Clinician assessment of future risk of cardiovascular events in asymptomatic individuals is often inaccurate without formal risk prediction tools. Prediction tools that are easy to use and that integrate Framingham criteria of age, sex, serum cholesterol, blood pressure, smoking status, diabetes, and left ventricular hypertrophy into one global risk score have evolved to aid risk assessment. In recent decades, new putative risk factors have been described, including clinical risk factors such as chronic kidney disease and metabolic syndrome, as well as numerous laboratory markers of disease (box 1). Each new risk factor attracts studies evaluating whether a certain ancillary test shows an incrementally higher cardiovascular risk after adjusting for traditional risk factors. This review asks whether ancillary testing in asymptomatic adults improves the accuracy of predicting cardiovascular risk in individuals, and what effects it might have on patients’ care, behaviour, and clinical outcomes.

What are the drawbacks of large scale testing?
Indiscriminate testing could waste resources on tests that will not affect intended management (and that may cause anxiety) and on treatment, started as a result of positive tests, in populations for whom efficacy has not been proved. In the 35% of adults deemed to be at low risk of cardiovascular events (10 year risk <3%), further tests, even with abnormal results, may not justify further investigation or treatment. Conversely, in the 25% of patients at high risk (10 year risk ≥20%), even normal test results should not necessarily prompt discontinuation of aggressive preventive strategies. The 40% of patients at intermediate risk (5% to 20%) are the most likely to benefit from testing. This review does not consider investigations used to screen for or diagnose existing disease (rather than risk) in asymptomatic people.

How do we assess the value of tests that predict cardiovascular risk?
A positive or abnormal value for a new risk factor test will be more useful in estimating disease risk if:

- The more abnormal the test value, the greater the risk of an event (as expressed by the relative risk, odds ratio, or hazard ratio)
- This strong association persists as a further contribution to risk after the contribution of traditional risk factors has been taken into account or adjusted for
- The test discriminates well between individuals who will have an event in the future and those who will not (expressed as a C statistic or C index, with values of 0.5 being no better than chance and 1.0 representing perfect discrimination)
- For tests integrated into risk scoring tools or algorithms, the tools are well calibrated, with predicted and observed risk estimates being similar for each stratum of risk such that ratios of predicted to observed risk are close to 1.0
- The testing method is reliable and standardised across different laboratories
- The test value (or related scoring tool) leads to a change in risk estimates large enough to justify altering the intended management
- Results of clinical trials predict that the altered management plan will improve outcomes.

In general, tests are clinically useful if they correctly predict an event or non-event in 70% or more of cases (C-index ≥0.70), which requires a strong association between test value and disease risk (unadjusted relative risk or odds ratio ≥10.0).
How accurate is risk assessment based on clinical risk factors?

Conventional risk factors and Framingham models

The Framingham risk score underpins most contemporary models of cardiovascular risk prediction that use conventional risk factors (box 2).9 Models based on the Framingham risk score discriminate best in white Western females (C-statistic 0.79) and worst in non-white African males (0.63).10

New clinical risk models and clinical risk factors

New prediction models such as QRISK11 and ASSIGN12 aim to supersede Framingham based models by using data from more contemporary cohorts of individuals, many of whom are receiving treatment for known risk factors, and by including additional risk variables (box 2). The C-indices do not differ much between the models, but QRISK is better calibrated than the Framingham risk score and ASSIGN, producing more accurate estimates in patients at low (<5%) and high (≥20%) 10 year risk (table).11

The clinical label of metabolic syndrome (defined as varying combinations of fasting plasma glucose, triglycerides, lipoprotein ratios, blood pressure, and measures of visceral adiposity) increases cardiovascular risk by 50% (relative risk 1.5) after adjustment for traditional risk factors.13 However, most studies note little or no added improvement in predicting risk in individuals,14 and its value in this context remains unclear.

What is the added value of resting and exercise electrocardiography?

Major abnormalities on the resting electrocardiogram—such as Q waves, left bundle branch block, and atrial fibrillation—are associated with up to a 3.5-fold increased risk of cardiovascular death at 10 years, but outcomes are incorrectly classified in a third of cases (C-statistics ≤0.67).15 Similarly, exercise stress tests that report a positive or negative result based simply on ST segment deviation are little better than Framingham based models in predicting event risk. Among 25 927 asymptomatic men at low risk (mean age 43 years; 8 year coronary mortality rate 0.6%), an abnormal stress electrocardiogram, which occurred in only 4.3% of cases, incorrectly predicted death in almost 40% of cases, although accuracy improved with increasing number of risk factors (relative risk 21 for no risk factors, 80 for three or more factors).16 More sophisticated stress electrocardiogram scores based on multiple variables (exercise time, extent of ST deviation, provocation of chest pain) and clinical risk factors (age, sex, diabetes, smoking status) show more promise, with C-statistics for 5 year survival up to 0.83.17

In patients who cannot undergo exercise stress electrocardiography (uninterpretable baseline electrocardiogram; inability to exercise; characteristics such as anaemia or left ventricular hypertrophy that predispose to false-positive ST segment changes), the prognostic value of pharmacologically induced stress imaging (echocardiography, myocardial perfusion imaging)
Multimarker panels have been claimed to have greater discriminatory power than single markers, but most studies, although not all, have reported disappointing results.

**Non-invasive imaging tests**

Can prediction be improved by directly imaging subclinical vascular atherosclerosis?

**Coronary artery imaging**

Using electron beam or multislice computed tomography, coronary artery calcium scanning visualises calcium accretions in atherosclerotic plaque lining the walls of coronary arteries, and computes a volumetric score (Agatston score) between 0 (no accretions) and over 1000 (heavy wall calcification). Other studies using multidetector tomography identify substantial obstructive coronary disease (>50% luminal stenosis), which includes non-calcified plaque.

The largest study to date of coronary artery calcium scanning measured scores and all cause mortality over seven years in 25,233 asymptomatic individuals, in whom scores above 10 were independently predictive of mortality after adjustment for traditional risk factors, with relative risk increasing from 3.6 for a score of 11-100 to 9.4 for a score of ≥1000. These values corresponded to 12 year event rates of ≤5.5% for scores of 11-400, 7.0% for scores of 401-1000, and 23.1% for scores ≥1000. However, only 10% of all patients, in whom multiple risk factors were present, had scores greater than 400. After adjustment for conventional risk factors (dichotomised sex adjusted age, family history, hypertension, lipids, smoking, diabetes), scores retained greater accuracy in predicting risk than did risk factors alone (C-statistic 0.76 versus 0.61; P=0.03). However, when scores were compared with age alone as a continuous variable, the discrimination difference was attenuated (C-statistic 0.81 vs 0.77), implying age is the single most important predictor of both death and extent of coronary artery calcification.

Current expert consensus recommends avoiding computed angiography in risk assessment for asymptomatic people at low risk, because of the carcinogenic risk associated with radiation (up to 2% for annual scanning over a lifespan), and the possibility of iatrogenic morbidity incurred by invasive investigation—pulmonary lesions are incidentally detected in 20% of people who undergo scanning, but most are benign.

**Carotid and peripheral artery imaging**

In asymptomatic populations, thickening of the intima media of the carotid artery or reduced arterial flow in the leg (low ankle brachial index), as assessed by ultrasound, is associated with as much as a threefold increase in cardiovascular risk after adjustment for traditional risk factors. However, studies of incremental predictive value in individuals are few and no recommendations exist for the routine use of vascular ultrasound in risk prediction.
What is the evidence that risk prediction alters clinical management or outcomes?

A systematic review found eleven studies, including five randomised controlled trials with reasonable methodological quality, that had evaluated the clinical benefits and harms of applying Framingham based risk scores to the care of asymptomatic people. None of these showed a significant overall change in care or risk factors, although somewhat harmful effects were seen. In one trial, an a priori subgroup analysis of patients at high risk showed significant improvements in prescribing of lipid lowering agents (absolute increase 11%) and antihypertensive drugs (absolute increase 13%). Two other trials showed improvements in systolic blood pressure (4.6 mm Hg decrease) and uptake of physical exercise (11% increase). A more recent trial not included in the above review found a significant but small (0.08 mmol/l) decrease in low density lipoprotein cholesterol. No effects on event rates were reported; studies have been under-powered to detect such effects.

No trials have directly assessed the effects of stress testing or laboratory biomarkers on control of risk factors or on clinical outcomes compared with no intervention. As many as 3% of patients undergoing stress electrocardiography in cohort studies subsequently showed severe coronary disease prompting revascularisation, but no trials have confirmed benefit from revascularisation in asymptomatic populations. Moreover, in populations with lower risk (<10% event risk at 5 years), at least 75% of positive test results are false positives, potentially resulting in unwarranted testing and anxiety.

One trial assessed the effect of coronary artery calcium scoring in 450 asymptomatic US army personnel (mean age 42 years, mean 10 year risk of coronary events 5.9%), of whom 15% had positive scores. Using a factorial design that randomised participants to usual care or intensive case management with or without feedback to doctor or patient about the coronary artery calcium score, awareness of the score had no effect on risk profile or lifestyle. Another trial, which randomised 1005 people with raised coronary artery calcium scores (above 80th percentile) to a statin and vitamins C and E or matching placebo, found no treatment effect on scores or cardiovascular event rates at four year follow-up.

Implications for clinical practice

According to the available evidence, ancillary testing in most asymptomatic people adds little to the prediction of individual cardiovascular risk, and does not affect care, lifestyle, adherence, or clinical outcomes. Randomised trials are needed to assess whether the improved accuracy of risk categorisation provided by some tests leads to therapeutic reductions of risk in patients not previously identified, or to reductions in the number of patients needing treatment by identifying low risk groups. Other areas in need of studies are the potential harms and cost effectiveness of additional testing, generalisability of results to populations with different ethnicities and comorbidities, standardisation of test assays in maximising precision and validation of population norms to guide interpretation of results, and observer bias and reliability.

A case may be made for further testing in patients at intermediate or high risk who are younger (<35 years), older (>75 years), or come from population groups not included in cohorts used to derive and validate current clinical risk models. However, ancillary testing in most middle aged people is premature and potentially wasteful of resources. An alternative strategy, which needs to be studied in randomised trials, is to ensure that all adult patients (and their doctors) are aware of their cardiovascular risk by using simple, accessible clinical risk calculators (such as QRISK) and adopt a management plan appropriate to their level of risk. In the case scenario presented, the 10 year cardiovascular event risk using QRISK2 is 33%, which should provide sufficient motivation for this patient and his doctor to optimise lifestyle and preventive treatments, making further testing unnecessary.
SUMMARY POINTS

Risk prediction tools based on the Framingham score are the most widely used for determining individuals’ absolute risk, based on clinical risk factors, although newer tools are better calibrated.

The clinical label metabolic syndrome and abnormalities on the resting electrocardiograph do not add prognostic information beyond that obtained by traditional risk factors.

Exercise stress electrocardiography that generates a positive or negative result based on ST deviation alone is not predictive, although scores that integrate several electrocardiographic and clinical variables may be predictive in patients at intermediate risk.

Laboratory biomarkers, even in the form of multimarker panels, are not helpful in refining clinical risk estimates. Imaging of subclinical atherosclerosis with computed coronary angiography can identify patients at significantly increased risk, but only a small proportion of patients screened fall into this group.

No randomised evidence to date has shown that informing clinicians and patients of absolute risk of cardiovascular events leads to changes in care or improvement in outcomes.

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