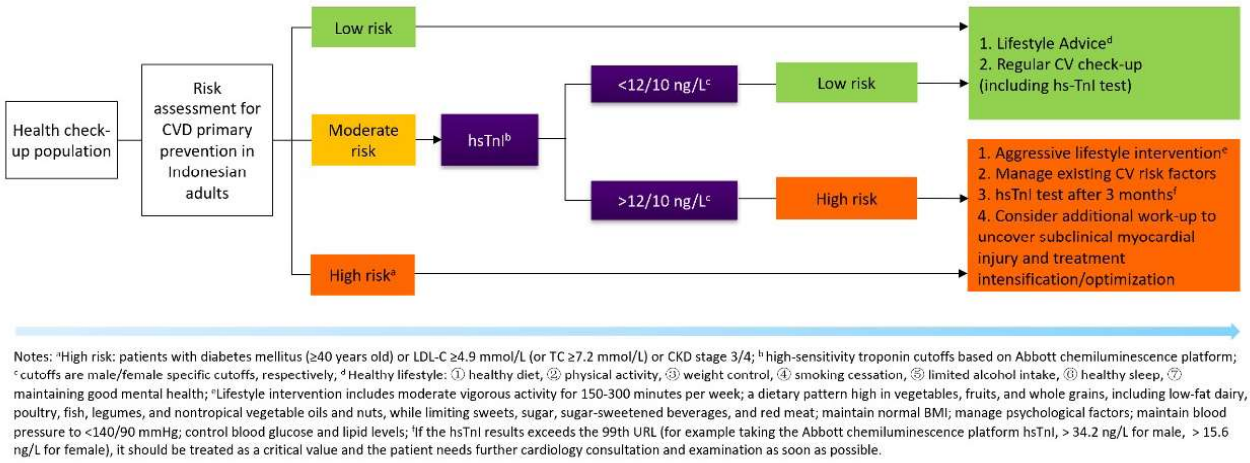
CVD prevention often relies on a set of well-established cardiovascular risk factors, e.g., age, sex, smoking status, LDL-cholesterol, blood pressure levels, and blood glucose levels.[5] Some of the well-established CV risk assessment tools that incorporate these CV risk factors, include the ACC/AHA risk calculator, the Framingham risk score, SCORE risk charts, and Q2Risk score.[5] However, these risk-scoring systems may have certain limitations. Despite being accessible and familiar, these scoring systems were mainly developed based on studies conducted in predominantly Caucasian populations, which may not accurately estimate CVD risk in other ethnic groups and different regions.[5,6] Studies in multi-ethnic countries have shown that CVD risk may be either overestimated or underestimated as a result.[5,6] Some individuals classified as low risk still experienced cardiovascular events.[5] In addition, the inclusion of newer risk factors, including biomarkers like high-sensitivity C-reactive protein (hs-CRP), has shown limited improvement in CVD risk assessment.[6] Furthermore, existing risk scores do not include a direct assessment of cardiac injury, such as the measurement of cardiac troponins.[6]

Therefore, newer risk assessment tools may allow for earlier and more targeted interventions in CVD prevention, offering the potential for improved accuracy and outcomes. Cardiac troponin I has been the biomarker of choice for diagnosing acute myocardial infarction (AMI) due to its high cardiac specificity.[7] Interestingly, recent studies have shown that troponin I, measured by a high-sensitivity assay, can be consistently detected in approximately 80-90% of the general adult population.[8-10] Moreover, studies have revealed that high-sensitivity troponin I (hsTnI) can independently predict CV events in individuals without evident signs or symptoms of CVD.[8-10] To acknowledge and raise awareness of the appropriate use of hsTnI as a biomarker for CV risk stratification in apparently healthy adults in Indonesia, a risk stratification advisory board was convened in Jakarta in March 2023. The board was comprised of renowned cardiologists, who are also members of the Indonesian Heart Association. They reviewed relevant literature and drew upon their clinical expertise to develop recommendations for the proper utilization of hsTnI in risk stratification. This article presents the key consensus statements resulting from the board's discussions, which aim to convey the message to healthcare providers and policymakers in Indonesia about the importance of early screening for CV risk factors. Furthermore, the potential benefits of using hsTnI for cardiac risk stratification are highlighted, which could aid in the development of effective prevention strategies and the reduction of cardiovascular disease morbidity and mortality in Indonesia.

Statements

Statement 1: The burden of CV diseases in Indonesia highlights the current gaps in the public health situation and emphasizes the need for early CVD prevention strategies.

According to Basic Health Research data, the prevalence of cardiovascular disease patients in Indonesia rose from 0.5 % in 2013 to 1.5% amongst the general population in 2018.[11,12] The Indonesian Case Base Group provided data on the healthcare costs per person



Notes: [a]High risk: patients with diabetes mellitus (≥40 years old) or LDL-C ≥4.9 mmol/L (or TC ≥7.2 mmol/L) or CKD stage 3/4; [b] high-sensitivity troponin cutoffs based on Abbott chemiluminescence platform; [c] cutoffs are male/female specific cutoffs, respectively, [d] Healthy lifestyle: ① healthy diet, ② physical activity, ③ weight control, ④ smoking cessation, ⑤ limited alcohol intake, ⑥ healthy sleep, ⑦ maintaining good mental health; [e]Lifestyle intervention includes moderate vigorous activity for 150-300 minutes per week; a dietary pattern high in vegetables, fruits, and whole grains, including low-fat dairy, poultry, fish, legumes, and nontropical vegetable oils and nuts, while limiting sweets, sugar, sugar-sweetened beverages, and red meat; maintain normal BMI; manage psychological factors; maintain blood pressure to <140/90 mmHg; control blood glucose and lipid levels; [f]If the hsTnI results exceeds the 99th URL (for example taking the Abbott chemiluminescence platform hsTnI, > 34.2 ng/L for male, > 15.6 ng/L for female), it should be treated as a critical value and the patient needs further cardiology consultation and examination as soon as possible.

Figure 1. The proposed risk assessment algorithm for CVD primary prevention in Indonesian adults. Patients who are apparently healthy and undergoing a health check-up are assessed for their CV risk based on the current CV prediction tools, e.g., Framingham score or ASCVD Prevention Guideline by the Indonesian Heart Association. For patients with low risk, recommendations include lifestyle modifications and annual CV check-up with hsTnI testing. For patients with moderate risk, hsTnI testing can be used to reclassify them into low or high-risk categories, and appropriate next steps can be taken accordingly. The hsTnI cut-off for high-risk patients is >10 ng/L for females and >12 ng/L for males. Below this cut-off, patients are classified as low-risk patients..

with coronary heart disease in 2018, which amounted to US$5720 (IDR 81,620,376).[13] These expenses include the costs of community-based and hospital-based care, as well as treatment expenses.[13] Moreover, during the World Heart Day 2022 conference, a representative from the Ministry of Health stated that the number of CV patients in Indonesia has increased by 14.4%, causing healthcare costs to rise to around IDR 7.7 trillion per year.[14] Hypertension and diabetes are among the most widespread and significant risk factors for CVD in Indonesia. A study in 2019 showed that hypertension accounted for 55.8% of the population, followed by obesity (14.4%), with an overall prevalence of diabetes (9.8%).[15] In addition, Basic Health Research 2018 revealed that the prevalence of diabetes among adults in Indonesia has increased from 6.9% in 2013 to 10.9% in 2018.[11]

Given the substantial increase in cases of non-communicable diseases (NCD), particularly cardiometabolic disorders and its related healthcare costs, it is essential for the Ministry of Health to prioritize these issues. Only three out of every ten patients with NCD are identified, as the rest are apparently healthy and asymptomatic until complications arise.[14] Moreover, awareness and knowledge of CVD symptoms and the risk factors among patients remain a significant challenge in Indonesia.[16] There is a general neglect towards personal health amongst average Indonesians, who tend to allocate very little towards their own health. Data showed that about 6.1% of household expenses are allocated towards non-health-related items, including tobacco.[17] This lack of understanding of the symptoms and consequences of cardiac disease can lead to delayed diagnosis and treatment.

Recognizing this current situation, during the meeting, the board proposed that the Ministry of Health could establish an indicator for the cardiovascular death ratio to effectively measure the progress of the CVD prevention program. In addition, identifying individuals in the general population who exhibit a higher susceptibility to illness or present comorbidities is vital for more targeted and effective prevention efforts. This may lead to early treatment options that could help reduce risks.

Statement 2: In achieving an effective and efficient measurement to reduce cardiovascular burden, CVD risk stratification tools are

recommended in an apparently healthy subject.

In 2019, WHO established a CV risk chart to help estimate the risk of a major CV event (e.g., MI or stroke) that could occur within 10 years. The calculation is based on factors such as age, gender, blood pressure, smoking history, cholesterol levels, and presence of diabetes, for 21 different sub-regions recognized by the WHO.[18] This chart is used by healthcare professionals (HCPs) to identify patients at high risk of developing CVD and thereafter advise appropriate prevention and management strategies. In Indonesia, the use of this risk chart has been acknowledged by the Ministry of Health and called "Carta Prediksi Faktor Risiko Penyakit Tidak Menular". Additionally, two working groups of the Indonesian Heart Association (Atherosclerosis, Thrombosis, Lipidology, and Regenerative Therapy Working Group and Cardiovascular Prevention and Rehabilitation Working Group) have each released consensus statements regarding dyslipidemia and the prevention of CVD. In both of these consensus statements, the recommended risk calculator for calculating the total cardiovascular risk in apparently healthy individuals is the WHO Risk Prediction Score.[19,20] However, its implementation and routine utilization within the Indonesian primary care settings have not been seamless. One major challenge has been the need to improve the knowledge and acceptance of the tool among HCPs in Indonesia, due to variations and discrepancies of knowledge among HCPs and cardiology experts.[16] This chart was more frequently used in Jakarta, but has not been seen to be used in other regions.[21,22] Another hurdle in its practical implementation is the increasing patient load that puts a strain on HCPs' time, thereby limiting their ability to administer this chart to patients effectively.

Statement 3: The performance of cardiac risk stratification scores can be improved by incorporating additional risk modifiers, such as cardiac-specific biomarkers and imaging.

Studies have examined the effects of incorporating established biomarkers and advanced imaging techniques as additional risk modifiers to enhance the optimization of cardiac risk stratification tools. The St. Francis Heart Study found that coronary artery calcium (CAC) scoring, a non-invasive imaging test, can also improve CVD risk prediction. The CAC scoring was found to be a superior predictor of coronary artery disease events than traditional risk factors and CRP. It also enhanced the stratification of individuals into low, intermediate, and high-risk categories.[23] However, there are limitations to consider, including accessibility, cost, and radiation exposure.

In addition, the performance of existing CV risk scores has yielded diverse findings in different studies. SCORE risk chart was found to underestimate CV risk in women, despite its accuracy for men.[24] In Malaysia, the FRS and SCORE risk chart demonstrated acceptable discrimination for estimating CV risk in the multi-ethnic population, while the WHO Risk Prediction Score did not.[24] On the other hand, in India, the 3rd Joint British Societies' risk calculator was found to identify the highest proportion of patients as 'high-risk' compared to the WHO Risk Prediction Score, FRS, and ACC/AHA risk calculator.[25] Furthermore, the AHA-ACC-ASCVD and FRS were found to overestimate CV events in the US.[26] More importantly, none of the existing risk stratification scores incorporate a direct measure of cardiac injury, such as cardiac troponins.[6] Recognizing the need of additional risk modifiers in any risk calculator or tool, the discussion will specifically focus on hsTnI.

Statement 4: hsTnI assay can detect low levels of troponin I, indicating its potential as a CV risk predictor in even asymptomatic individuals.

Cardiac troponins are proteins located in the myofibrils of cardiomyocytes, which are specific to cardiac myocytes and are useful in assessing myocardial damage. There are three types of troponins in myocardial cells: troponin I (TnI), troponin T (TnT), and troponin C, with the former two being specific to cardiomyocytes and thus can be clinically relevant markers for myocardial damage assessment.[6] The International Federation of Clinical Chemistry and Laboratory Medicine described a hsTnI assay as capable of detecting troponin in ≥50% of healthy individuals.[27] Additionally, coefficient of variation (%CV) at the 99th percentile upper reference limit (URL) should be ≤10%.[27] This means that hsTnI assay provides more precise and accurate results.[27] In comparison, for conventional troponin assay, a %CV of 20% at the 99th percentile was considered acceptable.[27] Such new high-sensitivity troponin assays have been

shown to detect low levels of cardiac troponins in the blood. Contrary to conventional troponin assays, the hsTnI assay exhibits higher sensitivity, has better accuracy and speed in diagnosis, improves patient outcomes, and is cost-effective compared to the conventional troponin assay.[28,29]

On the other hand, the detection of myocardial multi-directional strain and LV trabeculations, which is an emerging marker of cardiac remodeling, was associated with hsTnI independently and not hsTnT. Additionally, compared to hsTnT, the hsTnI assay exhibited enhanced sensitivity to identify measurable troponin values (> limit of detection) in younger individuals, particularly women.[30]

The prognostic feature of hsTnI as a CV risk predictor has been demonstrated by several studies. The HUNT 2018 study, which included 9,005 subjects ≥ 20 years of age without previously known CVD found that subjects in the highest hs-TnI category (>10 ng/L for women and >12 ng/L for men) had a hazard ratio (HR) of 9.76 compared to the lowest category (<4 ng/L for women and <6 ng/L for men), which indicated that subjects in the highest hs-TnI category were 9 times more likely to reach the composite endpoint of hospitalization for acute myocardial infarction or heart failure or cardiovascular death compared to the lowest category.[31]

Similarly, the BIOMARCARE study discovered that individuals in the top fifth of the troponin I distribution compared with the bottom fifth had: 160% increase in mortality from CV causes (HR 2.60, 95% CI 2.29–2.94; p < 0.001); 92% increase in risk for a first CV event (HR 1.92, 95% CI 1.76–2.10; p < 0.001); and 63% increase in the risk of overall mortality (HR 1.63, 95% CI 1.53–1.75; p < 0.001). Troponin I was found to be an independent predictor with an HR of 1.37 for CV mortality, 1.23 for CVD, and 1.24 for total mortality.[10]

However, it is important to consider creatinine clearance and skeletal muscle damage in analyzing cardiac troponin results (hsTnT and hsTnI) while including them in risk stratification scores.[32]

Statement 5: hsTnI assay is a potential risk modifier for stratifying apparently healthy individuals for future cardiovascular events.

Some studies have compared hsTnI with other biomarkers such as hsCRP. Despite being highly sensitive to general inflammatory responses, hsCRP does not address the current gaps in risk stratification in terms of cardiac specificity and cardiac myocyte injury detection.[32] Additionally, the use of hsTnI testing as a cardiac risk stratification tool could be more cost-effective than hsCRP testing, which requires multiple measurements over time to accurately assess risk. A recent study by Julicher et al showed that hsTnI screening in apparently healthy populations was cost-saving in Kazakhstan.[33] In Germany, it was found to be cost-effective, with an incremental-cost-effectiveness ratio of $6,755 per quality-adjusted life year gained.[33]

Furthermore, the HUNT study showed that incorporating hsTnI into the Framingham risk score resulted in a greater net reclassification improvement of 0.35 (95% CI 0.27–0.42) than the use of hsCRP (0.21, 95% CI 0.13–0.28).[31] In individuals free of CVD, the addition of troponin I to variables of ESC score improves the prediction of CV death and CVD.[10] Additionally, a recent study by Marston et al. assessed whether adding hsTnI testing to guideline-derived atherosclerotic cardiovascular disease (ASCVD) risk algorithms could lead to better risk classification and downstream treatment recommendations.[34] Their findings showed that incorporating hsTnI improved risk stratification, reclassifying approximately 11.9% of patients into a more appropriate risk group. This suggests that the addition of hsTnI testing may improve the accuracy of ASCVD risk prediction and lead to better management strategies.[34]

Moreover, Olson et al discovered a correlation between hsTnI and CAC score levels. The study found that 29% of individuals in the lowest quartile of hsTnI had detectable CAC (Agatston score >0), while this percentage increased to 55% in the highest quartile of hsTnI. This association suggested that hsTnI can aid in identifying individuals with elevated CAC who are at greater risk for future CVD.[35] Therefore, the addition of hsTnI testing could help improve existing cardiac risk stratification modalities leading to better prevention and early intervention strategies.

Statement 6: The hsTnI cut-off for identifying high-risk asymptomatic patients is 10 ng/L for females and 12 ng/L for males.

The HUNT 2015 study which involved 4.431 men and 5.281 women aged ≥20 years revealed a significant

correlation between hsTnI levels and gender. In women, low hsTnI concentrations were associated with a lower risk of CVD compared to men, whereas high hsTnI concentrations were associated with a higher risk of CVD in women than in men.[36] Additionally, the study found that women with detectable hsTnI were 1.44 times more likely to experience CV death compared to men (HR 1.10; 95%CI, 1.00–1.20; p<0.001).[36] These findings have important implications for the use of hsTnI in risk stratification for CV events in asymptomatic individuals. It also suggested that gender-specific cut-offs may be necessary for accurately identifying high-risk individuals.

The use of hsTnI for CVD risk stratification has been the subject of an established consensus in the Asia Pacific region. Experts from various countries, including Australia, China (Hong Kong), India, the Philippines, Singapore, Thailand, and Vietnam, have convened in 2018 to discuss its implementation.[5] In China and India, local advisory board meetings have provided guidelines on the use of hsTnI in this regard.[32,37] Following suit, the Indonesia board meeting also endeavored to develop local consensus guidelines for the use of hsTnI in CVD risk prediction. The board agreed that asymptomatic patients with moderate risk of CVD, as determined by CVD scoring, may undergo hsTnI testing to aid in identifying individuals at higher risk for future cardiovascular events. Findings from the HUNT 2018 study indicate that a cut-off value of <4 ng/L for females and <6 ng/L for males can identify low-risk patients.[31] On the other hand, for individuals with a higher risk of CVD, the hsTnI cut-off values for identifying high-risk asymptomatic patients were set at 10 ng/L for females and 12 ng/L for males.[31]

Statement 7: In terms of using hsTnI as an additional tool to refine CVD risk calculation in apparently healthy individuals, we recommended an algorithm.

The board decided to make a risk assessment algorithm presented in **Figure 1**.

The use of this algorithm in conjunction with hsTnI testing can significantly enhance the accuracy of risk assessment and facilitate appropriate interventions. For individuals with diabetes who are at a higher risk for cardiac injury, the American Diabetes Association has recommended to measure natriuretic peptides or high-sensitivity cardiac troponins annually.[38] This helps to detect the possible presence of heart failure and assess the risk of progression to symptomatic stages of the condition.[38]

On the other hand, the WOSCOPS study has shown that statin therapy may benefit moderate and high-risk individuals with elevated hsTnI levels. At 1 year, participants with statin therapy had a greater reduction in troponin concentration than those receiving placebo (19% vs 6%). When troponin concentrations decreased by more than a quarter, a 5-fold greater risk reduction in coronary events was observed rather than increased by more than a quarter, for both placebo (HR: 0.29 vs. HR 1.95) and statin therapy (HR: 0.23 vs HR 1.08).[39]

Statement 8: Monitoring and evaluation using hsTnI after aggressive risk factor control in high-risk patients is advisable.

A study in the Chinese population investigated the hsTnI reference interval in healthy adults aged 18-85 years. The study revealed that serum hsTnI concentration increased with age and the 99th percentile reference interval for hsTnI was found to be similar to the manufacturer's recommendation. This suggests that hsTnI can be utilized to monitor and evaluate CV risk in adults beyond 18 years old. It is essential to interpret the results in conjunction with other relevant clinical information by cardiologists.[40]

Moreover, hsTnI monitoring can provide valuable information about the effectiveness of risk factor control measures and help track changes in myocardial injury levels over time. Mills et al conducted a study that revealed patients with higher troponin I assay concentrations had a greater proportion of deaths or MI readmissions (27%) at the 3-month mark compared to those with lower troponin I assay concentrations (17%; p < 0.001). Therefore, repeat hsTnI testing after 3 months can be used to identify individuals who may require more intensive or targeted risk factor control interventions.[41] Similarly, the consensus of the Chinese Society of Health Management, the Chinese Society of Laboratory Medicine, and the Chinese College of Cardiovascular Physicians also advocates for high-risk individuals to undergo hs-TnI testing every three months. This helps assess the hsTnI levels and ensures they are managed below the established risk thresholds.[37] In accordance with this, the board also agreed to include

hs-TnI monitoring after three months for patients categorized as high-risk patients **(Figure 1)**.

Another study also demonstrated the usefulness of hsTnI monitoring in patients with diabetes at risk of developing CVD. The study found a strong relationship between increasing hsTnI levels, both at baseline and 6 months, and the incidence of CV events through 24 months ($p<0.001$ for each).[42] Additionally, hsTnI holds potential in pre-and post-operative monitoring of patients undergoing surgeries. Post-operative levels of hsTnI can serve as an indicator of damage to the heart muscle cells and can aid in identifying patients who are at increased risk of morbidity and mortality following major vascular surgery.[32] This indicates that hsTnI monitoring can help identify high-risk individuals and guide treatment decisions to prevent further cardiac damage and improve outcomes.

While hsTnI monitoring has the potential to improve patient outcomes, implementing this approach in real-world clinical practice may present some challenges. These challenges may include access to testing and standardization of testing protocols. In a study conducted in the United States among HCPs, 35% of participants identified education as the most common obstacle. Particularly, the challenge was ensuring that all individuals were informed and updated about the assay to avoid overlooking critical details or miscommunication.[43] Moreover, communicating with the Ministry of Health to advocate for the inclusion of hsTnI for CVD primary prevention may also present a challenge. Despite these challenges, hsTnI monitoring may prove to be a valuable tool in the management of high-risk patients and deserves further investigation.

Conclusion

High-sensitivity troponin I is one such cardiac-specific biomarker with the ability to predict the risk of future cardiac events and help reduce the burden of CVD. Incorporating hsTnI as a risk modifier in CVD risk calculation can improve CVD prediction in an apparently healthy individual. This consensus has proposed an algorithm by which a clinician can use hsTnI as one of the risk modifiers for CVD prediction. This consensus statement is created with the view to aid healthcare providers, policymakers, and the general population in Indonesia. This article emphasizes the importance of early screening for CV risk factors and the potential benefits of using hsTnI for risk stratification. Therefore, effective prevention strategies can be developed and CVD morbidity and mortality in Indonesia can be reduced.

Author Contributions

All authors contributed to the conception, drafting, and revision of the article, provided final approval for publication, agreed on the journal, and took accountability for all aspects of the work.

Conflict of Interests

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