Cardiovascular risk prediction for primary prevention

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Risk prediction tools such as QRISK identify those at higher risk of heart attack and stroke, based on traditional and emerging cardiovascular risk factors, with a view to primary prevention, eg with statins. This article considers how this important aspect of public health management can be optimised.

Cardiovascular atherosclerotic disease, often manifesting as ischaemic heart disease, myocardial infarction and stroke, remains a leading threat to life and is largely preventable. The NHS healthcare costs associated with cardiovascular disease are also considerable at currently just under £9 billion a year, according to Public Health England figures.

The ability to calculate total cardiovascular risk in general practice, based on the assessment of various risk factors, is therefore invaluable in communicating disease susceptibility to individuals and informing the need for primary prevention. This can be achieved using the QResearch cardiovascular disease risk algorithm (QRISK) score, which assesses the likelihood of stroke or heart attack over a 10-year period in the absence of cardiovascular disease.

Addressing cardiovascular risk

Risk counselling typically focuses on therapeutic lifestyle change to tackle risky behaviours like smoking and physical attributes such as obesity. A QRISK score of ≥10% is also the point where pharmacotherapeutic intervention is offered. This is commonly aimed at lowering non-HDL cholesterol (and hence improving the total cholesterol/HDL cholesterol ratio), using high-intensity statins (which predominantly target LDL cholesterol and are expected to lower it by more than 40%). This reflects the importance of dyslipidaemia as a readily modifiable risk factor and mediator of cardiovascular disease, as well as acknowledging the contribution of non-HDL cholesterol lowering to reducing global cardiovascular risk.

Similarly, elevated systolic blood pressure provides another traditional, modifiable target with a clear link to cardiovascular disease pathology. Furthermore, requiring anti-hypertensive medication to control elevated blood pressure will constitute an independent risk according to QRISK. This is in part an acknowledgement of the likelihood of underly-
So far, so good; but traditional risk factors, with rational claims to influence the atherosclerotic disease process, have failed to capture the entire cardiovascular risk burden. The response has been the ongoing search for additional factors that can better quantify risk for possible integration into clinical prediction tools. This will not only better identify individuals at higher risk but also help to remove health inequalities in primary prevention. Here, the detection of risk and eligibility for intervention (via either the QRISK score or the presence of conditions where cardiovascular risk is already established, eg type 1 diabetes, chronic kidney disease), is greatly assisted by public health screening programmes such as the NHS Health Check in England, which is bridging the diagnosis and primary prevention gap.

A plethora of cardiovascular risk factors and risk tools

In addition to featuring classic cardiovascular risk factors, such as diabetes, lipid profile, blood pressure, smoking status, age, gender, body mass index and first-degree family history of coronary heart disease, there are now a number of unconventional items of clinical information asked for in the latest version of the QRISK tool, QRISK3, developed in 2017 (see Table 1). QRISK3 therefore continues to build on the additional risk factors and refinements incorporated into the previous version, QRISK2, which itself saw the introduction of an extended age range (25–84 years) and risk factors such as ethnicity, separate categories for type 1 and 2 diabetes, treated hypertension, rheumatoid arthritis, chronic renal disease and atrial fibrillation (see Table 1). QRISK3 has been introduced as an improved cardiovascular risk prediction tool and is set to be the standard version of QRISK; but current NICE guidance refers to QRISK2* (the last iteration being QRISK2-2017*).

One of the new risk factors featured in QRISK3 is a measure of variability in systolic blood pressure readings, which represents a refinement in the use of a classic risk factor. This is expected to provide a contribution to risk independently of blood pressure per se (with higher variability carrying more risk). Diagnosis or treatment of erectile dysfunction has also made the list, along with the addition of: an earlier stage of chronic kidney disease; migraines; and severe mental illness (which contributes to cardiovascular risk through an association with poor diet and lifestyle). Furthermore, medication with second-generation (‘atypical’) antipsychotic drugs and the regular use of steroid tablets represent newly introduced specific therapeutic risk categories, relating to their adverse effects on lipid profiles.

In addition to requesting clinical information, the QRISK3 tool is complemented by a socioeconomic area measure of deprivation (based on the Townsend score and assessed using postcode), to further widen the predictive net. This is actually an innovative feature of QRISK, built in from the outset, but originally pioneered by the Scottish ASSIGN (Assessing Cardiovascular Risk using the Scottish Intercollegiate

| Table 1. QRISK3-2018 prediction algorithm cardiovascular risk factors

Guidelines Network) risk prediction tool, intended to avoid risk underestimation in vulnerable societies.

Conversely, there are some sources of cardiovascular risk not directly or comprehensively surveyed by QRISK3. Specifically, these relate to: diet and physical activity (although severe mental illness may capture this in certain cases); alcohol intake; and psychosocial factors including emotional state (although moderate/severe depression included under severe mental illness captures this in part), psychosocial stress and social situation. Indeed, these factors along with smoking, hypertension, abdominal obesity, dyslipidaemia, diabetes and cardiac causes (eg atrial fibrillation) have been identified to account for around 90% of stroke risk. Also, while many novel lipid risk factors have emerged (eg lipoprotein(a), apolipoprotein B, LDL density and particle number), QRISK3 continues the conventional assessment of dyslipidaemia as total cholesterol/HDL cholesterol ratio.

A diagnosis of HIV/AIDS is another suggested risk factor (possibly connected to antiretroviral treatment) that was in fact considered for inclusion in the development of QRISK3 but is not currently admitted owing to an inadequately significant association with outcomes in the UK population studied. However, this will be kept under review in future QRISK3 updates.

The Scottish ASSIGN algorithm and the UK QRISK algorithm are just two examples of the numerous cardiovascular risk prediction tools that have been developed, including: the US Framingham risk score (various modified versions); Joint British...
Societies (JBS) risk calculator; American College of Cardiology/ American Heart Association Atherosclerotic Cardiovascular Disease (ASCVD) risk score; German PROCAM (Prospective Cardiovascular Münster Study) risk algorithm; European SCORE (Systematic COronary Risk Evaluation) risk chart; and the World Health Organization/ISH risk chart. Perhaps unsurprisingly, such tools can be expected to perform differently with regard to accurately predicting cardiovascular events (both in terms of systematic overestimation and underestimation of risk) and subsequently informing eligibility for primary prevention, in association with clinical prescribing guidelines.\(^1,13\) Furthermore, 10-year risk tools only make short-term predictions and younger adults might be better served (in terms of opportunities for earlier intervention) by an estimation of lifetime risk.\(^1\)

Variations in the performance of risk prediction tools probably reflect limitations in the clinical applicability of multimarker risk algorithms to dissimilar populations (with possibly different susceptibilities to risk factors), in addition to significant discrepancies in the choice of risk factors and predicted clinical endpoints.\(^1,4\) In this regard, QRISK offers an important ‘home advantage’ in that it was developed and validated in UK populations for UK use and has been shown to be more discriminative in the UK setting (ie can better differentiate between high- and low-risk individuals) than some leading alternative risk prediction tools.\(^3\)

As well as providing an opportunity to add new risk factors and refine the assessment of established ones (eg gradations in smoking level), periodic (annual in the case of QRISK2) updates to the QRISK tool also allow for recalibration to changing population characteristics (eg the declining incidence of cardiovascular disease). Updating QRISK also allows access to the most recent census data (for the Townsend score) and the latest version of the QResearch UK primary care database (representing the anonymised health records of over 30 million patients across 1500 general practices throughout the UK).

**Emerging risk factors**

There is now a host of emerging, non-traditional cardiovascular risk factors that risk prediction tools could potentially draw from\(^15,16\) and biomarkers that may conceivably improve predictive accuracy can be suggested from a number of diverse biological domains (see Table 2). Indeed, current QRISK (ie QRISK3) clinical risk items may arguably be interpreted as already representing a number of these novel biological risk sources, which may point to their ongoing utility in evolving risk prediction tools. This is especially the case with the QRISK3 categories of: diabetes (signifying poor glycaemic control and insulin resistance); rheumatoid arthritis, systemic lupus erythematosus and the regular use of steroid tablets (signifying underlying inflammation); erectile dysfunction (signifying endothelial dysfunction, presuming a vascular cause); and systemic blood pressure variability (signifying to some extent arterial stiffness and subclinical atherosclerosis). However, the further incorporation of specific biomarkers (as opposed to more proxy, diagnostic indicators) representing these cardiovascular risk modalities might well capture risk more precisely and offer additional predictive value. It is interesting to note here that statins are thought to pleiotropically address several of these risk factors, in addition to their lipid-lowering effect.\(^2\)

Of course, the profusion of potential new risk factors promises to add to the complexity of risk profiling; and this, together with the costs of acquiring it, may begin to challenge the clinical practicality and affordability of incrementally improving global risk prediction in primary care. An instance of the ‘law of diminishing returns’ might also surface here, if marginal risk predictive gains prove costly. In this case, optimising the selection of established major risk factors/targets may assume greater relative importance in improving prediction/prevention, along

<table>
<thead>
<tr>
<th>Sources of risk</th>
<th>Suggested biomarkers and conditions</th>
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<tbody>
<tr>
<td>Inflammation</td>
<td>High-sensitivity C-reactive protein, interleukin-6, tumour necrosis factor-alpha, leukocyte count, gut dysbiosis, periodontal disease</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>F2-isoprostanes, lipid hydroperoxides, myeloperoxidase</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>Microalbuminuria, cyclic guanosine monophosphate, nitric oxide metabolites, flow-mediated dilation, homocysteine, pulse wave analysis, erectile dysfunction</td>
</tr>
<tr>
<td>Impaired glycaemic control</td>
<td>Glucose, HbA(_{1c})</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Insulin, insulin sensitivity</td>
</tr>
<tr>
<td>Neurohumoral activation</td>
<td>Brain natriuretic peptide, renin</td>
</tr>
<tr>
<td>Prothrombotic status</td>
<td>Fibrinogen, plasminogen activator inhibitor-1</td>
</tr>
<tr>
<td>Atherosclerotic status</td>
<td>Coronary artery calcium, carotid intima-media thickness, ankle-brachial index, arterial stiffness</td>
</tr>
<tr>
<td>Subclinical myocardial damage</td>
<td>High-sensitivity cardiac troponin T and troponin I</td>
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<tr>
<td>Renal dysfunction</td>
<td>Uric acid, cystatin C</td>
</tr>
<tr>
<td>Poor omega-3 index</td>
<td>Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)</td>
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<tr>
<td>Vitamin D status</td>
<td>25-hydroxyvitamin D</td>
</tr>
<tr>
<td>Bone turnover</td>
<td>Osteoprotegerin, osteocalcin</td>
</tr>
<tr>
<td>Respiratory instability</td>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>Drug therapy</td>
<td>Use of COXIBs and traditional NSAIDs</td>
</tr>
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**Table 2.** Emerging sources of cardiovascular risk and suggested biomarkers/conditions as novel risk factors
Multimarker cardiovascular risk prediction algorithms provide clinically useful tools for identifying individuals in general practice at higher global risk of heart attack and stroke, with a view to communicating personal risk and offering primary prevention (e.g. with statins).

- QRSK3 is a cardiovascular risk prediction tool developed, calibrated and validated in UK populations, which (in addition to a number of other standard and less conventional biological risk factors) considers the independent contributions made by ethnicity and social deprivation. This thereby avoids risk underestimation in vulnerable populations and helps reduce health inequalities.

- Primary prevention with statins is currently offered at a 10-year cardiovascular QRSK score threshold of ≥10%. Patients to be considered for statin therapy without measuring risk score include those with type 1 diabetes, chronic kidney disease or established cardiovascular disease. QRSK3 is set to be the new standard of QRSK but QRSK2 is recommended in current NICE guidance.

- The discovery of potential new cardiovascular risk factors is ongoing, with QRSK3 incorporating additional, increasingly novel risk factors intended to more accurately quantify risk. However, the clinical practicality and affordability of more sophisticated risk calculation may bring challenges in the primary care setting, in the form of growing complexity and the expectation for more tests.

- Primary prevention treatment recommended at progressively diminishing predicted 10-year cardiovascular risk thresholds may offer increasing returns in cardiovascular public health management in the short-term. However, while health check screening programmes and prediction algorithms attempt to target interventions to those at higher risk, overmedication and the incidence of side-effects in the absence of benefit remains an area of concern at the personalised medicine level.

- It is essential that cardiovascular risk prediction continues to be allied with clear, suitable clinical guidelines on how this information is to be used and that risk estimates are seen as an aid to, rather than a substitute for, clinical decision making in individual circumstances.

**Table 3. Cardiovascular risk prediction summary**

with medicines optimisation and better risk management in the young. At least the automatic calculation of QRSK (using data on the primary care electronic patient record) is likely to mitigate the effect of complexity on the take-up of QRSK3 in general practice.

**Discovering new risk factors**

Insights into the atherosclerotic disease process continue to drive rational risk biomarker/mediator discovery, which is often supported by technological advances facilitating their measurement, such as in vascular imaging and functional assessment. Limitations on pathophysiological insight will likewise curtail this route of discovery. One fresh way this discovery ‘gap’ may be closed is with the help of epigenetics and ‘omics’ high-throughput research, which potentially uncovers molecular differences between health and disease phenotypes at the levels of the genome, transcriptome, proteome and even metabolome. Such differences at the molecular level can offer characteristics of disease that might be translatable as novel risk factors and conceivably new therapeutic targets.

In addition to use in risk calculation, emerging risk factors might well also provide novel surrogate markers for use in clinical trials investigating cardiovascular outcomes, where hard, reproducible and clinically meaningful endpoints are often difficult to ascertain owing to the protracted nature of cardiovascular disease and relative infrequency of events.

**Personal vs population risk prediction**

The role of prediction tools such as QRSK in personalising global risk using a readily calculated estimate is naturally complementary to their wider public health roles in cardiovascular primary prevention (see Table 3). However, relating probabilistic outcomes to populations is more straightforward than applying it to individuals. Hence, when a prediction tool returns a 10-year cardiovascular risk score of 10%, the notion that at a population level, 10 individuals out of 100 with that absolute risk profile are likely to suffer, for example, a myocardial infarction or stroke over the next 10 years, carries considerable conviction, depending on the accuracy of the algorithm.

On the other hand, predicting exactly who will be those 10 out of 100 is currently not possible (in the absence of true precision medicine). After all, the personal odds of a cardiovascular event would be a resounding 9:1 against. Indeed, the odds of heart attack or stroke at which primary prevention with a statin would be recommended have significantly lengthened in recent years, reflecting drops in the recommended intervention threshold from (a 10-year cardiovascular risk of) 40% to 20% and now 10% risk. Of course, the odds must always be weighed against the calamity of the event actually occurring, however unlikely.

So while offering a good rate of return on a stake in primary prevention, the long-shot nature of the gamble (compounded by the temporal remoteness of the risk), may be less than compelling. This will clearly do nothing to encourage adherence to prescribed therapies (or risk-reducing behaviours), and non-compliance will of course undermine the translation of personalised medicine to public health. Furthermore, while the estimated risk score naturally directs treatments to people most likely to benefit, such interventions will not in any case be expected to achieve this benefit in 9 out of 10 individuals at 10% risk (i.e. they were not going to have a cardiovascular event anyway). Moreover, seeking to further improve national cardiovascular health by categorising more individuals as eligible for primary prevention (through wider health screening, better prediction algorithms or reducing the offered intervention risk threshold) inevitably raises the iatrogenic spectres of overmedication and increased incidence of side-effects.

**Conclusion**

The primary prevention of cardiovascular disease in the UK has been greatly facilitated by the development of QRSK as a multimarker global 10-year risk prediction tool, which is now available with the addition of number of novel risk factors as QRSK3. Being able to categorise more individuals at higher...
risk of heart attack or stroke in the short-term, combined with clear national guidance on when to recommend therapeutic intervention, epitomises the connection between personalised medicine and public health management, albeit at the possible expense of overmedication. However, while potentially further addressing health inequalities, capturing progressively more cardiovascular risk with increasingly complex algorithms may bring diminishing returns to the point that greater public screening, medicines optimisation and an appreciation of lifetime risk assume greater importance in primary care.

References

Declaration of interests
None to declare.

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