Excess cardiovascular risk in patients with type 2 diabetes: do we need to look beyond LDL cholesterol?

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Abstract

Despite impressive advances in treatment, cardiovascular disease (CVD) remains a significant healthcare burden in the UK and worldwide. The clustering of CVD risk factors in patients with type 2 diabetes underlines the need for a multifactorial treatment approach, yet even when receiving optimal therapy according to best standards of care, there remains a substantial risk of CVD and microvascular disease. Risk prediction tools traditionally provide an estimate of risk over 10 years, however this approach is dominated by chronological age and gender and has a number of recognised limitations. A move from 10-year to lifetime risk calculation has been proposed, and should encourage intervention at a much earlier stage. This move, alongside aggressive and broad control of modifiable risk factors, aims to ease the burden of atherosclerosis prior to the manifestations of CVD. This will be of particular benefit to those with type 2 diabetes, who have been exposed to hyperglycaemia and other risk factors for extended periods of time. The atherogenic dyslipidaemia common in this group also ensures they will benefit most from treatment strategies under investigation to further reduce macrovascular and microvascular risk.

Key words: residual risk, cardiovascular disease, type 2 diabetes, lifetime risk, atherogenic dyslipidaemia, macrovascular

Abbreviations and acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax® and Diamicron® Modified Release Controlled Evaluation
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
CARDS	Collaborative Atorvastatin Diabetes Study
CETP	cholesterol ester transfer protein
CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DCCT/EDIC	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
HbA_{1c}	glycated haemoglobin
HDL	high-density lipoprotein
HPS2-THRIVE	Heart Protection Study 2—Treatment of High-Density Lipoprotein to Reduce the Incidence of Vascular Events
HR	hazard ratio
LDL	low-density lipoprotein
MI	myocardial infarction
MRFIT	Multiple Risk Factor Intervention Trial
OR	odds ratio
NHS	National Health Service
PAR	population attributable risk
PCSK9	proprotein convertase subtilisin/kexin type 9
PPAR	peroxisome proliferator-activated receptor
REVEAL	Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification
RR	risk ratio
SPPARM-α	selective PPAR-α modulator
TG	triglyceride
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

Introduction

Annual mortality from CVD has almost halved in the UK in the last 50 years, to about 180,000 people in 2009 – representing a fall from 51% to 32% of all-cause mortality.[1] Nevertheless, CVD remains the leading cause of death both in the UK[1] and worldwide.[2] However, this progressive decrease in CVD mortality is being attenuated by the counterbalancing increase in obesity, metabolic syndrome and type 2 diabetes.

The prevalence of obesity has been increasing exponentially over the past two decades,[3] and is the most prevalent metabolic disease worldwide.[4] This increase in obesity is fuelling a rise in the numbers of people with metabolic syndrome or type 2 diabetes,[5,6] with prevalence estimates for metabolic syndrome varying between 20-30% of adults[7] and diabetes affecting 8.3% of the global population.[5,8] Until recently type 2 diabetes was con-

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sidered to be a disease of adulthood, however over the past two decades an increase in children and adolescents has been reported – from <3% of all cases of new-onset diabetes in adolescents in 1990 to 45% in 2005.[9] Young people with this disorder have an increased risk of morbidity and mortality during the most productive years of life.[10,11] As coronary disease is the major cause of death associated with diabetes,[12,13] it may be expected that the observed mortality decline would also be reflected in patients with diabetes. However, a large cohort study based in the USA showed that cardiovascular mortality rates in men with diabetes have not decreased to the same extent as those seen in the general population, and have even increased among women.[14]

The combined increase in prevalence of obesity, metabolic syndrome and diabetes is having tangible effects on CHD mortality. Recent epidemiological data from 1984–2004 in the UK show a significant overall reduction in CHD mortality among adults, but in younger men mortality rates increased in 2002 for the first time in over two decades. This was reflected in data for both men and women aged 45–54 where a slowing of the decline in mortality rates was observed, with trends reflected in data from the USA.[15] Unfavourable trends in risk factors for CHD were considered a likely explanation for the observed mortality rates.[15,16]

The increasing prevalence of diabetes and its attendant CVD risk makes management of this disease and its complications of paramount importance. Type 2 diabetes is a complex disease defined by hyperglycaemia due to insulin resistance and progressive beta-cell failure. Among the first studies to confirm independent associations between HbA_{1c} and vascular complications, including cardiovascular complications, were the landmark UKPDS[17] and its long-term follow-up analysis.[18] This association has also been highlighted in a number of large population-based observational studies,[19,20,21] and was subsequently quantified in a large meta-analysis including data from almost 700,000 patients. The meta-analysis found that serum glucose is independently associated with an increased risk of CHD (HR 2.00, 95% CI 1.83–2.19), ischaemic stroke (HR 2.27, 95%CI 1.95–2.65) and an aggregate of other vascular deaths (HR 1.73, 95% CI 1.51–1.98).[22]

The financial burden of excess CVD in type 2 diabetes

The cost burden of diabetes mellitus to the NHS is estimated to be up to 10% of the total resource expenditure, with a recent study estimating the annual cost in 2010/2011 to be around £9.8 billion.[23] Type 2 diabetes was responsible for around 90% of this cost, with less than a quarter relating to the treatment and ongoing management of diabetes and the remainder accounted for by treating its complications.[23] The large hospital care burden is a result of the treatment of retinal, renal, neuropathic, cerebrovascular and cardiac complications, which occur with increasing frequency and severity as the disease progresses.[24]

For example, a study conducted into secondary care treatment for patients with diabetes in Wales found that those with diabetes represented over a quarter of nephrology admissions and almost one-fifth for cardiology, contributing to around 20% of their total costs. Extrapolating these data to the UK as a whole, they estimated that £1.00 in every £8.00 spent on hospital care in the UK was spent on a patient with diabetes.[25] Hospital costs incurred in the final years of life have also been shown to be greater in patients with diabetes than those without diabetes at a ratio of 1.39 ($p<0.001$) after standardisation for age and sex, and accounted for 15.6% of revenue.[26]

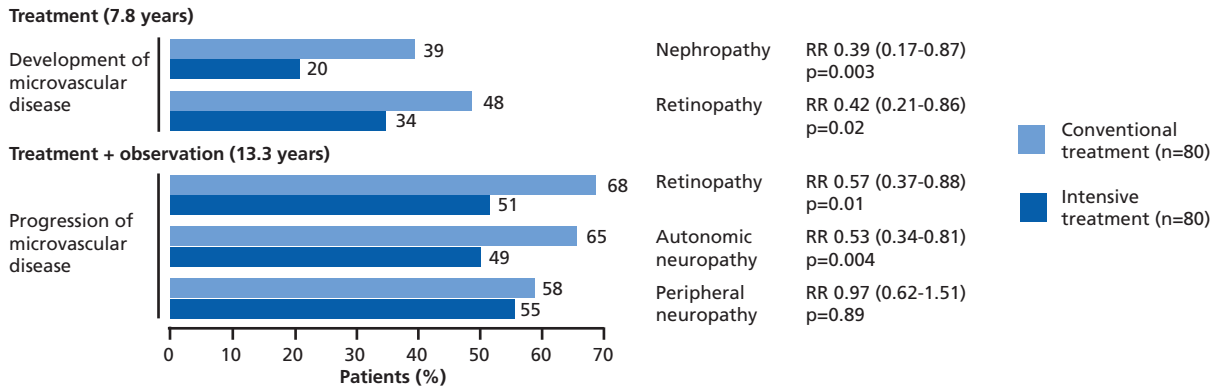
It is not just the direct cost to healthcare services that is important, the non-health-service costs (including the social and productivity costs of diabetes) are considerably higher and are largely borne by the individual or their carers. Diabetes was estimated to cost approximately £23.7 billion in the UK in 2010/2011, with non-health-service costs accounting for £13.9 billion of this figure. If no changes are made to the way diabetes is treated by 2035/2036 then costs are expected to increase further, with direct healthcare costs representing around 17% of NHS expenditure at £16.9 billion and non-health-service costs increasing to £22.9 billion.[23] Additional studies investigating the incidence and prevalence of diabetes from 2000–2060 estimate that a 3% annual increase in the UK resident population is likely to disguise a much greater increase amongst the elderly, resulting in a 20% increase in the number of people with type 2 diabetes from 2000–2030 and inflicting an increasingly large burden on the UK health service.[27]

Cardiovascular risk factors in patients with diabetes

The INTERHEART study arguably provides the most comprehensive global picture of the relative contribution of major modifiable risk factors to CVD.[28] INTERHEART is a case-control study of acute MI which enrolled almost 30,000 individuals from 52 countries, representing every inhabited continent. The study investigated the relationship of CVD risk factors such as smoking, hypertension, diabetes, blood lipids, diet and exercise to MI. It was found that smoking, a raised ApoB: ApoA1 ratio, history of hypertension, diabetes, abdominal obesity, and psychosocial factors were all associated with a significant increase in the risk of acute MI. Daily consumption of fruit and vegetables, regular alcohol consumption and regular physical activity were all associated with a significant decrease in the risk of acute MI ($p<0.0001$ for each risk factor other than $p=0.03$ for alcohol). These associations were noted in men and women, across all age ranges and in all regions of the world. Collectively, these nine risk factors accounted for 90% of the PAR for MI in men, and 94% in women.[28]

Some of the increased cardiovascular risk in patients with diabetes can be explained by a clustering of traditional risk factors within this population, and it has long been established that people with diabetes are more likely to have additional cardiovascular risk factors than those without diabetes.[29,30] Data from the UKPDS show that in patients with type 2 diabetes, increased concentrations of LDL, decreased concentrations of HDL, hyperglycaemia, hypertension and smoking are risk factors for coronary artery disease,[31] with all factors other than increased LDL also risk factors for peripheral vascular disease.[32] The MRFIT study

Figure 1. Intensive multifactorial intervention in the STENO-2 study significantly reduced the development or progression of diabetes-related microvascular disease, but failed to prevent this in many patients[39,40,67]



RR, relative risk (95% CI)

Diabetic nephropathy was defined as urinary albumin excretion >300mg per 24 hours in two of three sterile urine specimens. Diabetic retinopathy was graded according to the 6-level grading scale of the European Community-funded Concerted Action Programme into the Epidemiology and Prevention of Diabetes by two independent ophthalmologists who were unaware of treatment assignment. Peripheral neuropathy was measured with a biothesiometer. Autonomic neuropathy was diagnosed based on measurement of the RR interval on an ECG during paced breathing and an orthostatic hypotension test conducted by a laboratory technician who was unaware of patients' treatment assignment

also found that, compared with men without diabetes, 12-year CVD mortality rates were much higher at every level of serum cholesterol, systolic blood pressure and smoking among diabetic men.[30] In addition, a number of randomised trials that investigated the effect of intensified intervention on a single risk factor in patients with type 2 diabetes demonstrated microvascular benefits in the eyes and nerves and both micro and macrovascular benefits in the kidneys.[17,33,34,35]

For this reason, both national and international guidelines for the management of type 2 diabetes advocate a multifactorial approach including the treatment of risk factors such as hypertension, dyslipidaemia and encouraging smoking cessation in addition to glycaemic control.[36,37,38] The effect of implementing a multifactorial treatment approach for cardiovascular risk in patients with diabetes was evaluated in the STENO-2 study. This relatively small study of 160 patients compared an intensive, targeted, multifactorial intervention (including both behavioural and pharmacological therapy) to conventional treatment, and found that patients receiving intensive therapy had a significantly lower risk of CVD (HR 0.47, 95% CI 0.24–0.73), nephropathy (HR 0.39, 95% CI 0.17–0.87), retinopathy (HR 0.42, 95% CI 0.21–0.86) and autonomic neuropathy (HR 0.37, 95% CI 0.18–0.79).[39] The mortality benefits of such an intervention were also investigated in an extension of the STENO-2 study (mean 13.3 years follow-up), where the multifactorial intervention was shown to have a sustained benefit on both vascular complications and cardiovascular mortality.[40] Yet although a comprehensive risk factor approach is essential when treating patients with type 2 diabetes, data from the STENO-2 study show that despite reductions versus conventional treatment, multifactorial intervention is insufficient to prevent the development or progression of microvascular disease in up to 50% of patients (Figure 1). It is, therefore, clear that there is a need for renewed focus on effective interventions that are capable of reducing the residual risk of cardiovascular events and microvascular complications in patients with type 2 diabetes receiving optimal therapy according to current standards of care.

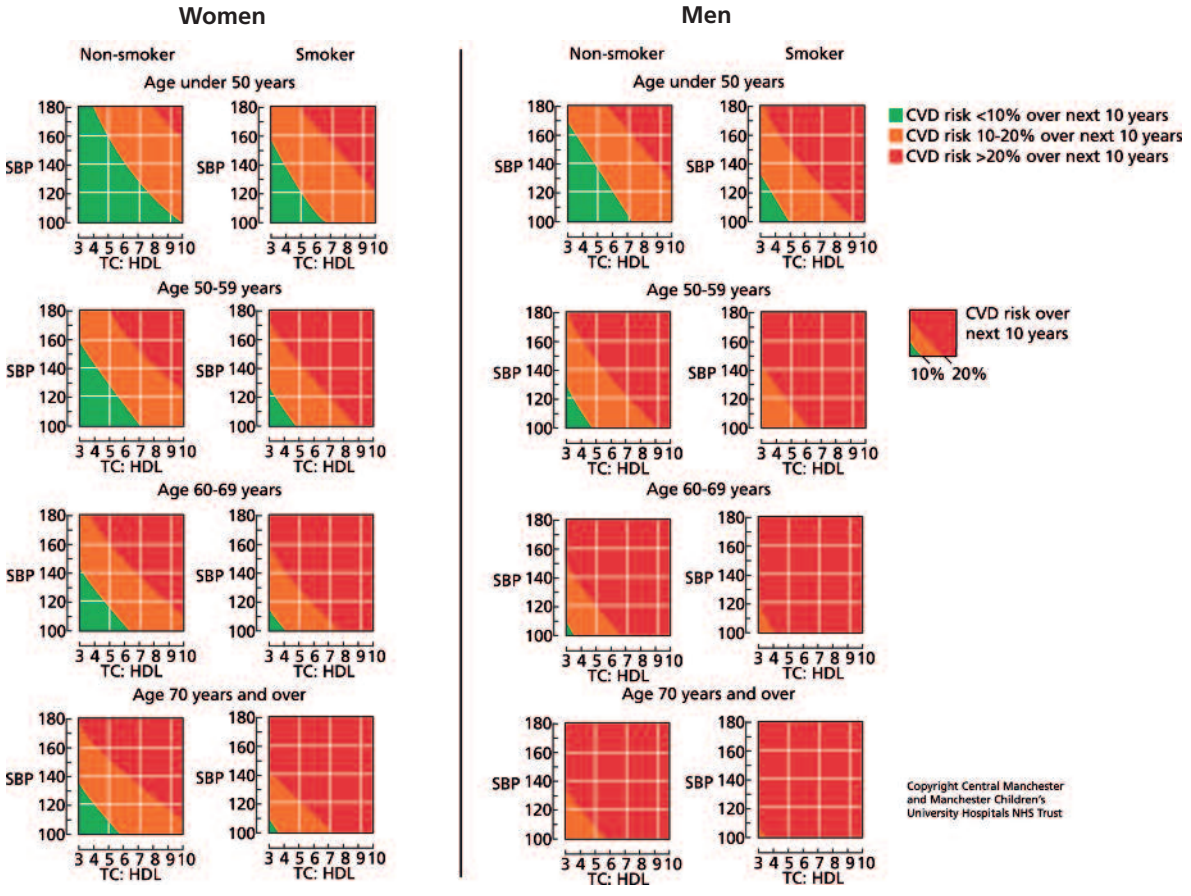
Quantifying cardiovascular risk

Patients with type 2 diabetes benefit from sustained and early intervention for risk factor control; however, treatment interventions are often initiated too late for maximum CVD benefit. Ensuring that we are quantifying risk correctly is crucial to achieving early risk factor control and addressing the residual cardiovascular risk seen in type 2 diabetes patients.

The concept of medical intervention based on estimated total CVD risk in asymptomatic patients is well established both in the UK[41] and internationally.[42,43] Underpinning this are studies such as the Framingham Heart Study, which to date has enrolled three generations of participants to identify the common factors or characteristics that contribute to CVD.[44] These data have enabled researchers to construct multivariate risk prediction algorithms intended to provide an estimate of CHD or CVD risk over a specified time period, generally 10 years.

The second edition of the Joint British Societies' guidelines on cardiovascular disease in clinical practice (JBS-2) uses a risk estimate tool adapted from the equations published from the Framingham study in 1991.[45] The tool estimates total CVD risk (a combined endpoint of CHD, stroke and transient cerebral ischaemia) for an asymptomatic individual from several, well-established risk factors such as age, sex, smoking habit, systolic blood pressure and ratio of total cholesterol to HDL cholesterol. This is then expressed as a probability of developing CVD over 10 years, based on the number of cardiovascular events expected over 10 years in 100 men or women with the same risk factors as the individual being assessed. Charts have subse-

Figure 2. JBS2 CVD risk prediction charts for men and women[41]



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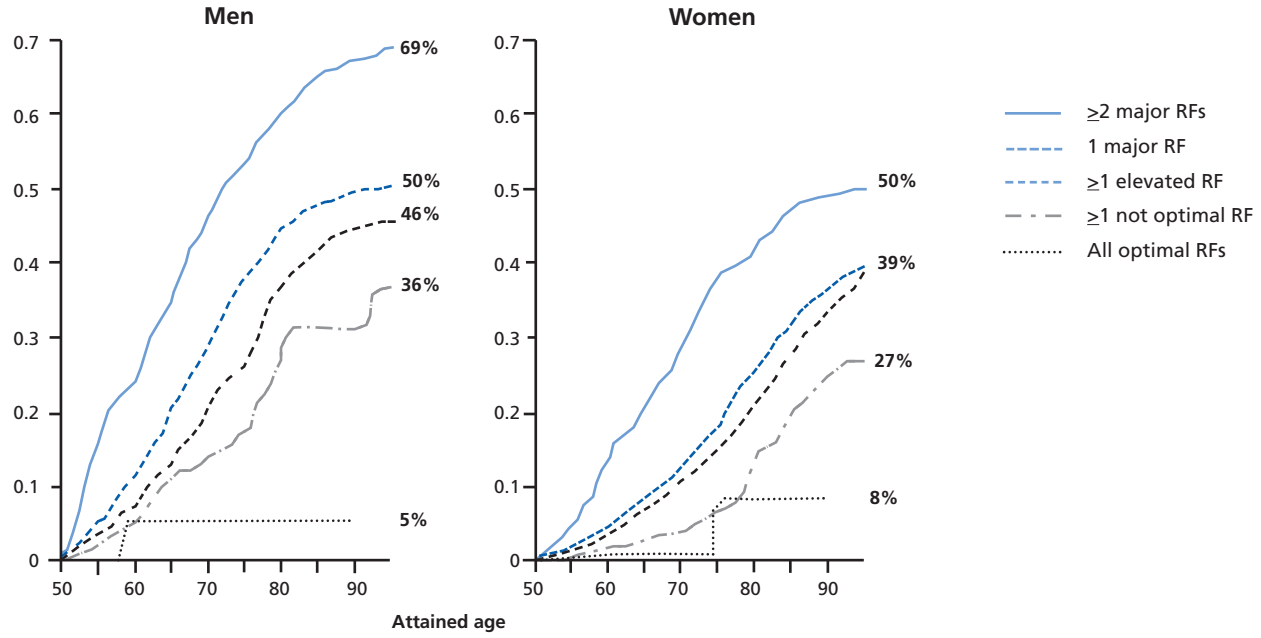
quently been created to easily assess risk based on these factors (Figure 2), and are split into CVD risk categories of ≥10%, ≥20% and ≥30% over 10 years. Asymptomatic individuals with a CVD risk of ≥20% are classified as high risk, with this level being a threshold for treatment with antihypertensive and lipid-lowering therapies. It should be noted that charts have not been created for patients with diabetes, and several studies have suggested that these types of equations considerably underestimate the risk of both cardiovascular disease and mortality in this group.[46,47,48] Guidelines instead recommend all patients with diabetes should be considered high risk and managed to the same lifestyle and defined risk factor targets as individuals with established CVD and others at high 10-year risk of developing CVD.[41]

However, there are well recognised limitations to a 10-year risk metric for the calculation of cardiovascular risk. The 10-year risk metric is dominated by two particular risk factors – chronological age and gender. This fact effectively disenfranchises the middle aged and females, resulting in a delay in initiating treatment until a particular chronological age is reached. Lloyd-Jones and colleagues evaluated data from the Framingham Study to examine the lifetime burden of CVD by traditional risk factor burden at 50 years of age. Participants were stratified into five mutually exclusive categories, as shown in Figure 3, and they found that an absence of risk factors at 50 years of age is associated with a very low lifetime risk for CVD (5.2% for men and 8.2% for women). Conversely, those with two or more major risk factors for CVD at 50 years of age had a markedly higher lifetime risk (68.9% for men and 50.2% for women), and for both men and women the adjusted cumulative incidence curves across risk strata separated early from those without risk factors and continued to diverge throughout the lifespan.[49]

The importance of early risk factor intervention is reinforced by observational data from patients with a nonsense mutation in the gene PCSK9, resulting in lifelong reductions in LDL cholesterol. It was found that in those with the mutation, a 28% lifetime reduction in mean LDL cholesterol translated into an 88 % reduction in the risk of CHD (p=0.08 for the reduction; HR 0.11, 95% CI 0.02–0.81).[50] Moreover, a recent meta-analysis of published data has estimated the effect of long term exposure to lower LDL cholesterol on the risk of CHD mediated by 9 poly-

Figure 3. Remaining lifetime risk for cardiovascular disease in men and women at 50 years of age[49]



Optimal risk factors are defined as total cholesterol <4.65mmol/L (<180mg/dL), blood pressure <120/<80mm Hg, nonsmoker, and nondiabetic. Not optimal risk factors are defined as total cholesterol of 4.65 to 5.15mmol/L (180 to 199mg/dL), systolic blood pressure of 120 to 139mmHg, diastolic blood pressure of 80 to 89mmHg, nonsmoker, and nondiabetic. Elevated risk factors are defined as total cholesterol of 5.16 to 6.19mmol/L (200 to 239mg/dL), systolic blood pressure of 140 to 159mmHg, diastolic blood pressure of 90 to 99mmHg, nonsmoker, and nondiabetic. Major risk factors are defined as total cholesterol ≥6.20mmol/L (≥240mg/dL), systolic blood pressure ≥160mmHg, diastolic blood pressure ≥100mmHg, smoker, and diabetic

morphisms in 6 different genes. Mendelian randomisation studies were combined in this meta-analysis and showed that all 9 polymorphisms were associated with a highly consistent reduction in the risk of CHD per unit lower LDL cholesterol with no evidence of heterogeneity of effect. A meta-analysis combining non-overlapping data from 312,321 participants revealed that naturally random allocation to long-term exposure to lower LDL cholesterol was associated with a 54.5% reduction in the risk of CHD for each mmol lower LDL cholesterol. This represents a three-fold greater reduction in the risk of CHD per unit lower LDL cholesterol than that observed during treatment with a statin started later in life.[51]

It is clear, therefore, that the use of a 10-year risk metric disenfranchises clinicians to control risk factors in younger patients and treatment interventions are often initiated too late for maximum CVD benefit. For this reason, the third edition of the Joint British Societies guidelines (JBS3) is expected to advocate a move from the current 10-year risk score to a lifetime CVD risk calculator. The lifetime risk calculator will tell patients how likely they are to suffer a cardiovascular event at various points in their lives. It is likely that this move to assessing lifetime risk will result in intervention to reduce cardiovascular risk at an earlier stage.

When should we intervene to reduce cardiovascular risk?

In recent years, it has become increasingly clear that despite the impressive gains made through the use of 10-year risk calculators, this approach may give individuals a false sense of security that they are at low risk for CHD when in fact their lifetime risk is high.[52] Indeed, studies from the USA have shown that around 50% of the population are classified as having a low 10-year risk but a high lifetime risk of CVD.[53,54] Those with a low 10-year but high lifetime risk have greater subclinical disease burden and greater incidence of atherosclerotic plaque progression (measured by techniques such as carotid intima-media thickness) compared with individuals with a low 10-year and low lifetime risk, even at younger ages.[53]

However, despite these advantages there are limitations associated with moving to a lifetime risk metric. In contrast to data from Lloyd-Jones and colleagues (Figure 3), a pooled analysis of over 900,000 person years showed high (>30%) lifetime risk estimates for total CVD for all individuals, even those who are middle-aged with optimal risk factors and without diabetes.[55] In addition, a comparison of lifetime risk for individuals with diabetes and stratified by obesity status from the Framingham Heart Study also showed a lifetime risk of CVD among normal-weight men and women with diabetes of 78.6% and 54.8% respectively, increasing to 86.9% and 78.8% among those who were obese.[56] These data must be considered when attempting to define the level at which a patient is considered to be at a high lifetime risk of CVD, particularly in those with type 2 diabetes given its increasing prevalence in young adults. There will also be a significant cost impact associated with developing CVD manage-

ment strategies based on lifetime risk due to both earlier intervention and the potential for a large increase in the number of patients considered at-risk.

In patients with type 2 diabetes, chronic hyperglycaemia often precedes diagnosis by several years, causing extensive vascular damage and leading to the early development of clinical complications. Up to 50% of patients have diabetic complications at diagnosis,[57,58] for example nephropathy and retinopathy are present in approximately 20% of patients.[58,59] These facts provide an imperative to intervene at an earlier stage in type 2 diabetes. This is not limited to improving glycaemic control but to address all modifiable cardiovascular risk factors. Data from patients in the Systolic Hypertension in Europe Trial showed that immediate antihypertensive treatment reduced the occurrence of stroke by 28% (p=0.01) and major cardiovascular events by 15% (p=0.03) compared with delayed treatment.[60] The principle here is that it is not simply the degree of elevation of a risk factor that is important but also the duration of time to which the vascular endothelium is exposed to this insult.

Glycaemic control

There is good evidence that tight glycaemic control improves the risk of microvascular complications in the patients with diabetes, but there is no such consensus in relation to macrovascular disease. Three trials, ACCORD,[61] ADVANCE[62] and VADT[63] investigated the effects of pursuing a more intensive treatment strategy to an HbA_{1c} level of either <6.5% (ADVANCE) or <6% (ACCORD and VADT). None of these trials demonstrated a statistically significant reduction in the primary combined cardiovascular end points. In the ACCORD study, there was a 22% increase in total mortality in the intensive therapy group largely driven by increases in cardiovascular mortality. Whilst there remains the possibility that this increase in mortality may be related to hypoglycaemic events, it has been noted that most of the deaths were amongst patients with poor glycaemic control who were not reaching target, there has been no consensus reached as to the precise cause.

However, a meta-analysis of five studies and over 30,000 patients included data from all three of these studies and found that a more intensive treatment strategy was associated with a significant reduction of incident cardiovascular events and MI (OR 0.89 [0.83-0.95] and 0.86 [0.78-0.93] respectively). Similar reductions were not, however, found for either stroke or cardiovascular mortality (OR 0.93 [0.81-1.07] and 0.98 [0.77-1.23] respectively).[64] Longer term macrovascular benefits also became evident in the 10-year follow-up of the UKPDS as more events occurred, with reductions in the risk of MI and death from any cause in both the sulfonylurea-insulin (RR 0.85 [0.74–0.97] and 0.87 [0.79–0.96] respectively) and metformin groups (RR 0.67 [0.51–0.89] and 0.73 [0.59–0.89]).[65]

Nevertheless, it is clear that not all patients will benefit from pursuing an aggressive strategy for glycaemic control.[36] Consequently, the EASD and ADA have recently released a joint position statement emphasising the importance of individualising glycaemic targets in managing patients with diabetes.[36]

Diabetic dyslipidaemia and cardiovascular risk

Managing dyslipidaemia is an important part of a multifactorial treatment approach in patients with diabetes, as it is a significant independent predictor of CHD and mortality.[66] Patients with type 2 diabetes may have a relatively normal total cholesterol level. However these patients may have an atherogenic dyslipidaemia characterised by elevated TGs, low HDL cholesterol concentrations and small-dense LDL particles.[43,41,67] The formation of small-dense LDL is of particular significance in this population as these particules have been shown to be the major determinant of the serum concentration of glycated ApoB.[68] Both small-dense LDL and glycation of LDL are associated with an increase in susceptibility to oxidative modification,[69,70,71] promoting its rapid uptake by macrophages to create foam cells central to the atherosclerotic process. In addition, patients often show elevated ApoB (reference range 55-140mg/dL in men and 55-125mg/dL in women) and non-HDL cholesterol concentrations. The risk associated with atherogenic dyslipidaemia is uncorrelated with, and additive to, that of the LDL cholesterol concentration alone.[67]

Extensive evidence shows that in diabetic patients, elevated TGs, low HDL cholesterol and ApoB are predictors for macrovascular complications such as CVD; and this relationship is independent of LDL cholesterol.[67,72,73,74,75] Non-fasting TG levels, measured 2–4 hours post-prandially, may be of even greater relevance to CVD risk since atherogenic lipoprotein remains, secreted by the liver and intestine after food, circulates in higher concentrations than when fasting.[76,77] Though LDL cholesterol levels in persons with diabetes tend not to be higher than those of persons matched for age, sex and body weight, the LDL particles are more numerous as they are smaller and more dense (depleted of cholesterol) than in the general population.[43] As each atherogenic particle such as LDL carries one molecule of ApoB, the ApoB concentration is often increased and has been shown as a better predictor for CHD risk than LDL cholesterol.[67] Non-HDL cholesterol reflects the combined cardiovascular risk of all changes in ApoB-containing lipoproteins in diabetes, and as such has also been found to be be a strong predictor for cardiovascular risk,[78] particularly in patients with diabetes.[79] The measurement and use of non-HDL as a therapeutic goal may therefore be of particular clinical utility in this population.

Dyslipidaemia is also implicated in the pathogenesis of diabetic microvascular disease.[80] Elevated levels of total and LDL cholesterol,[81,82,83] and high TGs83 may have causative roles in the development of retinal hard exudates and diabetic maculopathy. High TGs have also been linked with an increased risk for proliferative diabetic retinopathy.[84] The DCCT/EDIC study found the severity of retinopathy was positively associated with TGs and negatively associated with HDL cholesterol levels in all patients, and with ApoB and LDL levels in men.[85] Data from the UKPDS showed that elevated TGs are independently associated with incident microalbuminaemia (HR 1.13, 95% CI 1.07–1.19) and macroalbuminaemia (HR 1.19, 95% CI 1.11–1.27), both markers of nephropathy.[86] In addition, atherogenic lipid abnormalities have been implicated in the development of diabetic nephropathy.[87,88]

Despite the presence of other lipid abnormalities in atherogenic dyslipidaemia, there is evidence that reductions in LDL cholesterol levels with statins are of benefit in patients with type 2 diabetes. The HPS study investigated the effect on vascular mortality of a substantial LDL reduction among 5,963 patients with diabetes, and found that use of simvastatin was associated with a 22% reduction in the relative risk of vascular events.[89] These results were reflected in the CARDS study, which found a rate reduction of 37% for major cardiovascular events in the atorvastatin group.[90] A meta-analysis of 18,686 patients across 14 statin trials (21.7% of all participants) subsequently confirmed the benefits of statin treatment, with each 1mmol/L reduction in LDL levels associated with a 9% reduction in all-cause mortality, 13% reduction in vascular mortality, 21% reduction in major vascular events, 22% reduction in MI or coronary death, 25% reduction in coronary revascularisation and 21% reduction in stroke.[91]

It is clear from extensive large scale clinical trials that statin therapy is of benefit for people with diabetes, and should be considered for all diabetic individuals who are at sufficiently high risk of cardiovascular events[91] yet, despite reductions in event rates, a large residual macrovascular risk remains.[89,90,91] The reasons behind this excessive residual risk are unknown; however, it is postulated to be either the result of an underestimate of the benefits of long-term LDL lowering strategy as survival and event curves continue to diverge, or that it is not possible to further reduce risk through LDL lowering and the excess risk is instead a result of other factors such as the high TG and low HDL cholesterol levels seen in the atherogenic dyslipidaemia common in patients with diabetes.

Pharmacological interventions to reduce cardiovascular risk

The investigation of agents as add-on therapies to statin treatment to reduce cardiovascular risk may help to determine the cause of this excess risk, and several clinical trials have investigated – or are investigating – the use of existing agents such as nicotinic acid, as well as ongoing trials of novel molecules to treat dyslipidaemia in high-risk patients.

One of the more significant developments in recent times has been the undermining of the role of HDL as a suitable therapeutic target for cardiovascular risk reduction. Whilst the plasma HDL concentration remains a significant risk predictor and an essential component of patient diagnosis and risk evaluation, the central role HDL plays as a causal mediator in atherogenesis has been called into question.

Large scale Mendelian randomisation studies of both common and rare genetic variants that alter HDL concentration[92,93,94,95] show no relationship with clinical events, in marked contrast to the strong and consistent relationship seen with similar genetic variants affecting LDL concentrations.[54] The strengths and weaknesses of using studies of this type to determine causal mechanisms have been debated,[96] however it is argued that, if genetic variants determining HDL concentrations are not themselves independently associated with clinical outcomes, then HDL concentration in isolation is unlikely to be a direct cause of clinical events. Instead, HDL may be a surrogate marker of other, more fundamentally causal particles.

Recent clinical trials into therapeutic interventions to alter HDL concentration reinforce these findings. The use of nicotinic acid as an add-on to statin therapy was investigated in two large scale trials – the AIM-HIGH trial[97] and the recently published HPS2-THRIVE.[89,98] Both of these studies showed that adding nicotinic acid to raise HDL levels had no impact on clinical outcomes. Whilst the AIM-HIGH trial could be criticised for being insufficiently powered to detect clinical events, the results of HPS2-THRIVE are considered more definitive and are likely to bring to an end the use of niacin as a therapeutic agent to reduce cardiovascular risk. On a cautionary note, however, it should be noted that, while AIM-HIGH used an extended-release nicotinic acid preparation (Niaspan), HPS2-THRIVE used a combination of extended-release nicotinic acid with laropiprant, an anti-flushing agent and prostaglandin D-inhibitor. It is assumed that both of these agents are equivalent, yet there remains the possibility that off-target effects of laropiprant confounded the results.

Inhibition of CETP has been shown to have the potential to impact the lipid content and concentration of all lipoprotein factions, notably with significant increases in HDL concentration. However the development of two CETP inhibitors, torcetrapib and dalcetrapib, was terminated following Phase III trials showing, respectively, an increase in total mortality and a lack of clinical efficacy.[99,100] The problem with interpreting these clinical data is that the HDL particle is considered to have several independent functional characteristics such as reverse cholesterol transport and an anti-oxidant effect, and therefore merely measuring the HDL concentration may not be sufficient without more sophisticated functional assays.[101]

Novel molecules in development may provide additional options for this patient group. Two further CETP inhibitors, anacetrapib and evacetrapib, are currently in clinical development and in addition to their activity to raise HDL levels also reduce LDL over and above statin therapy.[102,103] The ongoing phase III REVEAL and ACCELERATE studies will determine whether this class of agents is able to reduce the risk of major coronary events in patients with established vascular disease,[104,105] and in light of recent evidence, it appears unlikely that any additional risk reduction observed will be able to be attributed to their effect on HDL levels.

The insulin-sensitising properties of PPAR-γ agonists in patients with diabetes are well-established following the development of the thiazolidinediones pioglitazone and rosiglitazone, and the PPAR-α agonists such as fibrates have been shown to decrease TG levels, increase HDL levels and reduce LDL levels.[43,106] Efforts have been made to combine these effects in a dual PPAR-α/γ agonist to effectively manage both glycaemic control and dyslipidaemia. However, several attempts to develop a dual PPAR agonist for diabetes have as yet been unsuccessful due to various safety concerns including renal dysfunction,[107] bladder cancer[108] and an increase in mortality and cardiovascular

Key messages

- CVD remains a significant healthcare burden in the UK and worldwide, and there is a substantial residual risk of CVD and microvascular disease in patients with type 2 diabetes even when receiving optimal therapy according to best standards of care
- Guidelines advocate the use of 10-year cardiovascular risk calculators, however these have recognised limitations and a move to lifetime cardiovascular risk calculators is likely to be advocated in the future
- The move to assessing lifetime risk should encourage intervention to at a much earlier stage, and alongside aggressive and broad control of modifiable risk factors looks to ease the burden of atherosclerosis prior to the manifestations of CVD
- Patients with type 2 diabetes will benefit most from this approach, and due to the atherogenic dyslipidaemia common in this patient group will also benefit from existing or novel treatment strategies under investigation to potentially further reduce residual cardiovascular and microvascular risk

events.[109] The latest dual PPAR-α/γ agonist in development was aleglitazar, which had been shown to decrease TGs and LDL, and raise HDL alongside insulin-sensitising properties.[110] However following an interim routine safety review the phase III ALECARDIO study was terminated due to safety concerns and a lack of efficacy.[111] It is expected that this will spell the end of development of this class of molecules, however a SPPARM-α known as K-877 remains under development and has been shown to have a more potent effect on triglycerides and HDL-C levels than fibrates with a reduced risk of adverse events. K-877 is currently in the early stage of clinical development, but if successful has the potential to supersede fibrates in the treatment of atherogenic dyslipidaemia.[112]

Conclusions

Despite impressive advances in its treatment, CVD remains a significant healthcare burden in the UK and worldwide. The clustering of cardiovascular risk factors often seen in patients with type 2 diabetes underlines the necessity of our current multifactorial treatment approach, yet even when receiving optimal therapy according to best standards of care, there remains a substantial residual risk of CVD and microvascular disease in this population. The move from 10-year to lifetime cardiovascular risk calculators should encourage intervention to reduce cardiovascular risk at a much earlier stage, and its proposal alongside aggressive and broad control of modifiable risk factors aims to ease the burden of atherosclerosis prior to the manifestations of CVD. This approach will be of particular benefit to patients with type 2 diabetes, who have been exposed to hyperglycaemia and other risk factors for several years prior to diagnosis and consequently have developed complications pre diagnosis. The atherogenic dyslipidaemia common in this patient group also ensures they will benefit most from existing or novel treatment strategies currently under investigation to potentially further reduce residual cardiovascular and microvascular risk.

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