The Economist INTELLIGENCE UNIT

Predicting heart disease: The future of CVD risk assessment

A report by The Economist Intelligence Unit

Key points:

- Current approaches to cardiovascular disease (CVD) screening have had minimal demonstrated effect on disease mortality or morbidity
- Existing risk prediction models cannot reliably inform any individual—regardless of age, sex, ethnicity, comorbidity or socioeconomic background—of their likelihood of developing a specific CVD outcome, such as a heart attack
- Elevated levels of cardiac troponin is highly specific to heart muscle damage and might improve the prediction of CVD and heart disease, specifically, in populations assessed for cardiac risks
- Even if risk prediction can be optimised, there remains a clear need to address health inequality if there is to be hope of reducing the CVD burden at the population level

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Cardiovascular disease: the leading global cause of mortality

Cardiovascular disease (CVD) is the leading global cause of mortality[1-3] and places an ever-increasing burden on healthcare systems and economies worldwide. The prevalence has doubled in the past 30 years, with 523 million cases and 18.6 million deaths globally in 2019.[6] Over a third of all CVD cases and half of deaths are caused by ischaemic heart disease (IHD), where fatty build-up in the lining of the coronary arteries (atherosclerosis) impedes blood supply to the heart muscle. Central and South Asia, Eastern Europe, the Pacific region, North Africa and the Middle East have the highest disease burden.[6]

Global IHD, 2019[6]

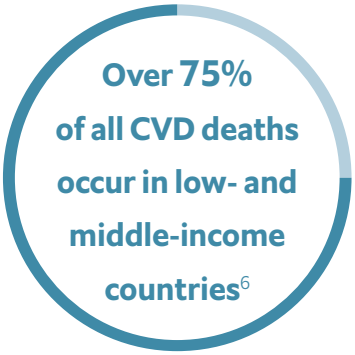
Cases
197 million

Deaths
9.14 million

DALYs*
182 million

*Disability-adjusted life years

Age, sex and hereditary factors are the principle non-modifiable risk factors for IHD.[6] The main modifiable risk factors have remained consistent for 30 years, reflecting only a rise in obesity prevalence and a decline in tobacco smoking.[6]



While some regional variation may be inevitable due to ethnic and cultural factors, inequitable access to preventive, diagnostic and therapeutic strategies are undeniable contributors to the disproportionately higher burden in low- and middle-income countries (LMICs).

Most deaths from IHD and CVD could be avoided by addressing modifiable risk factors and providing timely intervention for people at risk of acute events.[8] Such strategies have helped to stem the burden from CVD in high-income countries (HICs).[9]

However, there is a need to improve the effectiveness of these systems, and aim for standardisation in risk assessment that crosses sociodemographic boundaries, if we are to achieve the World Health Organization's (WHO's) targets to reduce global CVD burden.[4]

WHO targets for 2025[4]

Reduce global CVD mortality by 25%

Ensure that ≥50% of all adults at ≥30% risk of CVD receive treatment

Current population screening and risk stratification strategies

Atherosclerosis begins in childhood and adolescence and progresses insidiously through adulthood. The long asymptomatic period makes it ideal for risk stratification and meaningful early intervention.[7,9]

50% of deaths from IHD are not preceded by disease symptoms or diagnosis[7]

People at risk for CVD, or IHD specifically, are currently identified through three main routes:

1. Targeted testing or assessment of people already known to be at higher risk of IHD or CVD events due to established disease or risk factors (e.g. people with diagnosed CVD, diabetes or hypertension)
2. Opportunistic testing of people not known to be at CVD risk (e.g. people presenting to health services for other reasons)
3. Systematic population screening, where a whole population not known to be at CVD risk is routinely assessed

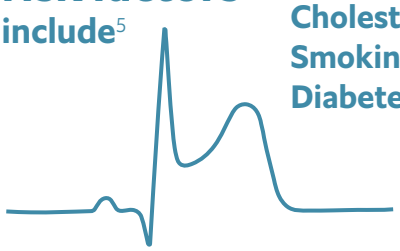
A population-wide approach that aims to systematically identify all high-risk individuals is ideal[10] and has been adopted in most HICs. However, the infrastructure and resource constraints often make this difficult to implement

in LMICs.[10] As highlighted by Carisi Polanczyk, Professor of Cardiology at Universidade Federal do Rio Grande do Sul and Moinhos de Vento Hospital in Brazil, "In Brazil, population screening is rarely done."

All guidance on CVD prevention recommends assessing overall cardiovascular risk.[1, 10] The most common population screening strategy used by HICs are routine health checks to assess modifiable and non-modifiable risk factors for CVD. Most countries start screening asymptomatic adults at around 40 years of age, though there is international variation.[1, 10-16] Assessments are typically repeated on a five-yearly basis (until set age cut-off), although frequency may vary depending on the individual's level of CVD risk.[1, 13-16]

Most frequently assessed risk factors include[5]

Age
Sex
Blood Pressure
Cholesterol
Smoking status
Diabetes



Overall CVD risk is assessed by putting a person's characteristics into a risk stratification model. Table 1 presents the characteristics of some models with guideline-recommended use, though this is far from exhaustive. A 2016 systematic review identified 363 models across the global literature, a number that has since increased.[5] Most models have been developed in the past 20 years, though not all are unique, with one in five derived from cohorts that informed the original Framingham Risk Score in the 1960s-80s. The models vary widely in risk factors incorporated, CVD outcomes predicted, risk thresholds used, and population validity. Most notable is the lack of models developed for, or valid for use in, South American, African and Asian populations.[5]

The WHO acknowledges that population-wide strategies are necessary to reduce the global CVD burden. However, the extent to which any one strategy is emphasised over another will depend on demonstrated clinical efficacy, cost-effectiveness and resource availability.[8] The following section explores whether current CVD screening and risk stratification systems meet these requirements.

How well are current strategies working?

Various factors influence the success of a screening programme. These include the implementation of primary preventive strategies; accuracy of the screening tests; effectiveness and safety of treatments; costs and resource issues; and awareness, acceptance and uptake of screening. It is not possible to give just consideration to all these issues here, but we will consider:

- the 'test'—which in this case can be considered to be CVD risk stratification models
- CVD screening programmes overall—which broadly encompass many of the above specifics

We will review how well current approaches fulfil the core requirements for a viable and ethical screening programme: evidence of effectiveness, lack of harms and equitable access.[17]

Risk stratification models

a Variable and imperfect prediction accuracy

A perfect screening test would be simple, easy to access and administer, and would have excellent accuracy for identifying the at-risk population. This would mean:

High sensitivity: 'true positive' identification of those with early CVD (or IHD) or at high disease risk

- few false negatives: few people given false reassurance that they are low-risk or disease-free, who do not receive the treatment they need, and are at high risk of morbidity or mortality

High specificity: 'true negative' (low risk) result in those without CVD (or IHD) or at low disease risk

- few false positives: few people given unnecessary intervention and monitoring when they are in fact low-risk and disease-free, causing needless anxiety and wasting resources

The area under the receiver operating characteristic curve (AUC), or equivalent C-statistic, gives an overall measure of test accuracy. This demonstrates the balance of sensitivity to specificity, or the ability of the test to distinguish between people with and without disease. A perfect test would have an AUC or C-statistic of 1.0, meaning it has 100% sensitivity and specificity. The most validated risk stratification models (Framingham, SCORE and Q-RISK) have an average C-statistic of around 0.75 (range 0.57 to 0.92).[5] Thus, there is some trade-off between sensitivity and specificity, with either more false negatives or false positives depending on where the risk threshold is set.

b Restricted population validity

Most risk stratification models were developed from European or North American cohorts, and most validations have been conducted in similar populations. Developmental cohorts typically date from over 30 years ago. Changes in CVD prevalence over time will affect model performance, even when used in the equivalent contemporary population. However, there are greater issues when applying these models to regions with different sociodemographics, in particular South American, African and Asian populations.[5] For example, Pooled Cohort Equations, recommended in the US, are not validated for Hispanic populations, are known to underestimate risk in people with socioeconomic disadvantage, and overestimate risk in people of high socioeconomic status.[1,18]

Recent developments such as the revised WHO Risk Prediction Models, recalibrated for use in 21 global regions, aim to reduce the CVD burden, equitably and sustainably.[19, 20] The WHO intends to limit the overtreatment of low-risk individuals and associated costs, and include a non-laboratory model for use in regions that lack the facilities to assess biochemical parameters. However, these models are informed by global data that are likely to be incomplete for many countries, and still suggest variable and imperfect predictive accuracy (C-statistic 0.68 to 0.83).[19]

C Issues around the risk factors modelled, outcomes predicted and meaning for the individual

Other factors may underlie the variable predictive accuracy of risk stratification models and influence their clinical utility. These include the risk factors modelled and cut-off values set, which may be of greater or lesser significance for different individuals depending on whether they have other hereditary or health risk factors that are not being taken into account.[1, 10, 18] Then there is the issue of the endpoint predicted. Most risk models predict fatal or nonfatal CVD events (e.g. myocardial infarction [MI] or stroke), some predict fatal events only, and some predict 'softer' outcomes such as overall CVD (e.g. angina)—all of which may have been variably defined. The outcome predicted influences the risk threshold set, its meaning to the individual and whether individuals are likely to adopt preventive measures as a result. For example, Pooled Cohort Equations define high risk as a ≥20% risk of a fatal or nonfatal CVD event in the next 10 years,[1] while SCORE defines high risk as a 5-10% risk of CVD death in the next 10 years (≥10% is very high).[10]

Overall it seems fair to say that most risk stratification models would not be able to inform any individual—regardless of age, sex, ethnicity, comorbidity or socioeconomic background—of their likelihood of developing a specific CVD outcome, such as an MI. As Professor Christie Ballantyne, Baylor College of Medicine, Texas, summarises: "The problem is that we give an incomplete picture. With our current tools we are not giving people the real information of what's going to go wrong with their cardio-metabolic health."

Despite these limitations, risk models are arguably simple tools that may help to standardise practice (at least nationally) and support objective decision-making. Professor Polanczyk says, "Pooled Cohort Equations have advantages too, and it is a tool that we trust! It is easy to use and reliable, backed by the AHA [American Heart Association] and other associations." However, perhaps due to the aforementioned issues, they are not universally liked and adopted. Some professionals prefer to use clinical judgement alone when assessing each individual.

> **Clinicians use SCORE sometimes to educate or give illustrative information to the patient. But in clinical practice, we often base an investigation on the symptoms or clinical characteristics of the patient and do not necessarily look at the score.**
>
> *Massimo Piepolli*
> *Professor of Cardiology at Guglielmo da Saliceto Hospital and University of Parma, Italy*

CVD screening programs overall

a Standard approaches to CVD screening have had minimal effect on the CVD burden

Systematic reviews by both Cochrane (2019) and the WHO (2020) concluded that systematic population screening is minimally effective in reducing morbidity or mortality.[17, 21] This was based on high-quality evidence from large trials with similar findings comparing screening with no screening. Because these trials assessed overall screening programmes (i.e. systematic population recruitment, any form of risk assessment, any subsequent intervention), it is difficult to identify the specific programme components that may contribute to lack of effectiveness. However, a 2017 Cochrane review identified the evidence on risk stratification models, specifically, and similarly found no evidence that they are effective in reducing CVD morbidity and mortality.[22]

b Uncertainty over harms

The WHO further concluded the possibility of serious adverse effects from CVD screening following the findings of two Danish trials.[17] One trial found that CVD screening was associated with a small increased risk of death from stroke.[23] The other revealed that in areas with high screening participation, there were more deaths from lifestyle-related causes (e.g. smoking) and cancer, specifically, among screened versus unscreened women.[24] Direct cause and effect cannot be attributed from these observations, but they leave uncertainty. Conversely, two other Danish studies found no evidence that CVD screening is associated with adverse psychological effects.[25, 26] However, this is a small body of evidence with a specific population and screening approach. It is not possible to conclude from this that wrongly categorising someone as high or low risk (false positive or negative) using the multitude of risk stratification systems in current global use is not associated with adverse effects.

c Issues around health inequality and poor screening access or uptake

Even a perfect screening test will not have the desired effect of reducing disease burden if it fails to reach the at-risk population. This limitation clearly exists in many LMICs, but also in HICs where screening is practised. A recent UK modelling study concluded that CVD health checks were unlikely to be cost-effective or increase life expectancy equitably by 2040 unless they targeted implementation in the most disadvantaged areas with the highest CVD burden.[27] A 2017 systematic review indicated that this is not an issue specific to the UK. There is little global evidence that CVD screening programmes are cost-effective, with no studies conducted in LMICs and none addressing effects on health inequality.[28] As highlighted by Professor Polancyzk, "The main problem is access; it is not accessible to the population that needs it."

For any CVD screening programme to have hope of reducing the global CVD burden, there are clear issues to address around ensuring equitable implementation, accessibility, and that programmes demonstrate cost-effectiveness across diverse economies. However, there may still be scope to optimise the screening tests—i.e. risk assessment and stratification—and achieve greater standardisation in testing, and more consistent and accurate risk prediction across populations.

The potential for circulating biomarkers to improve risk stratification

This section explores the potential to include additional biomarkers in CVD assessment and improve risk prediction. We review whether any may have the potential to meet some of the criteria for novel biomarkers as outlined by the AHA: being a significant predictor of CVD events; improving risk prediction; and meeting additional requirements such as simplicity of testing, safety and cost-effectiveness.[29]

In selecting which biomarkers to review we have considered:

- biomarkers that reflect the pathophysiology of atherosclerosis and that may improve the early identification of IHD in particular, given that this accounts for the majority of the CVD burden;
- biomarkers that may be consistent predictors of IHD, regardless of patient age, sex, ethnicity, socioeconomic factors or other risk characteristics; and
- circulatory biomarkers (blood tests) that are in current use and would be feasible to use as initial screening tests at the population level (acknowledging the need for laboratory facilities)

a Marker of arterial inflammation

C-reactive protein (CRP)

CRP, a nonspecific inflammatory marker, is the most studied of all potential circulatory biomarkers. Blood concentrations of CRP increase several thousand-fold in the acute-phase response to severe tissue damage, infection and inflammation.[30] However, more subtle increases—as detected by high-sensitivity (hs)CRP assays—are seen in the gradual disease process of atherosclerosis and may be a marker for subclinical disease.[30, 31]

The Emerging Risk Factors Collaboration (ERFC) pooled data from over 100 population studies in asymptomatic adults, and demonstrated a clear linear association between CRP level and risk of IHD. Each standard deviation (SD) increase in concentration was associated with roughly 30% increased relative risk (RR) of future IHD.[30] Despite this, hsCRP has not been shown to improve risk prediction. A 2018 systematic review by the US Preventive Services Task Force (USPSTF) identified 25 studies in which hsCRP was added into risk stratification models.[32] Central to the evidence, the ERFC added hsCRP to the Framingham Risk Score, finding that it improved the C-statistic by only 0.0039 upon baseline 0.71433 (i.e. overall model accuracy improved by <1%). Other studies gave heterogeneous findings, ranging from potentially improved to worsened discrimination.[32] It was uncertain whether hsCRP would help to reclassify patient risk[32] or would be a cost-effective addition to prediction models.[34] Professor Polanczyk considers it to be of limited value: "hsCRP has significantly lost importance. We know it is very sensitive to any conditions, so in practical terms it ends up disturbing our risk estimation."

Current guideline position—inconsistent: The USPSTF (2018) concluded that there is insufficient evidence on the balance of benefit to harm from adding hsCRP to CVD risk assessment.[32] The American College of Cardiology and American

Heart Association (ACC/AHA, 2019) described CRP as a 'risk-enhancing factor' that may inform clinician-patient discussions, but made no specific recommendation for its measurement.[1] The European Society of Cardiology (ESC, 2016) concluded that circulatory biomarkers (any/unspecified) are of limited value in CVD assessment, highlighting the extensive research on hsCRP but that it contributes little to risk stratification.[10]

b Oxidised lipid particles that trigger atherosclerosis

Apolipoprotein B (ApoB) and Apolipoprotein A (ApoA)

Oxidised phospholipid particles are known to trigger arterial inflammation and the adhesion of fats and other molecules that constitute the thrombotic plaque. Each particle of low-density lipoprotein (LDL) contains one ApoB particle, while high-density lipoprotein (HDL), which clears LDL from the blood, contains ApoA.[7, 31, 32]

The ERFC demonstrated that ApoB and the ApoB/A ratio have equivalent risk associations with IHD as LDL cholesterol and the LDL/HDL ratio (roughly 50% RR increase per SD increase in concentration). Likewise, ApoA has risk association equivalent to HDL cholesterol (roughly 20% RR decrease per SD increase).[35] Consequently there has been speculation as to whether they could replace or supplement standard cholesterol measures in risk prediction models.[35, 36] However, the ERFC found that replacing total and HDL cholesterol with ApoB and ApoA actually worsened model performance. Adding them to the risk model improved the baseline C-statistic by only 0.0006 upon baseline 0.72 and would help to reclassify only 1% of adults in the intermediate risk category.[36]

Current guideline position—inconsistent: The ACC/AHA (2010, 2014) concluded a lack of evidence that ApoB or ApoA improves risk stratification.[7, 37] However, their later 2019 guidance suggested that elevated triglycerides could be an indication for ApoB measurement.[1] The Canadian Cardiovascular Society (CCS), 2016) recommended considering ApoB as an alternative to LDL cholesterol measurement.[11]

Lipoprotein (a), or Lp(a)

Lp(a) is an LDL-like particle consisting of an ApoB particle attached to a large glycoprotein molecule (apolipoprotein (a)).[38] Lp(a) concentration shows weak correlation with total and LDL cholesterol level, and modest linear risk association with IHD (13-16% RR increase per SD increase).[38] The ERFC demonstrated that adding Lp(a) to risk models would improve the C-statistic by 0.0016 and help to reclassify around 4% of intermediate-risk adults.[36] Lp(a) levels are largely genetically determined.[11, 31] As such, Professor Polanczyk considers it to be more of a one-off measure: "Lipoprotein is one that will be used once in a lifetime: once you identify a person, you already know this person is at risk."

Current guideline position—inconsistent: The ACC/AHA (2010) concluded that Lp(a) did not warrant further assessment due to only modest association with IHD.[7] Their later 2019 guidance suggested family history of IHD to be a 'relative indication' for its measurement.[1] The CCS also considered that Lp(a) might help to refine risk in those with family history or intermediate risk classification.[11]

c Markers of arterial thrombosis

Lipoprotein-associated phospholipase A2 (Lp-PLA2)

Lp-PLA2 is an enzyme that hydrolyses oxidised phospholipids, resulting in pro-inflammatory products that form the core of the thrombotic plaque.[7, 39] There is also a hereditary component to Lp-PLA2, with levels known to differ by ethnicity.[7] Pooled analysis of 32 prospective studies demonstrated that Lp-PLA2 (activity or mass) has modest risk association with IHD (around 10% RR increase per SD increase), slightly stronger for people with pre-existing disease than those without.[39] The ERFC found that adding Lp-PLA2 (mass) to standard risk stratification would improve the C-statistic by 0.0018 and help to reclassify 3% of intermediate-risk adults.[36]

Current guideline position—inconsistent: The ACC/AHA (2010) noted that Lp-PLA2 may help to refine risk in those with intermediate risk classification.[7] However, the marker was not mentioned in subsequent guidance.[1, 37] The ESC (2012) previously suggested that Lp-PLA2 may help to refine risk in those with a prior CVD event,[40] but their latest guidance (2016) does not recommend use of any biomarker.[10]

Homocysteine

Homocysteine is an amino acid produced from the breakdown of animal proteins. High blood levels, most commonly caused by vitamin B deficiencies, are known to cause arterial damage and thrombosis.[31, 41] Pooled analysis of 12 prospective cohort studies found that a 25% lower homocysteine level was associated with a modest 11% reduced RR of IHD.[42] Further pooled analysis of eight RCTs demonstrated that vitamin B supplementation had no effect on the risk of IHD or any other CVD outcomes over a five year follow-up.[43] No evidence was identified assessing the value of homocysteine in risk prediction.

Current guideline position—no recommendation: Homocysteine was evaluated by the USPSTF in 2009, who concluded that there was insufficient evidence for its use.[44] No other guidelines mentioned homocysteine.

d Marker of myocardial damage

Cardiac troponin

In contrast to the other biomarkers of the general atherosclerotic process, elevated levels of cardiac troponin (specifically isoforms I and T) are highly specific to myocardial tissue damage as a result of ischaemia or infarction. Cardiac troponin I and/or T (cTnI and cTnT) measurement has long been the standard in the assessment and diagnosis of acute coronary syndromes. While thousand-fold increases may be seen in acute MI, more subtle increases—as may be detected by high-sensitivity (hs) assays—are seen across the full spectrum of the disease through micro-MI, stable angina and subclinical/asymptomatic IHD.[45]

A 2017 systematic review identified 28 studies that measured hs-cTnI/T levels in nearly 155,000 asymptomatic adults and looked at CVD incidence over ≥1 year follow-up.[46] People with the highest hs-cTnI/T levels had 59% increased RR of IHD, 67% increased risk of fatal CVD and 43% increased risk of overall CVD. The magnitude of association was equivalent across age, sex and geographic regions. Data on predictive accuracy came from the PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease) trial, which tested troponin T only. Adding hs-cTnT to standard risk factors improved the

C-statistic for predicting fatal CVD by 0.028 (upon baseline 0.600) and by 0.009 for overall CVD (baseline 0.593).[46]

Among further publications, the BiomarCaRE project compiled 10 European population cohorts looking at troponin I.[47] Adults with the highest hs-cTnI levels (vs lowest) had almost tripled risk of fatal CVD and a 92% increased risk of incident CVD during follow-up. Adding hs-cTnI to the SCORE risk model improved the C-statistic by 0.007 for predicting fatal CVD (baseline 0.84) and by 0.004 for overall CVD (baseline 0.80). It was estimated to reclassify around 10% of all adults.[47]

Other large cohort studies (Generation Scotland, Atherosclerosis Risk in Communities [ARIC] and Nord-Trøndelag Health [HUNT] Study) have similarly demonstrated linear associations between hs-cTnI and CVD, where adults with the highest levels had around a two- to three-fold higher risk of CVD events.[48-50] The Generation Scotland and ARIC studies indicated troponin I to have stronger association with CVD events than troponin T, though the two may have a complementary role in risk prediction. When added to Pooled Cohort Equations, hs-cTnI improved the baseline C-statistic of 0.714 by 0.015. Adding both troponins improved it by 0.019.[48] The HUNT study, meanwhile, demonstrated hs-cTnI to have stronger risk association with CVD development than hsCRP, and to give better prognostic accuracy when incorporated in the Framingham Risk Score (C-statistic 0.753 versus 0.644).[49] Initial studies indicate that screening with hs-cTnI could be cost-effective but will need further validation.[51] The cardiologists we spoke to were more positive about the value of cardiac troponin.

Current guideline position—no recommendation: Troponin is not mentioned in CVD primary prevention guidance, outside of standard use in the acute setting.

> **The success [of troponin] in the acute setting has confused people about it. They don't think of it as a test for risk assessment. It's very perplexing, because I see the emergency room doctors doing things that actually are better for risk stratification than we're doing in our clinics.**
>
> *Professor Christie M. Ballantyne, Chief of Cardiology and Cardiovascular Research, Baylor College of Medicine, Texas*

Future outlook

Within the confines of this overview, it seems possible that cardiac troponin might have potential in the future of CVD risk stratification. When added into risk prediction models alongside standard risk factors, cardiac troponin improved overall model accuracy more than other biomarkers. The improvements were small in terms of the AUC/C-statistic, though it is possible that this measure may not capture the full utility of the marker. Professor Carolyn Lam of the National Heart Centre Singapore supports this idea: "There are many incredible biomarkers that add a comprehensive look at the patient. It's not just that we have one biomarker and it's precise. There are multiple axes that you can cover that are complementary but not

completely overlapping. We get more nuanced information in each case."

This possibility and other areas require further research to better understand whether cardiac troponin and/or other biomarkers could be viable additions to CVD screening and risk stratification:

- confirming predictive accuracy when supplementing different risk stratification models or predicting different CVD endpoints
- confirming optimal threshold values to define risk and indicate intervention, including those already in use
- understanding optimal use, e.g. for routine use or to refine stratification in borderline/moderate/intermediate risk groups
- evaluating cost-effectiveness in different scenarios
- understanding public acceptance
- recognising issues around equitable access, e.g. the requirement for specialised assays or laboratory facilities, which may limit wide-scale implementation

Ultimately any potential biomarker needs to demonstrate clinical utility. Real-world application needs to show that including the biomarker in CVD risk stratification improves upon standard approaches and benefits CVD health.

> **"And then it requires receptivity from patients. It's pointless if we have all these things and then patients do not want it. So education and communication about all of this is very important. It's a multi stakeholder thing that needs to happen for this to be widely accepted.**
>
> *Professor Carolyn Lam, Senior Consultant, National Heart Centre, Singapore*

Conclusion

Cardiovascular disease is the leading global cause of mortality and morbidity, and IHD accounts for half of this burden. The WHO aims to reduce the burden of CVD equitably and sustainably over the next decade: ensuring that people across global regions receive validated risk assessment; that high-risk individuals receive treatment; and reducing over-treatment of those at low risk. To achieve these objectives, there appears need for a new approach. Current strategies are not working.

Risk stratification models give variable and imperfect risk prediction.

There is no standardisation in approach to CVD risk assessment, and no strategy to assess risk of IHD, specifically. Over 350 risk stratification models have been developed globally, which are inconsistent in the risk factors assessed and outcomes predicted, with few able to inform risk of specific outcomes such as MI. Prediction accuracy is 75% on average, but this varies widely and is notably poor in South American, African, Asian and disadvantaged populations. In some cases risk prediction may be little better than chance. This can lead to uncertainty for both professionals and patients when interpreting the result and deciding on the need for preventative action.

High-sensitivity cardiac troponin may improve the prediction of IHD across populations.

We assessed whether incorporating additional circulatory biomarkers into risk models could give more consistent and accurate prediction of CVD and IHD, specifically, across all populations. High-sensitivity cardiac troponin, a highly specific marker of heart muscle damage, demonstrated the strongest risk association with CVD and IHD, and most improved prediction accuracy when added into standard risk models. Cardiologists spoke positively of its potential. If future study shows it to improve decision-making and cardiac outcomes, this could support its role in CVD risk assessment and risk stratification

> **I think that for high-sensitivity troponin, the evidence is robust and adds information.**
>
> *Professor Carisi A Polanczyk, Assistant Professor at Federal University of Rio Grande do Sul, Brazil*

Health equality is of paramount importance in addressing the CVD and IHD burden.

Even if CVD screening and risk stratification were optimised by the inclusion of high-sensitivity cardiac troponin and/or other biomarkers, this will not have the desired effect of reducing disease burden if it fails to reach the at-risk population. LMICs may lack the infrastructure and resources to support population-wide screening and use of specialised laboratory assays. In HICs, uptake of CVD screening has been shown to be low among disadvantaged and minority populations who may have the highest CVD risk. If high-sensitivity cardiac troponin is to be a viable addition to CVD screening, particularly on a wide-scale, ensuring equitable access and that it is cost-effective across diverse economies are key considerations.

The EIU would like to thank the following experts for sharing their insights and experiences:

- **Professor Christine M. Ballantyne**
  Chief of Cardiology and Cardiovascular Research, Baylor College of Medicine, Texas
- **Professor Carolyn Lam**
  Senior Consultant at the National Heart Centre, Singapore
- **Professor Carisi A Polanczyk**
  Assistant Professor at Federal University of Rio Grande do Sul, Brazil
- **Professor Massimo F Piepoli**
  Director Heart Failure and Cardiomyopathy Unit, Guglielmo da Saliceto Polichirurgico Hospital, Italy

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Appendix, Table 1:

Examples of risk stratification models with current guideline-recommended use (primarily informed by ESC 2016 guidelines,[10] with additional sources[1, 7-9, 11, 12, 14-16, 19, 37, 52-56])

	Risk stratification model						
	Framingham Risk Score (FRS-CVD)	**Pooled Cohort Equations (PCE)**	**SCORE**	**Q-RISK2**	**ASSIGN**	**PREDICT**	**WHO CVD risk prediction charts**
Risk factors included in the model	Age (30 to 74) Sex/gender SBP TC and HDL-C Smoking status Diabetes Treated hypertension	Age (40 to 79) Sex/gender SBP TC and HDL-C Smoking status Diabetes Treated hypertension	Age (40 to 65) Sex/gender SBP TC and TC/HDL-C ratio Smoking status	Age (35 to 74) Sex/gender SBP TC/HDL-C ratio Smoking status Diabetes Treated hypertension BMI Ethnicity Family history Socioeconomic status Other diseases (RhA, AF, CKD)	Age (30 to 74) Sex/gender SBP TC and HDL-C Smoking status Diabetes Family history SEC status Other diseases (RhA)	Age (30 to 74) Sex/gender SBP TC/HDL-C ratio Smoking status Diabetes Treated hypertension Ethnicity Family history SEC status Lipid-lowering treatment Antithrombotic treatment Other diseases (AF)	Age (40 to 80) Sex/gender Smoking status *plus laboratory model:* SBP TC Diabetes *or non-laboratory model:* BMI
Outcome predicted	10-year risk of CVD events (fatal or nonfatal)	10-year or lifetime risk of CVD events (fatal or nonfatal)	10-year risk of fatal CVD	10-year or lifetime risk of CVD events (fatal or nonfatal)	10-year risk of CVD events (fatal or nonfatal)	5-year risk of CVD events (fatal or nonfatal)	10-year risk of CVD events (fatal or nonfatal)
Development population	US, Massachusetts 3 cohort generations (1968 to 1987)	US, 4 cohorts: ARIC; CARDIA; CHS; Framingham (all 3 cohorts) (1968 to 1993)	Europe 12 cohorts, 11 countries (1971 to 1991)	UK QRESEARCH primary care database (1993 to 2008)	Scotland general population cohort (1984 to 1987)	New Zealand general population cohort (2002 to 2015)	85 cohorts in the ERFC (1960 to 2013) Further validation in 19 cohorts (including PREDICT) and patient data from 79 countries in WHO STEPS
Validated use and other notes	The first prediction model, developed in a mainly white, high socioeconomic US population; the original tool (FRS-CHD) predicted 10-year risk of IHD events; the updated models assessed all CVD	Greater US geographic diversity than Framingham but representative of white and African American populations only; not valid for other ethnicities	Includes separate prediction tools for use in high- and low-risk European countries (according to age-adjusted CVD mortality rates, 2012)	Validated for the UK population; QRISK2 incorporated comorbidity and ethnicity to l QRISK1; QRISK3 has since been developed (2017)[54] to incorporate: SBP variability Steroid use Atypical antipsychotic use Expanded definition of CKD Additional diagnoses (migraine, SLE, mental illness, erectile dysfunction, HIV status)	Validated for the Scottish population; no incorporation of ethnicity	Based on Framingham, validated for the nationally representative New Zealand population	Validated for use in 21 global regions; Recalibration of the original WHO/ISH risk charts[9] using age, sex and risk factor data from the Global Burden of Disease and Non-Communicable Disease Risk Factor Collaboration
Current guideline recommendation	Canada (CCS, 2016)[11] Australia (2012)[12]	US (ACC/AHA 2019, 2014)[1, 37]	Europe (ESC 2016)[10]	UK (NICE 2014)[15] NB; subsequent update is expected to recommend QRISK3	Scotland (SIGN, 2017)[16]	New Zealand (2018)[14]	WHO (HEARTS technical package 2018)[8]

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; CCS, Canadian Cardiovascular Society; CARDIA, Coronary Artery Risk Development in Young Adults; CHS, Cardiovascular Health Study; CKD, chronic kidney disease; ERFC, Emerging Risk Factors Collaboration; ESC, European Society of Cardiology; FRS-CVD, Framingham Risk Score-Cardiovascular Disease; FRS-CHD, Framingham Risk Score-Coronary Heart Disease; HDL-C, high-density lipoprotein cholesterol; IHD, ischaemic heart disease; ISH, International Society of Hypertension; NICE, National Institute for Health and Care Excellence; RhA, rheumatoid arthritis; SBP, systolic blood pressure; SCORE, Systematic Coronary Risk Evaluation; SIGN, Scottish Intercollegiate Guidelines Network; SLE, systemic lupus erythematous; STEPS, Stepwise Approach to Surveillance; TC, total cholesterol; WHO, World Health Organization.

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