Cardiovascular risk

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Cardiovascular disease is a major, growing, worldwide problem. It is important that individuals at risk of developing cardiovascular disease can be effectively identified and appropriately stratified according to risk. This review examines what we understand by the term risk, traditional and novel risk factors, clinical scoring systems, and the use of risk for informing prescribing decisions. Many different cardiovascular risk factors have been identified. Established, traditional factors such as ageing are powerful predictors of adverse outcome, and in the case of hypertension and dyslipidaemia are the major targets for therapeutic intervention. Numerous novel biomarkers have also been described, such as inflammatory and genetic markers. These have yet to be shown to be of value in improving risk prediction, but may represent potential therapeutic targets and facilitate more targeted use of existing therapies. Risk factors have been incorporated into several cardiovascular disease prediction algorithms, such as the Framingham equation, SCORE and QRISK. These have relatively poor predictive power, and uncertainties remain with regards to aspects such as choice of equation, different risk thresholds and the roles of relative risk, lifetime risk and reversible factors in identifying and treating at-risk individuals. Nonetheless, such scores provide objective and transparent means of quantifying risk and their integration into therapeutic guidelines enables equitable and cost-effective distribution of health service resources and improves the consistency and quality of clinical decision making.

Introduction

Those employed in the healthcare sector are familiar with the concept of risk. This is especially true in the area of cardiovascular disease, where risk 'scores' are widely established and risk factors such as blood pressure (BP) are easily quantified. Cardiovascular disease is a huge burden on society. It costs the UK economy an estimated £30 billion per year and accounts for over 190 000 deaths annually in the UK [1]. Cardiovascular medicines encompass 30% of all community prescribing, the 286 million drugs issued in England in 2010 cost £1.5 billion [2] and the issue is world-wide, ranked top of the World Health Organization (WHO) list of global health problems [3]. Thus, knowing the risk of developing cardiovascular disease and the merits of appropriate treatment is of significant importance.

Clearly, cardiovascular risk covers an extremely broad subject area and this review endeavours to give a general overview rather than focusing on a specific topic. It examines what we understand by the term risk, traditional and novel risk factors for cardiovascular disease, clinical tools

used to calculate risk and the use of risk for informing prescribing decisions. It focuses more on risk from the perspective of primary prevention, although clearly the concept has great relevance to secondary prevention too.

What is risk?

The question 'what is risk?' has been subject to considerable philosophical debate [4] and the word risk has several definitions, some more quantitative than others. The term may mean an unwanted event (e.g. myocardial infarction), the cause of an unwanted event (e.g. smoking), the probability of an unwanted event, the expectation value of an unwanted event (i.e. probability multiplied by a measure of event severity, e.g. the probability of myocardial infarction and the associated probability of death) and a decision made in the context of known probabilities [4]. An additional commonly used term is uncertainty. This may refer to either unpredictability (e.g. the throw of a die) or lack of knowledge (about something which can potentially be

verified) [5]. When used in the clinical context, it often means a combination of both.

In the clinical setting, the word risk is commonly equated to the percentage probability (relative frequency) of an adverse event. Risk is generally considered over a fixed, finite period of time (say 10 years), although there is interest in lifetime risk [6]. Risk can be considered in absolute or relative terms. Absolute risk is the probability of an individual developing an adverse event over a given time period. Relative risk is the probability of an individual with specific risk factors developing an event, compared with a similar individual without those risk factors. When considering therapeutic interventions, the term relative risk reduction is often used – that is, the reduction in absolute terms, expressed as a proportion of the untreated absolute risk. It is absolute risk that enables prioritization of treatment on an equitable basis. Those with higher absolute risk have most to gain, even though the relative risk reduction may be similar. However, both absolute and relative risk are important independent influences on patients' perceptions of risk [7].

In medical practice, we usually fail to consider the severity of the event. Yet it has been proposed that by distinguishing between the probability of an adverse outcome and the consequences of that outcome, clinical decisions will be more consistent and of a higher standard [8]. There is also a tendency to discuss potential benefits of treatment and not the risk of adverse effects, despite drug dosage regimens requiring adjustment to maximize the balance of benefit to harm [9], and increasing patients' knowledge of their drugs being beneficial [10].

Of course, the public's understanding of risk may be poor. Indeed, this has been observed in individuals involved in policy decision making, who showed a lack of understanding of the relationship between ideas such as relative and absolute risk reduction [11]. Clearly, many patients are similarly unfamiliar with such concepts. They are also strongly prejudiced by emotions rather than simply facts, may be influenced by prior personal experience and may have inadequate understanding of their own risk [12–14]. The way in which risk is conveyed may, therefore, influence patients' decisions about treatment options [15] and affect medication adherence [16]. The concept of relative risk appears preferred by patients over absolute risk [17], with an 'average patient' providing a frame of reference. Ideally, both should be presented together, with absolute risk offering a sense of scale [12]. Natural frequencies appear preferable to probabilities in conveying absolute risk [18]. Supporting quantitative measures of risk with qualitative terms (e.g. 'rare', 'high') may be helpful [19], although isolated descriptive terms may be misleading, as they reflect the physician's rather than patient's perspective and lack standardized meaning [20]. The way in which risk is framed is also important, with biased framing hindering informed decision making. For instance, positive framing is more effective than negative

framing at persuading patients to take potentially risky treatment options [12]. Simple visual presentations of risk may also be helpful [17], such as using colour, providing comparative information and including the effect of changing behaviour [21]. Importantly, simpler approaches to communicating risk may be more effective for motivating behaviour change [22].

Cardiovascular risk factors

Clearly, risk is a complex concept, requiring careful interpretation and good communication to facilitate appropriate therapeutic decision making. It also necessitates the evaluation of various risk factors. It is impossible to provide a definitive list of the numerous cardiovascular risk factors. Many established factors are incorporated in risk models described later in this review. However, numerous newer factors have been identified, raising issues such as the amount of added predictive value they provide, practicalities of implementation in clinical practice and the potential for therapeutic interventions.

Classic unmodifiable risk factors

Age, gender, family history and ethnicity are all key cardiovascular risk factors. Although not themselves amenable to direct therapeutic intervention, they remain important for stratifying risk. They also have implications for medication efficacy and adherence.

The strongest predictor of adverse cardiovascular outcome is age [23], and of particular relevance given our ageing population. However, it can be difficult to separate the ageing process (e.g. degenerative vascular changes [24]) from concurrent age-related disease (e.g. atherosclerosis). Conventional clinical measures of cardiovascular function may underestimate the effects of age on the cardiovascular system, explaining in part why age remains such a dominant factor. Age is associated with increased co-morbidity too, and may itself influence behavioural risk factors (e.g. creating barriers to exercise [25]). There are also implications for pharmacological risk factor management, due to altered pharmacokinetics and pharmacodynamics [26] and a lack of drug trials in the elderly [27].

Patient gender is also important [28]. Although cardiovascular disease is the biggest cause of mortality in women, incidence rates are comparable with those of men 10 years younger [29]. Hypoestrogenaemia in women is a risk factor [30], although age may predominate post-menopause [31]. There are also gender differences in the prevalence [28] and strength of effect [32] of other risk factors. Gender may also have implications in terms of risk factor management, with conflicting evidence for statin efficacy in women [33, 34] and differences in adherence to antihypertensives [35].

Premature family history, both parental and sibling, is significant [36, 37], and likely measures shared factors

beyond simply genetics. It is incorporated in various risk prediction models [38–40], although it may have limited added value [36].

Ethnicity is a further well recognized risk factor, with higher prevalence of cardiovascular disease in South Asian and Black populations. The reasons are not entirely understood, but likely encompass both biological and behavioural factors [41]. Ethnicity is already incorporated into clinical risk prediction models [38, 42], and has implications for drug choice [43] and medication adherence [44, 45].

Classic modifiable risk factors

Although the above characteristics are highly useful for risk stratification, modifiable factors have the additional benefit of being potentially suitable targets for pharmacological intervention.

There is a large body of evidence that systolic and diastolic BP are strongly, positively associated with cardiovascular disease [46]. Antihypertensive therapy has clear benefits [47]. Although efficacy may differ between pharmacological agents, the largest effect on event reduction relates to the degree of BP lowering [43]. Within-individual BP variation necessitates repeated measurements to improve diagnosis [43]. Variability may also have prognostic relevance [48], although it is not easily amenable to therapeutic intervention [49, 50].

Cholesterol and triglyceride abnormalities constitute almost half the population attributable risk [51, 52]. Statins remain the principal drug treatment for reducing low-density lipoprotein cholesterol (LDL-C) [53] although treated patients have considerable residual risk. Attention has been particularly focussed on the triad of high triglycerides, high LDL-C and low high-density lipoprotein cholesterol (HDL-C), which is strongly associated with type 2 diabetes and the metabolic syndrome. Disappointingly, combining statins with additional medications targeting these other lipid abnormalities, including fibrates [54] and niacin [55], has lacked efficacy. Numerous other biomarkers involved in lipid metabolism are recognized as having predictive value, such as apolipoprotein B [56], lipoprotein-associated phospholipase A2 [57] and LDL particle size [58] and some of these may be potential therapeutic targets [59].

Diabetes mellitus is a growing problem. Patients are considered high risk regardless of other factors. It is progressive, and increasing glycaemic levels are positively correlated with vascular complications [60, 61]. Indeed, there is evidence that even impaired glucose tolerance conveys increased risk [62]. Complication rates may vary between genders [63] and with genetic heterogeneity [64]. Numerous treatments are available, and treatment generally reduces both microvascular and macrovascular complications (less so the latter in type 2 diabetes) [65–68]. Arterial wall injury is also aggravated by the frequent coexistence of other metabolic syndrome risk factors [69], the treatment of which brings additional benefit [70].

Behavioural risk factors

Behavioural characteristics are also important. Smoking is one example, demonstrating a dose effect and undesirable interaction with other risk factors (e.g. lipids, diabetes) [71]. In addition to psychological approaches, several anti-smoking medications are available. Prescription of these drugs in the UK is generally independent of overall cardiovascular risk, although there is evidence that certain people are more susceptible to smoking-related DNA injury [72]. Obesity is a similar global public health problem, with adverse cardiovascular consequences due to multiple pathophysiological changes [73]. Diet remains the most appropriate intervention, with pharmacotherapy currently limited to the lipase inhibitor orlistat [74]. Although use of orlistat is supported by UK guidelines in obese (and some high-risk overweight) patients, evidence of long term cardiovascular benefit is unavailable [75]. Lack of exercise, high dietary salt and excess alcohol are additional behavioural risk factors.

Novel risk factors

Numerous new markers of cardiovascular risk have been described in recent years. Several are discussed below. The list is not exhaustive, with many other biochemical markers known to be involved in vascular pathophysiology, but not formally used to predict hard outcomes.

The inflammatory hypothesis of atherosclerosis has led to interest in markers of systemic inflammation. In particular, C-reactive protein (CRP) has been shown to be positively associated with adverse cardiovascular outcome [76], although the association is weak following correction for conventional risk factors and eliminated by adjustment for coronary artery calcium [77]. Moreover, Mendelian randomization studies suggest that this association is not causal [78]. Nevertheless, there have been calls for the inclusion of CRP in clinical risk assessment [79] and CRP has been incorporated in risk prediction models [40]. The decrease in CRP and cardiovascular events with statins, independently of LDL-C lowering, suggests these drugs may have beneficial anti-inflammatory effects [80]. Some small studies in rheumatoid arthritis suggest that directly targeting inflammation may improve vascular function [81, 82], although this may reflect indirect benefits of improved disease status. Further, large studies examining the impact on hard end-points are warranted.

Technological advances have resulted in numerous genome-wide association studies searching for genetic cardiovascular risk biomarkers. Examples found include several single nucleotide polymorphisms at the 9p21 locus, possibly involving vascular remodelling [83] or inflammatory regulation [84], and the LPA locus 6q26-q27 [85]. Genetically targeted treatment may be of value, with statins eliminating the excess risk conveyed by the apolipoprotein E ϵ 4 allele [86], and the antiplatelet effect of clopidogrel modulated by genetic variants in cytochrome P450 2C19 [87]. Despite these important findings, however,

genetic profiling currently adds little to models based on conventional risk factors [88] and more sophisticated risk models are required [89].

Awareness of the importance of additional biochemical markers is growing, although not all are new discoveries. For example, the increasing use of estimated glomerular filtration rate, derived from serum creatinine measurement, has led to increased identification of chronic kidney disease, an important cardiovascular risk factor [90] in routine clinical practice. Further biochemical markers include microalbuminuria [91], cystatin C [92], uric acid [93] and homocysteine [94], although the causal nature of these associations and the benefits of therapeutic intervention remain unclear. Pro-coagulant factors such as fibrinogen are associated with increased risk, although confounded by the relationship with other traditional risk factors such as smoking [95]. The cardiac biomarkers troponin T and B-type natriuretic peptide both have predictive value in patients without established cardiac disease [96–98]. Less well known markers include the adipokines, leptin [99], adiponectin [100] and resistin [101], and osteoprotegerin which modulates bone metabolism [102]. However, it is unclear exactly which of the above biomarkers are most useful, and whether or not they add clinically significant information above and beyond the extensive list of established and other novel factors.

Vascular imaging and haemodynamics

Non-invasive measurement of vascular function may also have a role in risk stratification for patients without overt cardiovascular disease. This includes haemodynamic measures [103] and techniques for evaluating endothelial function [104]. Carotid intima-media thickness measured by ultrasound has predictive value (particularly for stroke), albeit limited over conventional factors [105]. Directly assessing carotid plaque may be more valuable. Coronary artery calcification is also a strong, independent predictor of future cardiovascular events [106], although cost and exposure to ionizing radiation are problematic. Implementation of all these technologies into clinical practice may be restricted, however, by time, cost and lack of training and equipment.

Clinical conditions

Many non-cardiovascular conditions are associated with future cardiovascular events. These include chronic kidney disease [90], atrial fibrillation [107], rheumatoid arthritis [108] (all three of which are implemented in the QRISK2 risk model [109]), depression [110], sleep apnoea [111], HIV infection [112] and pre-eclampsia [113]. Features on clinical examination, such as xanthelasmata, may also predict adverse outcome [114].

Socioeconomic status

Socioeconomic deprivation is recognized as an important risk factor and is implemented in newer predictive models

[38, 39]. Deprivation identifies those with a higher prevalence of conventional risk factors (e.g. smoking, obesity) [115], sub-optimal preventative treatment [115] and otherwise difficult to quantify social and personal factors. Furthermore, measuring deprivation helps address the inverse care law, where those in socioeconomically disadvantaged circumstances are most in need of treatment but least likely to receive it [116].

Medications

Finally, it is worthwhile remembering that certain medications may increase patients' risk of cardiovascular events. A recent example is the withdrawal of rofecoxib in 2004 [117], although non-selective non-steroidal anti-inflammatory drugs, which are often available without prescription, may also increase risk [118].

Antidepressants are also of interest. Evidence exists that longer term use of tricyclic antidepressants may be associated with myocardial ischaemia [119], although this finding is inconsistent. Selective serotonin re-uptake inhibitors do not appear to confer such risk [120], potentially due to inhibition of platelet aggregation [121]. Antidepressants may also increase the risk of type 2 diabetes [122]. The picture is further complicated by depression itself being a cardiovascular risk factor [110], and over a short period, antidepressant treatment may decrease adverse cardiovascular outcomes [123].

Examples of other pharmacological classes conferring cardiovascular risk include chemotherapeutic agents such as aromatase inhibitors [124] and fluorouracil [125], the migraine treatment sumatriptan [126], a number of insulin secretagogues [127] and various anti-epileptics [128]. However, whether these issues are considered by clinicians in everyday practice is questionable.

Calculating risk

Cardiovascular disease management is unusual in the widespread utilization of objective risk scores, based on routinely measured established risk factors. In the UK, risk scores are implemented in GP computer systems and their use is required by the primary care payment for performance scheme [129]. Most clinicians are familiar with basing cardiovascular prescribing decisions and the provision of lifestyle advice on these scores, although likely ignore the uncertainty in the probability estimate. A number of different risk scores are discussed below, with the key differences between models summarized in Table 1.

Framingham

A number of risk scores have been developed based on data from the Framingham Heart Study. One early and widely used model published in 1991 [23] estimates the absolute risk of six different cardiovascular outcomes from

Table 1

Summary of risk model characteristics

	FHS 1991	FHS 2008	ASSIGN	QRISK2 ¹	SCORE	Reynolds	PROCAM ²
Reference number	23	133	39	109	137	40, 139	138
Coefficients							
Age/gender	✓ ³	✓ ³	✓	✓ ⁴	✓ ⁵	✓	✓ ⁵
Smoking	✓	✓	✓ ⁶	✓ ⁷	✓	✓	✓
Systolic BP	✓ ^{3,8}	✓ ³	✓	✓	✓	✓ ³	✓
Total cholesterol		✓ ³	✓		✓ ⁹	✓ ³	✓ ¹⁰
HDL-C		✓ ³	✓			✓ ³	✓
Total/HDL-C	✓ ³			✓	✓ ⁹		
HbA1c						✓ ¹¹	
Diabetes	✓	✓	✓	✓		✓ ¹¹	✓
Family history			✓	✓		✓	
Ethnicity				✓			
BMI				✓ ⁴			
BP treatment		✓		✓			
Deprivation			✓	✓			
Other	LVH			AF, CKD, RA		hsCRP ³	Triglycerides ³
Separate models							
Gender		✓	✓	✓	✓ ¹²	✓	✓ ¹²
Country risk					✓		
Interactions	age × gender gender × DM LVH × gender	SBP × treatment		Age × all other factors		Gender × DM × HbA1C	Gender × DM
Valid age range (years)	30–74	30–74	30–74	30–84	40–65	45–80	20–75
Outcome type¹³	CVD ¹⁴	CVD	CVD	CVD	Fatal CVD	CVD	CHD
Model type	Parametric	Cox	Cox	Cox	Weibull	Cox	Weibull
Cohort size (% men)	5573 (46%)	8491 (47%)	13 297 (49%)	1.591 M (50%)	205 178 (57%)	27 124 (40%)	26 975 (68%)
Events	626 (CHD)	1174	2619	55 626	7934	1576	511
Follow-up (years)	12	12	10–21	7.1 ¹⁵	13.2 ¹⁵	10.2 ¹⁶	11.7 ¹⁵
Location	US	US	Scotland	England/ Wales	Europe	US	Germany

¹QRISK details based on 2011 update (2010 for cohort size, events and follow-up). ²PROCAM details are for CHD model (separate model available for stroke based on cohort subset).

³Log-transformed continuous variable (for FHS 1991, there is also a log² age term). ⁴Fractional polynomials used. ⁵Hazard function based on age rather than time. ⁶Number of cigarettes per day. ⁷Five smoking categories (including ex-smoker). ⁸Alternative coefficients available for diastolic BP. ⁹Uses either total cholesterol or total : HDL-C ratio. ¹⁰LDL-C rather than total cholesterol. ¹¹Female model only. ¹²Separate hazard functions. ¹³Definitions of CVD are not consistent across models. ¹⁴Six separate outcomes for CHD, MI, stroke, CVD, fatal CHD, fatal CVD. ¹⁵Mean follow-up. ¹⁶Median follow-up for women; median follow-up for men 10.8 years. FHS, Framingham Heart Study; LVH, left ventricular hypertrophy; AF, atrial fibrillation; CKD, chronic kidney disease; RA, rheumatoid arthritis; DM, diabetes mellitus; SBP, systolic blood pressure; CVD, cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction.

various traditional risk factors. It also includes alternative coefficients to enable use of diastolic rather than systolic pressure. This model has been criticized for using a small population and under-representing patients with diabetes [130]. It also appears to over-estimate risk in contemporary populations [131], although the fact that the model was developed prior to the widespread implementation of preventative treatment strategies might be considered an advantage [132]. The risk score advocated in the second Joint British Societies (JBS2) guidelines [42] and published as familiar charts in the British National Formulary is based on the sum of the coronary heart disease and stroke risks from the 1991 Framingham equation [53]. Framingham data have also been used to generate newer risk models, most recently by D'Agostino in 2008 [133].

UK specific scores

A desire to develop UK specific risk scores, driven in part by concerns over the generalization of Framingham, led to

the development of two alternative measures. The first to be published was the Scottish ASSIGN score [39], the most significant aspect of which was the inclusion of area-based deprivation. The second, also incorporating deprivation, is QRISK [38]. Interestingly, the total : HDL cholesterol ratio was not statistically significant in the original 2007 model, and this issue together with extensive missing data, raised concerns over the model's validity, not helped by an apparent reluctance by the authors to publish openly the model coefficients [134, 135]. A revised QRISK2 score was published in 2008 [109], based on a larger cohort and incorporating features of the clinical history. The coefficients of this model are annually updated. There is also a lifetime (as opposed to 10 year) QRISK model [136], accounting for death as a 'competing' event.

Europe

In Europe, the most recognized risk algorithm is SCORE (Systematic COronary Risk Evaluation) [137], based on 12

largely Nordic and Western European cohort studies. The major difference from the models described above is that it only estimates fatal cardiovascular outcomes. This was due to incomplete non-fatal outcome data, although it enables the calibration of SCORE to the national cardiovascular mortality data of individual countries. Less used are the Prospective Cardiovascular Münster (PROCAM) models [138], implemented as simple point-scoring systems based on a few traditional risk factors.

Reynolds risk score

Another well used North American model is the Reynolds risk score. Originally developed for women [40], it included various novel plasma biomarkers, although only CRP was included in the simplified model developed for clinical practice. A similar model was published subsequently for men [139].

World Health Organization

The World Health Organization has published risk prediction charts for a number of low and middle income countries [140]. These were developed using a hypothetical cohort, based on cardiovascular disease incidence rates and the distribution of and correlation between traditional risk factors, in various geographical regions. These charts are a welcome addition to the raft of other risk algorithms mentioned above, which are biased towards developed countries with Caucasian populations.

Disease and population specific scores

A number of other scores, or correction factors, have been described for specific ethnic or disease populations. For instance, the Framingham-derived New Zealand risk score recommends a 5% absolute increase for persons of Māori, Pacific or Indian subcontinent ethnicity, and certain diabetic patients [141]. An ethnicity 'multiplier' is also used by JBS2 [53]. Ethnicity is included as a factor in QRISK [38]. The UK Prospective Diabetes Study (UKPDS) has been used to generate diabetes-population-specific risk models [142, 143]. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study group has developed a prediction model incorporating glucose tolerance and fasting plasma glucose [144]. Work is being conducted to create risk prediction models for chronic kidney disease [145]. The CHADS₂ score has been developed for prediction of stroke in patients with atrial fibrillation [146].

Important caveats to consider

Important caveats must be considered when using such risk scores. They are considered invalid in patients with existing disease or end-organ damage. Lifetime exposure to tobacco smoke should be considered. Risk is generally underestimated if factors such as high triglycerides or CKD are unaccounted for. Care should be taken using unvalidated scores in ethnic minorities. Risk should also be evalu-

ated following repeated assessment of risk factors [42]. Furthermore, many models are based on untreated BP and cholesterol. Risk based on treated values is not equivalent [147].

Comparison, validation and improvements of current risk scores

Unfortunately, the predictive power of the above models is rather poor. Accuracy of a model can be portrayed in terms of calibration and discrimination. Calibration describes how well the predicted probability corresponds to the observed outcomes. It may be simply quantified in terms of the ratio of observed to expected events, or graphically illustrated by plotting over a range of predicted probabilities. A formal test for calibration is the Hosmer–Lemeshow test [148]. Discrimination describes how well the risk score can accurately stratify or rank patients, thus discriminating between those who will and will not have events. The receiver operator characteristic (ROC) curve, plotting sensitivity against 1 – specificity, is one method of assessing discrimination. The area under the ROC curve (AUC) is the probability of two randomly selected participants being correctly ranked [149]. Generalizability, or external validity, of a risk score relates to the accuracy in a population which is not that from which the model itself was generated [150].

Many validation studies of the aforementioned models have been conducted. A recent systematic review found Framingham models to be the subject of 60 external validation studies, performing well in US populations but with less good generalization [151]. SCORE and PROCAM have each been subject to 11 external validations [151]. A number of studies have also compared different algorithms. For instance, ASSIGN has been favourably compared with Framingham, but with better discrimination for the widely used 10 year 20% risk threshold and a superior deprivation risk gradient [152]. In addition, in a diabetic population, UKPDS outperforms Framingham [153]. It is, of course, unsurprising that different models may better suit particular circumstances, and what is perhaps most clear is that there is no single preferred score.

Another use for measures of risk score accuracy is in determining the predictive utility of adding new risk factors. This may be assessed by improvements in AUC. However, novel biomarkers generally show little improvement over existing models [154]. An alternative is examining improved reclassification of patients [155]. However, to make clinically significant improvements to risk models is likely to be challenging. It may be achieved by the use of far more sophisticated mathematical models and the Archimedes model is one example [156]. Complex models may be rendered practical by the use of electronic clinical records, relatively straightforward biochemical and genetic measurements, and novel oscillometric sphygmomanometer technology. However, costs and availability would need to improve considerably. The importance of 'relatively

minor' risk factors may also increase when one considers that 'irreversible' factors, such as age and gender, are not amenable to intervention. Finally, one must consider the possibility that, even in the absence of noticeable improvements in risk prediction accuracy, new biomarkers may facilitate individualized drug treatment and provide new therapeutic targets.

Implementation of risk scores in primary prevention

Risk scores are widely used for making decisions about primary prevention. Cardiovascular risk assessment may form part of the evaluation of specific patient groups, such as newly diagnosed hypertension as required by the UK primary care payment for performance system [129]. Alternatively, it may be used for identification of high risk individuals within the general population, although a more selective approach appears preferable [157, 158]. Interestingly, however, there is little evidence that using risk scores is effective (i.e. that it positively impacts on clinical outcomes) [159].

Various guidelines advocate cardiovascular risk assessment to inform prescribing for primary prevention. Lifestyle changes are generally recommended regardless of absolute risk. Use of risk prediction engines in patients with diabetes (who are considered high risk regardless) or established cardiovascular disease, is generally considered inappropriate. However, in diabetic patients with atypical low risk phenotypes, a specific diabetes risk model may be appropriate [70], and specific algorithms may have a role in guiding secondary prevention (e.g. CHADS₂ for established cerebrovascular disease) [160].

Although risk is a continuum, specific thresholds can facilitate more objective, consistent, transparent and equitable decisions about the distribution of finite resources. Lowering the threshold will result in treatment of more patients but at a higher cost per quality-adjusted life year (QALY), potentially unacceptable to society [161]. The 10 year 20% threshold advocated in the UK for initiating statins is justified by a number of economic models which suggest an acceptable cost per QALY [162]. However, there is considerable variation with age and risk in these models. The 20% threshold was supported by questionable cost-effectiveness below this point, the potential for adverse effects in a lower risk population, and the fact that cost-effectiveness is generally maintained even in older patients [162]. Cost of treatment also has a major bearing on cost-effectiveness [163] and, importantly, many drugs for primary prevention are available in generic forms.

Of course, alternatives to the commonly used 10 year absolute risk values are available. The New Zealand guidelines use a 5 year period [141], which fits better with the follow-up in most clinical trials, and thus may be potentially more accurate [164]. More recently, the use of lifetime

risk has been advocated [136]. This has the advantage of targeting younger patients, whose 10 year risks would be otherwise too low to justify preventative treatment. However, lifetime risk is difficult to interpret – for instance, there are no agreed thresholds for instigating treatment, and certain groups such as smokers may have a lower risk, due to the possibility of premature death from other causes like cancer [6]. Furthermore, the benefits of extremely long term treatment in such young patients are unknown. Alternative approaches are to consider relative risk alongside absolute risk, or to base risk calculations on only reversible factors.

Risk scores are widely used to guide instigation of anti-hypertensive treatment and statins. The same is no longer true for aspirin. Although its use was previously advocated in high risk patients, evidence suggests that its use in primary prevention is no longer justified, due to the adverse effects [165]. However, many guidelines are yet to be revised accordingly [39, 42, 79, 140, 166], and age and gender specific use has been argued to increase benefit [167].

The commencement of antihypertensive drug therapy relies not simply on the level of BP but also the absolute risk. UK recommendations are that patients with stage 1 hypertension (140–159/90–99 mmHg) be started on drug treatment if the 10 year cardiovascular risk is $\geq 20\%$, or if there is evidence of target organ damage, established cardiovascular disease or other major risk factors. Higher BP is treated regardless [43]. The European guidelines advocate a similar approach, although high risk is defined based on a combination of the number of risk factors and BP level, rather than a specific 10 year cut-off, resulting in more equitable treatment across all age groups [79]. The WHO recommends different BP treatment thresholds dependent on absolute risk [140]. In contrast, the American JNC7 guidelines recommend treatment of all patients with BP $\geq 140/90$ mmHg, albeit with a lower threshold of $\geq 130/80$ mmHg in the presence of chronic kidney disease or diabetes [168]. Economic analyses suggest that strategies based on absolute risk rather than a specific BP threshold are less expensive and more effective in both the American population [169] and a less developed country (South Africa) [170].

The decision to use statins for lipid lowering generally employs measures of risk, unless there is evidence of established cardiovascular disease or cholesterol concentrations are very high. Although widely advocated, there is, however, little evidence of cost-effectiveness for primary prevention and reporting of rates of adverse reactions is limited [171]. Nevertheless, NICE, the Scottish Intercollegiate Guidelines Network (SIGN) and the European Society of Hypertension all recommend statin treatment for primary prevention in patients with elevated 10 year risk [39, 53, 79]. The European Society of Cardiology, American National Cholesterol Education Program Adult Treatment Panel III (ATPIII) and WHO recommend drug intervention

dependent on a combination of lipid concentrations and 10 year risk [140, 172, 173]. It has been shown that guidelines targeting all high risk individuals with statins are more effective than those based on plasma lipid concentrations, and that screening and treating large numbers of low risk individuals is less efficient [174]. However, because risk reduction may be lower in older patients, strategies based solely on risk are not necessarily more cost-effective than more complex policies [163].

Conclusion

In summary, cardiovascular disease is a global and growing problem and identification of at-risk individuals is essential. As discussed, there are numerous cardiovascular risk factors. Well established factors, such as increasing age, remain powerful predictors of adverse outcome, and in the case of BP and dyslipidaemia are the major targets for contemporary intervention strategies. Novel biomarkers are of interest too, but are yet to prove of value beyond conventional risk factors. Nonetheless, they may offer exciting new therapeutic targets, as well as facilitating the individualization of patient care. Several risk algorithms are widely used in clinical practice, largely based on established risk factors, providing objective and transparent means of quantifying risk, despite relatively poor predictive power. The integration of these scoring systems into many national and international guidelines enables the equitable and cost-effective distribution of finite resources, and improves the consistency and quality of clinical decision making. Nevertheless, considerable uncertainty remains with regards to how best to use these scores, including choice of risk equation and the roles of different absolute risk thresholds, relative risk, lifetime risk and reversible factors in identifying and treating at-risk individuals. Finally, it is important that risk is communicated in an accurate and unbiased way, to patients, clinicians and policy-makers alike, to ensure that therapeutic decisions, guidelines and strategies are made in an appropriately informed manner.

Competing Interests

There are no competing interests to declare.

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