UK National Screening Committee

University of Leicester

UPDATED
The Handbook for Vascular Risk Assessment, Risk Reduction and Risk Management

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Foreword

It is always satisfying to run out of hard copies of a publication and be asked to print more or even better, update it with the latest evidence. In 2006 the UK NSC recommended the introduction of a Vascular Risk Management Programme. In order to support the implementation of the programme, the UK NSC commissioned the Handbook of Vascular Risk Assessment, Risk Reduction and Risk Management. The handbook brought together in one place information on the current state of knowledge about vascular risk assessment, risk reduction and risk management. It was designed to be comprehensive, giving an overview of the latest state of knowledge. The handbook reviewed the clinical context and the available evidence in relation to risk assessment for cardiovascular disease, diabetes and chronic kidney disease. These diseases manifest themselves in very different ways, but they share the same set of risk factors: poor diet, obesity, lack of physical activity, high blood pressure and smoking. And the risk factors interrelate with each other - somebody with diabetes is at much higher risk of developing heart disease than someone without it.

The handbook was the product of great deal of dedicated hard work by Professor Melanie Davies and her team of colleagues at the University of Leicester. I am now pleased to present this Update to the Handbook prepared by the same team in Leicester. It is designed to be read in conjunction with the original document and we hope that it will continue to be an invaluable resource for the healthcare and public health community. Implementation of Vascular Risk Management programmes are proceeding across the UK and clinical and commissioning colleagues should find this evidence update a practical resource to support their ongoing work.

I look forward to being asked to update the update in a few years time!

Dr Anne Mackie

Director of Programmes
UK National Screening Committee

Remit of the Handbook

- To update sections of the handbook including Vascular Risk Assessment, Risk Reduction and Risk Management
- Review new evidence available in the intervening period since the original handbook was released
- Highlight updated national guidelines relevant to the conditions described in this handbook
- Describe the context and outline evidence for a coordinated vascular disease control programme to identify and reduce risks of vascular disease in the population
- Suggest aims, objectives and a delivery strategy framework appropriate for a vascular disease risk management programme

The original handbook (2008), commissioned by the UK National Screening Committee available online at www.screening.nhs.uk/vascular

Introduction

The UK National Screening Committee (NSC) has commissioned an update to the Handbook of Vascular Risk Assessment, Risk Reduction and Risk Management[1], which was originally published in 2008. The evidence base for the components of a vascular risk programme is continually changing and new topics are regularly being proposed for inclusion. Throughout this report, the term vascular disease is used to include:

- Coronary Heart Disease (CHD)
- Cardiovascular Disease (CVD)
- Stroke
- Transient Ischemic Attack (TIA)
- Peripheral Arterial Disease (PAD)
- Chronic Kidney Disease (CKD)
- Type 2 Diabetes Mellitus (T2DM)

The following sections have been updated by reviewing the evidence available up to November 2011:

- CVD Risk Assessment
- CKD
- Hyperglycaemia (Non-diabetic hyperglyceamia (NDH) & T2DM)
- Hypertension
- Hyperlipidaemia
- Other vascular disease risk factors

The updates address certain areas including methods of prevention, early disease detection, diagnosis or management (and their limitations), of vascular disease.

This updated version of the handbook should be used in conjunction with the original Handbook of Vascular Risk Assessment, Risk Reduction and Risk Management. Supporting information and the wider implications of a vascular risk programme has already been discussed in the original handbook (version 1). For further information, please refer to Part 1 Section 4 (Implications and Public Health Perspective), Part 2 Section 1 (Implementation of Vascular Risk Assessment Programme; Broad Overview) and Part 2 Appendix and Standard Operating Procedures in the original handbook, page 55-145.

Background

The World Health Organisation (WHO) defines a disease control programme as 'the co-ordination of disease prevention, screening and early detection, as well as disease management' (Fig. 1, page. 6).

Several international organisations have highlighted the need for a coordinated vascular disease control programme to integrate prevention, screening, early detection and management for CHD, stroke, TIA, PAD, T2DM and CKD. These conditions overlap considerably and often have similar risk factors. In recent years, such a control programme has been championed by the Joint British Society Guidelines Group (JBS 2) in their report on prevention of cardiovascular disease in clinical practice[2], the Scottish Intercollegiate Guidelines Network (SIGN) in their guidelines on risk estimation and the prevention of cardiovascular disease[3], in addition to the National Institute for Health and Clinical Excellence (NICE) in a recently re-issued lipid only clinical guideline[4] and are currently in the process of updating the guideline on secondary prevention of cardiovascular disease.

In England, the NHS Health Check programme (formerly known as 'vascular checks') is an initiative offering checks to all those aged between 40 - 74 with the aim of assessing individual risk of vascular disease followed, where appropriate, by risk management including lifestyle and therapeutic interventions (Fig. 2, page. 7).

Proposals for the programme were originally set out in 2008 with the publication of 'Putting Prevention First'[5], which aimed to ensure a greater focus on the prevention of vascular disease and a reduction in health inequalities. Implementation of this programme began in 2009 with publication of the NHS Health Check 'Best Practice Guidance'[6].

Countries outside of England have translated key elements of the vascular risk assessment and management programme in accordance with local evidence. These countries are applying similar implementation plans within their own healthcare systems which combine primary, secondary and tertiary care[7-9].

Risk Surveillance

- ➔ To reduce future risk of vascular disease
- ➔ To ensure that all communities have equal access to an appropriate vascular risk assessment adjusted according to ethnic group and socio-economic status. This should include strategies to engage communities who may otherwise decline routine screening, prevention advice or disease management opportunities
- ➔ To ensure that all potential interventions (including those for single/multiple risk factors or for existing vascular disease) are delivered in simple terms relative to the individual's understanding. Delivery of healthcare should utilise resources available and account for any potential barriers

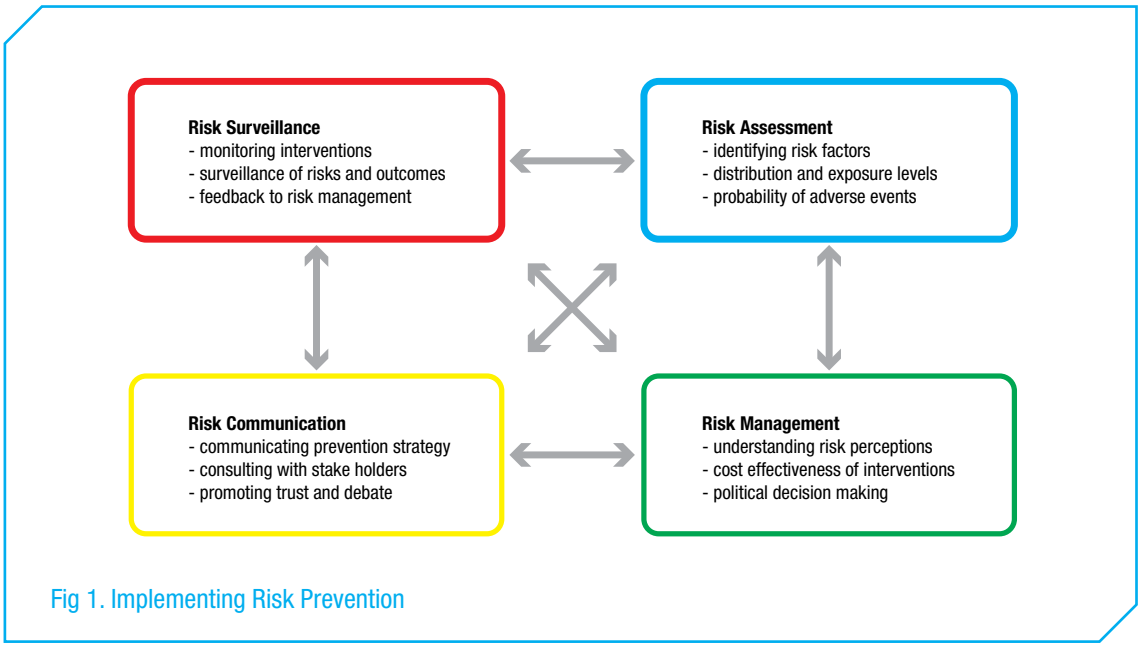

Fig 1. Implementing Risk Prevention

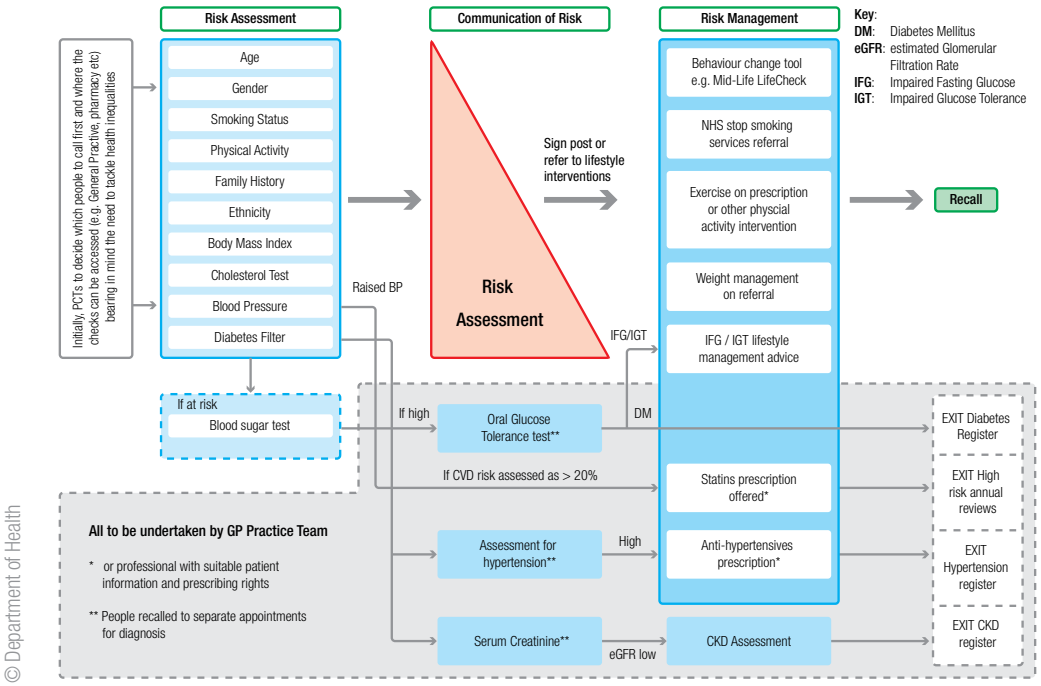

Fig 2. Vascular Checks Programme

Risk Assessment

- To offer adults access to an individual risk assessment through a number of different validated strategies
- To promote healthy lifestyle advice focusing on potential benefits of reducing vascular disease risk
- To detect undiagnosed T2DM facilitating early implementation of prevention strategies (including screening for eye, kidney and foot complications) and vascular disease intervention at a lower threshold

Risk Communication

- To offer all adults undergoing a risk assessment, appropriate feedback of the results with subsequent care planning (i.e. to simply and effectively communicate their current risk of vascular disease)
- To agree an action plan designed to reduce risk of incident vascular disease

Risk Management

- To integrate activities of the programme with primary prevention activities in the general population
- To ensure individuals with existing vascular disease are offered optimal secondary prevention measures in-line with current NHS standards
- To ensure those identified as high risk of T2DM are offered appropriate diagnostic testing delivered according to agreed Standard Operating Procedures (SOPs)
- To ensure level of health care delivered is re-assessed together with ongoing programme surveillance and its performance
- To ensure that there is clear guidance from SOPs for the implementation of vascular risk assessment
- To ensure the overall programme addresses potential inequalities in healthcare
- To ensure the optimal integration of these policies with existing systems and initiatives, for example Quality and Outcomes Framework (QOF), to avoid duplication and unnecessary testing and/or assessment

Health Inequalities

Although people are living longer overall, the long-term trends show that the gap in mortality between the professional (social class I) and unskilled manual (social class V) groups has increased by two and a half times in the last 60 years[10]. Unemployed men are four times as likely to classify themselves as being in bad health as those in the top social class[11] and the geographical variation in health inequalities can largely be explained by deprivation[12].

Any programme must consider its impact on, and aim to minimise, health inequalities. An example of a potential impact on health inequalities is the choice of the use of the CVD Risk Assessment tool, as there is evidence that use of conventional CVD risk calculators based on the Framingham data tend to overestimate CVD risk in low prevalence populations and underestimate it in those at highest risk[13,14]. This is of particular relevance to the South Asian population and other BME groups living in the UK and all those living in deprived areas. Those at highest baseline risk as defined by ethnicity or socio-economic circumstances are less likely to access or benefit from screening and early treatment, thus potentially leading to increasing inequalities[15]. One approach is to develop a CVD risk score which takes account of social deprivation and uses FH as a proxy for the impact of ethnicity. The relative merits of CVD risk assessment tools are discussed further in Section 1.

It will be important to ensure that certain, already higher risk groups (for example those from South Asian groups or from deprived areas) respond to invitations for screening, otherwise this approach may inadvertently widen health inequalities. Practices need to guard against this by monitoring uptake and where uptake is low but risk/need is high they will need to use other approaches to improve uptake in these groups/geographical areas. This may require more innovative approaches with full use of the multi disciplinary team, social services and community facilities.

There is potential to use routine information sources and audit data to target resources in communities at higher risk in order to reduce inequalities as well as reduce the overall burden of cardiovascular disease.

This requires commissioners to:

- ➔ Identify communities and population groups at increased risk of cardiovascular disease and diabetes
- ➔ Raise local awareness of the potential to reduce risk through both population-wide initiatives (physical activity, healthy eating, smoking cessation) and individual risk assessment and clinical intervention (management of hypertension, lipids, diabetes)
- ➔ Target support for general practices with the greatest unmet need for risk reduction
- ➔ Use routine clinical management data to target treatment, for example look at QOF CHD scores verses CHD mortality rates to identify practices who appear to be providing below standard care. This may highlight practices with the most scope for improvement and allow targeted use of financial incentives provided by QOF

Communication of Risk

All patients should expect to be given targeted and individualised advice about what they can do to reduce their own risk rather than the all or nothing concept of a positive or negative result. The terminology needs to be clear. Rather than “screening” one should use “risk assessment” and “risk reduction”. There is also a need to manage patient expectation to avoid increasing dissatisfaction and the recognition that many patients expect blood tests as part of their assessment process. This is particularly pertinent to blood glucose testing where a ‘negative’ test result for diabetes itself may not be helpful to exclude those at high future risk of DM and vascular disease.

In communicating risk the key factors are:

- ➔ Communicating the continuum of risk
- ➔ Patient centred decision support
- ➔ Standardisation of measurement and recording of risk factors

Risk assessment involves identifying and recording risk factors. Within primary care this may be carried out by a number of individuals and therefore standardising how these are measured and recorded is a priority. Patients may have their blood pressure, weight, height, family history, smoking and alcohol status recorded without any communication as to the reasons why this has been done and yet the act of doing so can be regarded by some patients as receiving good care.

Risk communication is defined as 'the open, two-way exchange of information and opinion about risk, leading to better decisions about clinical management'[16]. Discussing risk with patients in the clinical consultation has become increasingly important. Patients who are better informed and involved in decisions about their own care are more knowledgeable and also more likely to adhere to their chosen treatment plan[16,17]. Patients' values and preferences vary widely, as do their attitudes to risk. A two-way exchange of information is therefore important to explore the patient's personal beliefs to facilitate treatment decisions. It is possible for the healthcare professional to record risk factors, calculate risk scores and prescribe appropriate treatment without involving the patient in the decision-making process. Our aim should be to create a system where decision support is patient-centred and focused towards increasing patient understanding, and allow patients to use this to their best advantage.

It is increasingly apparent that most risk factors have a continuous relationship to risk of CVD and therefore it is important to move away from using the "all or nothing" or "positive or negative" concept when talking to our patients, but talk in terms of risk and risk reduction. Although some research has looked at issues of risk communication in the areas of CVD and other areas of health, there is still much to be learned. Changes in attitude or behaviour mainly occur when the individual or group identify with the threat, and people's perception of risk may be inaccurate and influenced by dramatic or sensational causes, e.g. with media coverage.

Risk perceptions are socially constructed, and individual behaviours are driven by perception, or beliefs about risks, and not with the technical risk estimates provided by healthcare professionals. Clinicians need to support patients in making choices by turning raw data into information that can be used to aid discussion of risk. Decision aids are one way of facilitating this process. Decision aids are systematically developed tools to aid patients to understand and participate in medical decisions. Decision aids often include visual representations of risk information and relate this information to more familiar risks. There is, however, very little evidence of the effectiveness of these aids in communicating risk in patients at high cardiovascular risk[18].

Everyone is at risk

If people are not in a high risk category, it does not mean they have no risk - just a lesser risk. All will be able to reduce whatever risk they have by relevant changes in lifestyle.

Key messages are:

- ➔ stop smoking if you smoke
- ➔ eat a healthy diet
- ➔ keep your weight and waist in check
- ➔ take regular physical activity
- ➔ cut back if you drink a lot of alcohol

Key points

- ➔ Everyone is at risk of CVD, even those with no apparent risk factors
- ➔ Most risk factors have a continuous relationship to risk of CVD and therefore it is important to move away from using the "all or nothing" or "positive or negative" concept when talking to patients. Instead talk in terms of risk and risk reduction
- ➔ Risk factors can be reduced by following lifestyle advice e.g. exercising, healthy diet, reducing alcohol consumption
- ➔ A Vascular Risk programme must consider its impact on, and aim to minimise health inequalities
- ➔ It is important to ensure that higher risk groups (for example South Asians or those from deprived areas) respond to invitations, otherwise this may inadvertently widen health inequalities. Uptake should be monitored and where it is low, other approaches will be needed to improve uptake

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SECTION 1: Cardiovascular Risk Assessment

Overview of UK guidelines for CVD risk assessment

Cardiovascular disease (CVD) is a collective term for disorders affecting the heart and blood vessels[1]. Common examples include CHD, cerebrovascular disease (stroke), CKD and PAD. Primary prevention of CVD is recommended for those over 40 with a 10-year risk of developing symptomatic atherosclerotic disease of at least 20%[2,3].

UK guidance broadly endorses the use of validated CVD risk assessment tools to achieve this, without specifically identifying preferred risk equation(s). This lack of consensus is largely a reflection of known population variation in CVD risk frequency and the inevitable lack of validation data within most populations. For example, the Scottish Intercollegiate Guidelines Network (SIGN) recommend ASSIGN[4,5], which has been specifically developed for use in the Scottish population. NICE Guidelines for England and Wales are less prescriptive[3], recommending practitioners should have the power to adopt tools likely to predict CVD risk in the population they serve.

NICE continues to define those at high risk as those possessing a total 10-year risk of developing CVD of ≥20%. Those identified as high risk should be offered appropriate risk-lowering intervention(s), such as lifestyle modification and pharmacotherapy targeting blood pressure reduction, lipid modification and improved glycaemic control[2,3,5,6]. Some patient groups are automatically categorised as high risk and CVD risk assessment using validated risk assessment tools is inappropriate for such individuals. High risk patient groups include those[2, 3]:

- ➔ Over the age of 75
- ➔ With pre-existing CVD
- ➔ With a family history of premature CVD
- ➔ With familial hypercholesterolaemia
- ➔ With T2DM
- ➔ With CKD

Clinical judgement remains a key feature of CVD risk assessment irrespective of the adopted tool as known contributors (eg. abdominal obesity and impaired glucose regulation) may not be factored into all risk estimates.

Overview of CVD risk assessment scores

The original handbook acknowledged the dynamic nature of this field and the expanding number of CVD risk assessment tools available. As indicated, all of these tools are highly dependent upon local population characteristics and the nature of routinely collected CVD risk data.

Potential Risk Scores

The Framingham equations

The Framingham Heart Study, established in 1948, is a large observational study aiming to determine the epidemiological causes of CVD[7]. Amongst various risk scores developed from the Framingham Study data is the "General CVD (10-year risk) profile"[8]. This multivariable risk assessment tool predicts absolute CVD risk (over a 10-year period) from the following variables: age, sex, treated- and untreated-systolic blood pressure, total cholesterol, HDL cholesterol, smoking status and presence of diabetes. Framingham estimates have tended to over-estimate risk in low risk populations and under-estimate it in high risk populations[8]. This may in part be the result of evolving risk factor frequencies (e.g. obesity and smoking status) together with often unpredictable effects of new treatments for existing risk factors and CVD itself. Under prediction has been shown to be particularly likely in people with diabetes or a significant family history of premature CVD[9]. Potentially important risk factors have emerged since the cohort began which are not included in the Framingham equations. These include family history, body mass index (BMI), the metabolic syndrome, socioeconomic status and physical inactivity. NICE recommends adjustments when using the Framingham equation when the following risk factors are present; South Asian origin, severe obesity (>40kg/m^2), and family history of CVD[3].

QRISK 1 and 2

QRISK is a British CVD risk assessment tool introduced in 2008[10-12]. QRISK is the first score to use electronic health records to produce a continuously updatable prediction algorithm. The first model included the following variables: age, sex, smoking status, systolic blood pressure, total serum cholesterol/high density lipoprotein cholesterol, BMI, premature family history, social deprivation and anti-hypertensive medication. This model has demonstrated marked reductions

in the over-estimation of CVD mortality in comparison to Framingham. A revised model (QRISK II) includes the contributions of an increased number of variables incorporating self-assigned ethnicity and chronic kidney disease[12].

QRISK has number of advantages over Framingham. Importantly, it includes independent contributions of ethnicity and deprivation, as well as an improved quantification of risk for people with T2DM. The equation also accounts for anti-hypertensive treatment and through sophisticated modeling techniques allows for differing effects of risk factors associated with increasing age.

A major drawback of QRISK is missing data which may undermine confidence in its predictive capacity. However, further use will improve the accuracy of the algorithm and it undoubtedly reflects current UK population demographics. It may therefore become the CVD risk assessment method of choice in England[13,14].

Assessing cardiovascular risk using SIGN guidelines to ASSIGN preventive treatment (ASSIGN)

The ASSIGN score is recommended by SIGN guidelines for cardiovascular risk assessment[4,15]. The score was developed within Scotland and performs favourably compared with Framingham and QRISK within this population[11]. It is derived from cardiovascular outcomes from the Scottish Heart Health Extended Cohort (SHHEC) and later by the 2003 Scottish Health Survey. The variables included are similar to that of Framingham but include family history and social deprivation. This risk score has yet to be validated in an independent cohort and is confined to a relatively limited geographical area. It correctly identifies a greater proportion of people who are socially deprived and with a positive family history, theoretically abolishing the effects of social gradient on CVD risk. However, this score once again appears to over-estimate 10 year CVD risk, with a similar incidence as Framingham[4].

Systematic COronary Risk Evaluation (SCORE)
The SCORE system is based on a large dataset of 205,000 cases derived from twelve European cohort studies[16]. The score is based on five routinely available variables (sex, age, smoking status, systolic blood pressure and either total cholesterol or cholesterol/HDL ratio) and predicts only the risk of fatal events. This diverse cohort is potentially highly representative of a contemporary British population. However, it has once again been shown to over-estimate death rates[16].

United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine

The UKPDS risk engine is based on 53,000 patient years of data from the UKPDS study[17]. Estimation of fatal CVD and CHD risk using the Framingham score is not reliable in the T2DM population[18]. This may be due to a relatively small number of people with diabetes within the Framingham study together with lack of consideration of diabetes and glycaemic control. The UKPDS risk score differs from others in that 'diabetes' is not simply coded as a dichotomous value. Rather age at diagnosis and time since diagnosis are recorded in addition to HbA1c.

ETHRISK

ETHRISK is a web-based tool capable of estimating CVD risk in seven Black and minority ethnic groups and was developed through recalibration of the Framingham risk score. Rates of CVD vary considerably between ethnic groups and this tool was developed to avoid over- or under- definition of 'at risk' status common to other risk scores[19]. Validation of this tool in a prospective cohort study has not yet taken place.

Potential shortcomings of using a CVD risk assessment approach in isolation

There are a number of disadvantages of using a CVD risk assessment tool in isolation:

- ➔ Important risk factors are not included in the Framingham-based risk score as outlined above
- ➔ Treatments will tend to be concentrated in older people and especially in those >70 years unless the potential effect of a lifetime risk factor exposure is taken into account
- ➔ Evidence-based medicine that favours single intervention RCTs as opposed to complex lifestyle interventions that may be effectively offered to patients at a much younger age even though they may not reach 'high vascular risk' thresholds
- ➔ It may increase inequalities unless adjustments are made, for example, in socio-economically deprived and ethnic minority populations

Risk Equation	Variables	Population type and size	Baselines
FRAMINGHAM[8]	Age, sex, treated- and untreated-systolic blood pressure, total cholesterol, HDL cholesterol, smoking status and presence of diabetes	3,969 men and 4,522 women; general population, Framingham, Mass, U.S. Volunteer	1968 - 1971, 1971 - 1975, 1984 - 1987
QRISK2[10-12]	Age, gender, current smoker, premature family heart disease, treatment for hypertension, social deprivation, BMI, systolic blood pressure, total and HDL-cholesterol, ethnicity, rheumatoid arthritis, chronic kidney disease, atrial fibrillation	2.29 million; health records of general practic Attendees in the UK - not random	1993 - 2008
ASSIGN[4]	Sex, age, total cholesterol or total cholesterol/ HDL-cholesterol ratio, Systolic blood pressure, smoking status	117,098 men and 88,080 women; majority random samples from general population, some occupational cohorts	1984 -1987
SCORE[16]	Sex, age, total cholesterol or total cholesterol/ HDL-cholesterol ratio, Systolic blood pressure, smoking status	117,098 men and 88,080 women; majority random samples from general population, some occupational cohorts	1972 - 1991
UKPDS Risk Engine[17]	Age, sex, ethnicity, smoking status, presence or absence of atrial fibrillation and levels of HbA1c, systolic blood pressure, total cholesterol and HDL-cholesterol	5,102 people with type 2 diabetes; recruited to UK Prospective Diabetes Study	1977-1997
ETHRISK[19]	Ethnicity, gender, age, systolic blood pressure, total cholesterol, HDL-cholesterol, current smoker	3,778 men and 4,544 women; two community-based surveys	1998 - 1999

Table 1. Comparison of CVD risk scores

QRISK-Lifetime

The QRISK-lifetime is the newest validated QRISK model that was designed to estimate lifetime risk of cardiovascular disease[20]. Age is a dominant variable in both of the previous QRISK models which calculate absolute10 year CVD risk and utilise a 20% risk threshold for intervention. A problem arises with younger patients who may score below this threshold due to their age but have a high relative risk of CVD when compared to their peers. The new model addresses this issue by providing an estimated lifetime risk. It measures the cumulative risk of developing CVD in the remainder of the patient's life and includes variables such as ethnicity and social deprivation. The practical effect is that identifying high risk people using Lifetime Risk identifies younger patients with a high lifetime risk who would not otherwise be identified using 10 year risk estimates, as it may be a long time before they do develop CVD.

Overview of Interventions

The Joint British Society Guidelines on the Prevention of Cardiovascular Disease in Clinical Practice is a joint collaboration between the British Cardiovascular Society, British Hypertension Society, Diabetes UK, Heart UK, the Primary Care Cardiovascular Society and the Stroke Association[2]. The aim of these guidelines is to promote a consistent multidisciplinary approach to the management of people with both established CVD and also those at high risk of developing symptomatic atherosclerotic disease.

An emphasis of this guideline is that CVD prevention in clinical practice should focus equally on people, not only with established atherosclerotic CVD or T2DM but also on apparently healthy individuals who are at high risk of developing symptomatic atherosclerotic disease (defined as ≥20% risk over 10 years)[2].

This has been reinforced by guidance from SIGN[5] and more recently from NICE[3]. Lipid modification guidance was revised in 2010 following a decision by NICE Guidance Executive to modify recommendations regarding the choice of equation for assessment of cardiovascular risk.

There is a clear recognition that lifestyle and risk factor intervention including appropriate drug therapies to lower blood pressure, modify lipids and improve glycaemic control are indicated in those at risk. The above guidelines all include clear targets for blood pressure, lipid and lifestyle management in addition to CVD protective drug therapies[2,3,5].

In addition to intervening at an individual level, a wider population level approach is important. Foreseeing the additional benefits of changes in CVD risk factors that can be brought about by intervening at population level, NICE has also published detailed guidance[21]. The details of these recommendations are beyond the scope of this update but are accessible online[21].

Other Considerations

Novel and Emerging Risk factors

Novel risk factors have emerged as a result of improved understanding of pathogenesis of CVD.

Examples include:

- circulating blood or urine biomarkers e.g. C-reactive protein (CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP)
- genetic markers
- non-invasive measurements/ imaging such as carotid intima-media thickness, coronary artery calcification score, pulse wave velocity and ankle brachial pressure index

Risk models based on conventional risk factors fail to correctly categorise up to a quarter of CVD risk[13, 21]. This has led to a growing interest in non-traditional risk factors, which may add to the predictive value of current risk models. Therefore there is the potential to re-classify an individual's risk for CVD (for example those classified as intermediate risk who should be high-risk). This process, known as re-classification metrics, can help assess the potential benefit of adding a novel risk factor to a current prediction model.

CRP and NT-proBNP are extensively studied novel risk factors which are practically favourable in that they may be routinely measured and that robust assays are commercially available for both markers[23]. Although correlations between serum CRP concentration and CVD risk have been demonstrated[24, 25], the evidence does not support the use of CRP concentration as a single risk factor for CVD prediction nor does it significantly increase the predictive capacity of existing CVD risk scores[23, 26]. When used as a single risk factor for predicting CVD risk, a stronger association is demonstrated for NT-proBNP than CRP. Moreover, NT-proBNP concentration significantly increases the predictive capacity of existing CVD risk scores[23].

Interest in incorporating CVD-related genetic polymorphisms into existing CVD risk scores stems from the fact that a family history of CVD is associated with incident CVD[27]. However, in order for such an incorporation to improve the predictive capacity of existing CVD risk scores, candidate genetic markers should be unrelated to conventional risk factors.

Genome-wide association studies (GWAS) have led to the identification of many novel genetic loci related to CVD. In some instances, these are genes with currently unknown effects; presenting a possibility for delineation of a completely novel mechanism for pathogenesis of CVD. The addition of such markers to current risk scores might be expected to appreciably increase their predictive capacity. However, the vast majority of these are genes involved in the control of conventional risk factors, which do not appreciably increase the predictive capacity of CVD risk scores[27].

To date, attempts to integrate CVD-related genetic factors into existing CVD risk scores has not appreciably increased risk prediction[28]. However, it is possible that as more CVD-related genetic markers are identified, this barrier will be overcome. It is also possible that genetic factors account for a lower proportion of familial CVD risk than previously thought, or that many of the currently identified genetic factors are strongly associated to conventional risk factors already accounted for in existing scores[27].

Although novel risk factors are clearly associated with CVD risk, questions remain on their utility (alone or in combination) in increasing the predictive capacity of existing risk scores. Furthermore, their potential impact on clinical decisions, potential harm and cost-effectiveness remain to be determined.

Novel markers must be cost-effective and provide acceptable diagnostic sensitivity and specificity[13]. A perfect risk factor / marker should refine identification of those at risk of disease occurrence or progression; improve prediction of complications of disease, and/ or guide and help tailor responses to different therapies. Until such a novel risk factor is found this largely remains a research area.

Key points

- ➔ There are a number of risk scores used in the UK population; Framingham, QRISK2, UKPDS risk engine, ASSIGN, SCORE, and ETHRISK (table 1). Age, sex, smoking status, total cholesterol, HDL ratio and blood pressure are considered significant risk factors for cardiovascular disease in all individuals
- ➔ There is no current consensus as to which risk assessment tool is superior for the UK population. QRISK2 may become the equation of choice because of the incorporation of social deprivation and ethnicity variables and its capacity to be continuously updated. However, concerns remain regarding the accuracy of the outcome data and validity for use in routine practice
- ➔ At present there is not enough evidence to justify the inclusion of emerging novel risk factors as part of routine CVD risk assessment
- ➔ In general, scores are useful but should be developed in the population in which they will be applied. Some attention should be paid to the addition of non-traditional risk factors relevant to individual populations to form a comprehensive toolkit for CVD risk assessment

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SECTION 2: Hyperglycaemia

Due to inherent overlap, Type 2 Diabetes Mellitus (T2DM) and Non-Diabetic Hyperglycaemia (NDH) are combined in this section.

T2DM is a multifactorial disorder characterised by profound disturbances of carbohydrate and lipid metabolism, resulting in relative insulin deficiency and chronic hyperglycaemia. It is believed that environmental triggers; such as the hypercalorific "Western" diet and sedentary lifestyle, combine with genetic susceptibility, to promote excessive fat deposition, low grade inflammation and a resistance to the physiological effects of insulin.

Common clinical manifestations of this complex pathophysiological process often occur together and include elevated blood glucose, dyslipidemia and hypertension, resulting in the so-called "metabolic syndrome". It is this recognised, and often co-existing, clustering of risk factors which places people with diabetes at risk of specific target organ diseases (complications) as a result of small (microvascular) and large (macrovascular) blood vessel damage[1, 2].

T2DM is at one end of a continuous spectrum with normal glucose control at the opposite end. In between there exists a condition where blood glucose levels are elevated above the normal range but do not satisfy the criteria for T2DM. These intermediate states were originally introduced as a means of identifying glucose cut-offs conferring an increased risk of progression to T2DM, and have been variously referred to as pre-diabetes, intermediate hyperglycaemia, non-diabetic hyperglycaemia or impaired glucose regulation. Lifestyle and pharmacological interventions have been shown to delay progression to T2DM within defined NDH populations[3] and the most abundant data here still relates to Impaired Glucose Tolerance (IGT) range hyperglycaemia[3-6]. An update of diabetes prevention literature is provided at the end of this section and for consistency, the term non-diabetic hyperglycaemia (NDH) is used to indicate WHO defined IGT and Impaired Fasting Glycaemia (IFG) ranges[7].

Diagnosis

The current diagnostic criteria for T2DM as established by the World Health Organisation (WHO) and American Diabetes Association (ADA) are outlined in Table 1[7-9]. Familiar ranges associated with fasting plasma glucose and oral glucose tolerance testing are now accompanied by an additional diagnostic test, glycated haemoglobin HbA1c (see below). Importantly, cut-offs for diabetes based upon fasting and 2-hour post oral glucose tolerance test (OGTT) glucose values are determined by thresholds for the future development of microvascular complications, specifically diabetic retinopathy. Even though CVD, and stroke are major causes of death in patients with T2DM and IGT, macrovascular complications were never considered in the derivation of either classification. Consequently, as the capacity of existing diagnostic criteria to identify patients at the greatest vascular risk is called into question, T2DM screening programmes are increasingly likely to adopt strategies targeting cumulative CVD-risk rather than isolated glucose abnormalities[10]. This philosophy is reflected in the 2008 NSC vascular handbook and will become increasingly pertinent with diagnostic HbA1c testing[11].

Use of HbA1c for diagnosis of Type 2 Diabetes Mellitus

Glycated Haemoglobin, HbA1c, has utility as a diagnostic screening tool as inherent difficulties of glucose sampling are avoided and it has greater pre-analytical stability than other methods[12]. An emphasis on the importance of quickly identifying those at risk of vascular disease[13] appears to be a common goal of the new diagnostic criteria, as HbA1c may be a better predictor of CVD events than FPG or 2 hour plasma glucose[14]. However the selected HbA1c diagnostic thresholds remain based upon onset of prevalent diabetic retinopathy, to align this with chosen cut-offs for glucose-based criteria. There are also logistical advantages associated with using HbA1c for diagnosis. Fasting is not required therefore screening appointments are not limited to the morning, increasing scope for screening. HbA1c is a weighted average of the last two to three months and is therefore less affected by concurrent stress or anxiety, potentially reducing false positive results and random high readings.

The International Federation of Clinical Chemistry (IFCC) led changes to standardise HbA1c laboratory methods in order to reduce variability in HbA1c measurement across the world[15]. For two years dual reporting of both DCCT% and IFCC units were in place in advance of their universal use. This period has now ended, so HbA1c units are expressed using IFCC standards. HbA1c 'point-of-care tests' (near testing) must conform to expert consensus reports on appropriate use and national quality specifications.

Diagnostic Category	Source	Classification mmol/l (mg/dl)
Normal Glucose Regulation (NGR)	WHO (2006)	FPG <6.1 (110) + 2h* PG <7.8 (140)
	ADA (2003)	FPG<5.6 (100)
Impaired Fasting Glucose (IFG)	WHO (2006)	FPG ≥6.1 (110) and <7.0 (126) + 2h PG <7.8 (140)
	ADA (2003)	FPG ≥5.6 (110) and <7.0 (126)
Impaired Glucose Tolerance (IGT)	WHO (2006)	FPG ≤7.0 (126) + 2h PG≥7.8 (140) and <11.1 (200)
Impaired Glucose Homeostasis (IGH) or Impaired Glucose Regulation (IGR)	WHO (2006)	IFG or IGT
	WHO (2011)	HbA1c >42 mmol/mol + HbA1c <48 mmol/mol
	ADA (2010)	HbA1c >39 mmol/mol + HbA1c <48 mmol/mol
Diabetes Mellitus (DM)	WHO (2006)	FPG ≥7.0 (126) or 2h PG ≥11.1 (200)
	ADA (2003)	FPG ≥7.0 (126)
	ADA (2010) & WHO (2011)	HbA1c >48 mmol/mol

Table 1. Diagnostic criteria for Type 2 Diabetes

FPG = fasting plasma glucose; FPG=fasting plasma glucose; 2-h PG=two-hour post-load plasma glucose (1mmol/L=18 mg/dL). IGT can only be diagnosed by OGTT. OGTT is performed in the morning, after 8–14h fast; one blood sample is taken before and one 120 min after intake of 75 g glucose dissolved in 250–300 mL water over 5min (timing is from the beginning of the drink).

The WHO[9] has recently followed the ADA[8] and International Expert Committee[15] consensus 48 mmol/mol as defining T2DM, in addition to previous glucose-based criteria. In the NICE Guidance for risk identification and interventions for individuals at high risk the UK expert group has also recommended this criteria for the diagnosis of HbA1c[11]. It is important to note that a value of less than 48 mmol/mol does not exclude diabetes diagnosed using glucose tests and that the diagnostic use of HbA1c is currently limited to non-pregnant adults with 48 mmol/mol should be confirmed by a follow-up test within an appropriate timeframe (for example two to four weeks). However if typical diabetes symptoms are apparent, the diagnosis of T2DM can be made without the need for repeat testing.

The argument for selecting HbA1c cut-offs for NDH are more complex. NDH has traditionally been defined through fasting and 2-hour post-challenge glucose (see Table 1). Recent statements from an international expert committee and the ADA have recommended that an HbA1c can also be used to identify high risk states at levels of 42 to 48 mmol/mol or 39 to 48 mmol/mol respectively[8,16]. Therefore, these cut-offs form a point where prevention strategies should be initiated. In recently published NICE guidance[11], the UK expert group recommend that individuals with an HbA1c of 42–47 mmol/mol should be classified at high risk of diabetes[2]. The WHO currently states that there is insufficient evidence to make any formal recommendations for NDH on interpretation of HbA1c below 48 mmol/mol[9].

There are potential disadvantages of using HbA1c for diagnosis. HbA1c detects different diabetic populations to those identified utilising glucose criteria. Patients previously detected as having diabetes via glucose testing may now be 're-classifed' as either high risk or even low risk[17]. The degree of 're-classification' varies from one population to another. Furthermore, the degree of discordance in people detected using HbA1c for NDH is larger than that of T2DM[18].

Other clinical considerations include patients with haemoglobinopathies and haemoglobin disorders whose HbA1c values may not reflect true glycaemic status. Similarly, ethnic minority groups appear to have higher HbA1c values independent of glycaemic control[19]. The advantages and disadvantages of glucose and HbA1c tests should be considered by the health care professional before a choice is made.

Early Detection of T2DM and NDH

The significance attached to the prompt diagnosis of T2DM is well-recognised by UK health care providers with widespread implementation of disease specific registers, complication surveillance and vascular risk reduction strategies in established cases. There are however an estimated 850,000 undiagnosed cases of T2DM not currently accessing these services but at risk of premature cardiovascular disease[20]. It is estimated that diagnosis is typically delayed by seven to ten years, by which time 50% of patients already have demonstrable vascular complications[21,22].

There is evidence that earlier identification of T2DM through screening is feasible in general practice and identifies patents at increased and readily modifiable risk of both micro and macrovascular disease[23-26]. Increasingly sophisticated tools are available to identify those at increased risk of T2DM and vascular disease[27,28], whilst economic modelling studies suggest screening is likely to be a cost-effective practice[29,30] with little evidence of detrimental long-term physical or psychological harm[31,32]. It has also been shown that screening simultaneously for both T2DM and NDH, is potentially more cost-effective than screening for T2DM alone[29].

Programmes which screen for T2DM should aim to reduce the prevalence of undiagnosed diabetes and improve long-term outcomes. The recent ADDITION-Europe study (based in UK, Denmark and Holland) showed that screening for diabetes identifies people with a large burden of modifiable cardiovascular risk and that early multifactorial intervention leads to non-significant clinical improvements in composite CVD outcomes[33].

There are three main methods of early detection[34]:

- ➔ utilisation of available demographic, biomedical data and laboratory tests to risk stratify people and determine the likelihood of future incident diabetes
- ➔ introduction of proactive, self-administered questionnaires providing a subjective assessment of diabetes risk
- ➔ measurement of blood glucose or HbA1c to provide definitive evidence of glucose status

A population wide or universal screening strategy attempts to screen all adults in a given population for T2DM.

Data from the US demonstrates screening for T2DM to be cost-effective when started from 45 years of age[30]. It is estimated that approximately 50% of Primary Care Trusts (PCTs) in England are currently actively engaged in population screening[35]. The obvious advantage of this strategy is that it is easy to apply and is highly sensitive at identifying true cases. The disadvantages include the impracticality and likely cost of screening entire populations, given the variability of T2DM prevalence.

Targeted or "stepped" screening focuses upon sub-groups known to be at increased risk of diabetes.

Identification of those "at risk" often utilises information readily available at practice level, such as BMI, family history, smoking status and previous NDH. These data can be combined in a validated risk score for predicting the risk of prevalent diabetes, examples of which are described below.

The ADDITION-Cambridge study showed high response rates of over 70% can be achieved by targeted stepwise screening of high risk individuals by using routine data in general practices[36]. A recent study from the EPIC Norfolk cohort retrospectively compared targeted and population screening[37]. The results demonstrated that a targeted approach, consisting of cardiovascular risk stratification using routine clinical data, is equally effective at identifying high cardiovascular risk and is cheaper than population screening.

The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD) recommend that efficient primary screening for T2DM probably requires a non-invasive risk score combined with a diagnostic oral glucose tolerance testing in people scoring highly[34]. NICE guidance recommend that healthcare professionals undertake a two-stage strategy, initially using a validated risk-assessment score and subsequently either a fasting plasma glucose, HbA1c or an oral glucose tolerance test (OGTT), according to World Health Organization (WHO) criteria[38].

Opportunistic screening or case finding individuals during routine visits to healthcare providers for usual care.

This requires fewer resources to reach individuals and can be performed in either primary or secondary care settings. Data from research studies suggests uptake for systematic screening (e.g. population/ mass screening) of common conditions can be low in the UK, and this may be even more problematic in ethnic minority groups[39]. The obvious theoretical advantage of this approach is time and cost-saving efficiencies. However this approach may have poor coverage of a given population as it will only include those who make contact with the health service. This approach may not be appropriate where early morning fasting screening tests are required (e.g. lipids, fasting glucose). In addition, the majority of patients present to health services because they are unwell and therefore screening tests performed at this time may not give a true reflection of actual risk.

The evidence base behind opportunistic screening is generally lacking. However, isolated studies report the feasibility of this approach in primary care[39]. The Diabscreen study was an opportunistic screening programme for T2DM in patients aged 45-75 years in primary care in the Netherlands[39]. During usual care, physicians achieved stepwise fasting glucose testing in 39% of patients with an initial response rate of 90%. Clearly there are advantages and disadvantages of opportunistic screening and these should be explored further in future research, including long-term cost-benefit analysis.

Risk Scores for T2DM and NDH

Risk scores may offer a structured methodology for identifying those at high risk of either NDH or T2DM. Various non-invasive risk scores have been developed and generally follow one of two approaches, either being applied as questionnaires to the individual being assessed - "self assessment" or as a query to a general practice database where all those "at risk" are identified using routinely collected data. Scores can also be categorised based on the outcome they predict. Scores which have been developed using cross-sectional data can predict prevalent disease in contrast to scores which have been developed using longitudinal data, where incidence can be predicted.

No risk scores have been specifically developed for use in the UK for detecting either prevalent or incident NDH alone; with most scores targeting T2DM and NDH. Here we focus on those scores which have been developed and tested using data from the UK. Studies have found that scores which have been developed elsewhere and used on a different population tend to have low validity[41,42]. Two self-assessment scores have been validated and are widely used within the UK[27, 43].

Finnish Diabetes Risk Score (FINDRISC)

The Finnish Diabetes Risk Score (FINDRISC)[43] is a self-assessment score for predicting the risk of future drug-treated diabetes. The variables collected are: age, BMI, waist circumference, blood pressure, history of high blood glucose, physical activity and diet. This risk score is reliable at predicting future diabetes over a 10-year period. A revised version of FINDRISC incorporates age categories, and family history of diabetes[44].

Validation using a UK-based dataset (Whitehall II study of civil servants in London) gave a lower area under the ROC curve, 0.67 (95% confidence interval 0.62 to 0.72), compared to the validation on the population the score was derived from[40].

Although the FINDRISC was designed to predict future diabetes risk, it has proved to be a reasonably reliable method of identifying any degree of abnormal glucose tolerance (including diabetes, IGT and IFG[45]), insulin resistance[4] and indeed progression from NDH to T2DM. The FINDRISC can be found at www.diabetes.fi/english/risktest. Although the FINDRISC has been extensively validated[46] and is widely used it does not take into account ethnicity and therefore may under-predict risk in a multiethnic setting. Its utility in the UK in terms of case-finding is further reduced by incorporating variables that are unlikely to be available on existing databases.

Leicester Risk Assessment

The Leicester Risk Assessment[27] score is based on the FINDRISC but gives an increased score to those not from a White European background. The score predicts prevalent NDH or T2DM as a composite outcome, with a score of ≥16 having a sensitivity of 81% and a specificity of 45%. This cut-point has been shown to have a higher sensitivity and positive predictive value than an equivalent point on the FINDRISC. The Leicester Risk Assessment score, recommended in NICE guidance[11], is now available online at www.diabetes.org.uk/Riskscore/ and has been completed by over 179,756 people since its launch in July 2010.

Three scores have been developed within the UK for use within general practice for identifying all those "at risk" using routinely collected and stored data.

Cambridge Risk Score

The Cambridge Risk score was designed to identify undiagnosed diabetes[47]. Variables include age, gender, BMI, steroid and anti-

hypertensive medication, family history of diabetes and smoking history. This score has also been used to predict undiagnosed hyperglycaemia, yielding a sensitivity of 51% and specificity of 78% for detecting a HbA1c of ≥7.0%[48]. Although this score does not take into account ethnicity, a post hoc study using data collected from both Caribbean and South Asian populations demonstrated that acceptable levels of prediction for undiagnosed hyperglycaemia can be achieved by modifying cut-points for different ethnic groups[49]. Incorporating measures of diet and physical activity did not improve the prediction of the Cambridge Risk Score[50].

Leicester Practice Risk Score

The Leicester practice risk score is similar to the Leicester Risk Assessment but only contains variables which are routinely stored in GP databases (age, sex, BMI, ethnicity, anti-hypertensive use, and any family history of diabetes). Validation of the score on an external dataset showed that 62% of the population would need to be invited for further testing to detect NDH or T2DM with 80% sensitivity. 41% of those that score the highest (i.e top 10%) would have NDH or T2DM (positive predictive value (PPV) 40.6%, 95% CI 34.8, 46.5)[51].

QDScore

The QDScore predicts 10-year risk of developing diabetes[52] and includes similar variables to the Cambridge Risk Score but with the addition of ethnicity, deprivation and vascular disease. This score was developed by modelling risk factor data from general practice data on 2.5 million patients aged between 25-79 years, with 78,000 patients developing diabetes over the 15 year study period. Compared to the Cambridge Risk Score the QDScore shows greater levels of discrimination, i.e. it is better at distinguishing between those with and without the condition of interests. If so the QDScore can also be used as a self assessment questionnaire, and can be found at www.qdscore.org.

Prevention of NDH

No clinical trials have investigated the efficacy of intervention aimed at reducing the prevalence of NDH, therefore no specific recommendations or guidelines exist. Indeed given that NDH is considered a risk factor for T2DM and is not a classified disease, it is unclear whether specific recommendations are needed at all. Given that T2DM and NDH are lifestyle-related conditions, ensuring that national guidelines on the prevention and treatment of obesity, CVD and physical activity are implemented within primary care is likely to be the most effective policy in reversing the increasing prevalence of NDH.

Although screening and providing intensive lifestyle management for those with NDH conforms to recommended international best practice and national initiatives, such as the NHS Health Checks Programme, it is relevant to draw a distinction between this approach for high risk populations and interventions aimed at shifting the degree of risk in the entire population. This latter approach will be more relevant to upstream interventions aimed at the prevention of NDH. Shifting the distribution of body weight in the general population for example is likely to have a dramatic public health benefit[53]. This is particularly important because single factors such as obesity and physical inactivity are known risk factors for NDH and T2DM, but the size of the groups identified by such factors are so large that even small changes could have a dramatic effect on a population level[53].

Therefore policy makers and commissioners need to weigh up the costs and benefits of investing in individually focused intervention programmes, which are likely to have a large impact on relatively few, and population based approaches which are likely to have a small impact on many; in the latter case the benefits may not even be noticed at an individual level.

Preventing progression from NDH to T2DM - Lifestyle intervention

Randomised controlled trials conducted in many countries have consistently shown that lifestyle interventions can successfully reduce the risk of progressing from IGT toT2DM by 30 to 60%[3,54-58]. Importantly, successful lifestyle change programmes have also been shown to have lasting benefits long after the active intervention has ceased[59-61]. Lifestyle intervention for those with NDH has also been estimated to be highly cost-effective for the NHS[29].

There are important considerations when it comes to translating diabetes prevention research into practice. Firstly all previous diabetes prevention trials have focused on IGT which is a subset of the broader classification of NDH. Therefore it is largely unknown from RCT level evidence, how effective lifestyle interventions are in those with isolated IFG or a HbA1c-based NDH classification. However it is known that IFG and IGT are defined by different pathophysiological profiles with IFG theoretically being less susceptible to modification through lifestyle change[62]. These findings support UK and European guidance which recommends that OGTTs should continue to be used to accurately define glycaemic status and risk profile and that those identified with IGT should be prioritised for intensive lifestyle counselling[63].

	Risk Scores					
	FINDRISK[42,43,45,46]	Leicester Risk Assessment[27]		Cambridge Risk Score[47-49]	QDScore[52]	Leicester Practice Score[51]
Sample	Population based random sample of 4.435 subjects	Population based random sample of 6,390 subjects		Population based sample of 1,077 plus additional cases from 41 practices	Population based sample of 2540,753 subjects	Population based random sample of 6,203 subjects
Self-assessment/ database	Self assessment	Self assessment		Database	Database and self assessment	Database
Outcome	Drug-treated T2DM	non-diabetic hyperglycaemia or T2DM	T2DM	T2DM	T2DM	non-diabetic hyperglycaemia or T2DM
Prevalent / incident	Incident	Prevalent	Prevalent	Prevalent	Incident	Prevalent
Performance						
Sensitivity	77%	72%	81%	77%	-	80%
Specificity	66%	54%	41%	72%	-	44%
PPV	7%	28%	4%	11.3%	-	32%
NPV	-	89%	99%	98.6%	-	87%
AUC	80%	69%	-	80%	-	70%

Table 2. Risk Scores for T2DM & NDH and their performance

Secondly, the majority of tested lifestyle intervention studies have used intensive behaviour change strategies which are unsuitable for implementation within a national health care service. Even national diabetes prevention initiatives in Finland and Germany have not been able to fully replicate the resource intensive nature of the Diabetes Prevention Study or the Diabetes Prevention Project[64].

Therefore pragmatic diabetes prevention interventions that are tailored to the resources and infrastructure limitations inherent within national health care services need to be developed and rigorously evaluated. Several countries, including Finland, Germany and the United States (US) have responded to this need by developing and evaluating theory-driven group-based educational programmes[64]. In the UK it has recently been shown that structured education can be successfully utilised to promote behaviour change and improved glucose tolerance at 12-months in those with NDH[65]; these changes were sustained at 24-months[66].

In the UK, group-based structured education is recommended for individuals with newly diagnosed type 2 diabetes and has been shown to be highly cost-effective[67]. Therefore there is an existing infrastructure within primary care for the delivery of structured education that could be extended to the management of NDH.

Pharmacotherapy

Several oral hypoglycaemic agents have been shown to reduce the risk of developing type 2 diabetes in double-blind RCTs, including metformin[54, 57], acarbose[68], and rosiglitazone[69].

Although no national health regulatory body currently recommends the use of pharmacotherapy to prevent/slow progression to T2DM in at-risk individuals, a recent consensus statement from the American Diabetes Association recommended for the first time that metformin be considered for treatment as a adjunct to, or instead of, lifestyle

modification in those with both IGT and IFG and one other risk factor[70]. Metformin was chosen because it has a proven preventive efficacy, it is relatively cheap and is not associated with serious long-term side effects.

However, this approach remains controversial for several reasons. Firstly, few studies have assessed the impact of metformin and lifestyle modification in combination; the only study to do so, the Indian Diabetes Prevention Program, found that there was no additive benefit of combining meformin with a lifestyle modification programme in those with IGT[57]. Secondly, given the causal factors of T2DM, lifestyle modification programmes should be the primary focus of diabetes prevention initiatives. Importantly, not only have lifestyle interventions been shown to be equally or more effective at preventing diabetes over the longer term then than pharmaceutical agents, lifestyle change is also associated with multiple wide ranging health benefits that target the known co-morbidities accompanying T2DM; lifestyle interventions are therefore likely to be more cost-effective[3]. However, pharmacotherapy may have a role to play when lifestyle modification programmes have been tried and found to fail. This is consistent with European guidelines[63] which recommend that in people with IGT, metformin or orlistat can be used as a second-line strategy for preventing diabetes. In the UK, NICE guidance also advises the use of metformin or orlistat as second-line strategies[11].

National Guidance and Recommendations

Both the Public Health White Paper "Healthy Lives, Healthy People"[64] and the House of Lords Science and Technology Committee's Inquiry into Behaviour Change[65] recognise that long term strategies are required to enable health related behaviour changes at the individual and community level which can be sustained in the longer term.

Supporting this philosophy, NICE have issued public health guidance around population and community approaches to diabetes prevention and risk identification and interventions for individuals at high risk[11]. Identifying those at high risk of diabetes and providing an intensive lifestyle modification programme is a cornerstone of the NHS Health Checks Programme in England. NICE Guidelines recommend that healthcare professionals undertake a two-stage strategy using a validated risk-assessment score combined with either fasting plasma glucose, HbA1c or an oral glucose tolerance test (OGTT), according to World Health Organization (WHO) criteria[1]. Exclusions for risk assessment based on age should not be made as everybody can reduce their risk. Healthcare professionals should also consider a blood test for those aged 25 and over who are either of South Asian or Chinese descent whose body mass index (BMI) is greater than 23 kg/m^2.

A confirmatory blood test (either fasting plasma glucose, HbA1c, or an oral glucose tolerance test) should be offered to individuals that have no symptoms of diabetes and who either have a fasting plasma glucose ≥ 7.0mmol/L or HbA1c ≥ 48mmol/mol.

Individuals identified as being at high risk of diabetes should be offered a quality assured lifestyle intervention that offers ongoing tailored support, encouraging people to undertake healthy lifestyle behaviour changes, such as increasing physical activity and weight loss to within a healthy range.

Key points

- ➔ Screening for diabetes identifies a population with a significant burden of modifiable cardiovascular risk. Early intervention on such people leads to as yet unproven clinical improvements
- ➔ Progression from NDH to T2DM can be slowed or reversed through lifestyle or pharmaceutical intervention
- ➔ Screening for both T2DM and NDH is likely to be cost effective provided that those with NDH are offered evidence-based prevention programmes
- ➔ There is insufficient long term evidence from randomised trials to quantify the effect of diabetes prevention programmes on cardiovascular mortality and morbidity
- ➔ There are different approaches for screening for hyperglycaemia:
  - Population based screening aims to tests all individuals within a geographical region but is a relatively intensive process and probably has a poor yield of T2DM cases
  - Targeted screening aims to pre-select those at highest risk of developing diabetes and has potential time and cost savings
  - Opportunistic screening through routine contact with healthcare providers may be a practical alternative augmenting targeted approaches

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SECTION 3: Chronic Kidney Disease

Chronic Kidney Disease (CKD) is fast becoming a public health issue[1]. It is a spectrum of disease that includes evidence of kidney damage with normal excretory function, reduced excretory function, and irreversible established kidney failure. Markers of kidney damage are proteinuria, haematuria (after exclusion of other causes) and structural damage. Reduced excretory function is defined as an estimated Glomerular Filtration Rate (eGFR) of <60 mL/min/1.73, on at least two occasions over ≥3 months[2]. Those identified with CKD, even in its mild form (stages 1 and 2, see Table 1) are known to have an elevated risk of CVD. Indeed the link between CKD and CVD is so strong that the American Heart Association states that those with CKD should be included in the highest risk category for subsequent CVD events. Patients with CKD are particularly susceptible to vascular disease and at assessment should be considered at high risk independent of other risk factors[3].

CKD can be caused by inherited or acquired disease (including diseases affecting the glomeruli, the tubules, or the blood supply, and including episodes of acute kidney injury). Progressive kidney damage is more likely in the presence of risk factors[4]. T2DM is the most common cause of CKD globally[5]. The burden of CKD is anticipated to rise markedly in parallel with the emerging "epidemic" of obesity-related disease. The estimated global prevalence of CKD in individuals over 30 years of age is 7.2% rising to nearly 40% in elderly populations[6]. In the UK, prevalence of moderate to severe CKD as defined by stages 3–5 (see Table 1) is between 6.8-8.0%[7].

Diagnosis

eGFR is now routinely reported by all UK laboratories using the MDRD equation (based on serum creatinine, age, sex, and race)[8]. Although is a more accurate reflection of kidney function compared to serum creatinine alone, the diagnosis of CKD may be missed in some individuals, such as those with low muscle mass, low protein intake or significant glomerular, tubular, or vascular kidney disease but with higher estimated GFR of greater than 60 mL/min/1.73m^2[2,8]. Recently the CKD-EPI equation has been shown to more accurately classify individuals with respect to risk of mortality but identifies more CKD in individuals aged >75[9]. This has implications for screening because the diagnosis of CKD for individuals with an eGFR of greater than 60 mL/min/1.73m^2 can only be made in the presence of other tests of kidney function. Therefore in primary care for people without T2DM, CKD should only be diagnosed following a confirmatory early morning test after an abnormal first result through stages 3 to 5[2,10-12].

Along with eGFR, urine albumin constitutes another potent predictor of kidney function and an even more powerful predictor of cardiovascular disease than the eGFR. Albumin constitutes the major protein within the blood and is not normally found in urine except in renal disease. The spectrum of urinary albumin excretion runs with increasing severity from microalbuminuria (>2.5mg/mmol in men and >3.5 mmol in women) to overt or macroalbuminurea (>30mg/mmol). Micro-and overt albuminuria are independent risk factors for cardiovascular morbidity and mortality in individuals with and without diabetes[13, 14].

NICE recommends that to detect and identify proteinuria, urine Albumin Creatinine Ratio (ACR) should be used in preference, as it has greater sensitivity than PCR for low levels of proteinuria. For quantification and monitoring of proteinuria, Protein Creatinine ratio (PCR) can be used as an alternative. For people with diabetes, ACR is the recommended method[11].

Risk Identification

Results of a recent meta-analysis using data from community populations showed eGFR and albuminuria independently predict all-cause and cardiovascular mortality. Particularly, eGFR <60 mL/min/1.73 m^2 and ACR >1.1 mg/mmol (10 mg/g) were independent predictors of mortality[14]. However, patients with a preserved eGFR above 90 mL/min/1.73 m^2 and stage 1 or 2 disease have an increased risk[3, 13].

The co-existence of albuminuria and CKD stages 3 to 5 has a significant effect on vascular disease risk; therefore, suffixing '(p)' to the CKD stage is recommended to denote "significant proteinuria" in more advanced CKD[10]. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for classification and staging of CKD propose a new classification system that adds three albuminuria stages at each GFR stages and splitting CKD3 into two subcategories:

- ➔ CKD3A (GFR 45-59 ml/min/1.73m^2)
- ➔ CKD3B (GFR 30-44ml/min/1.73m^2)[14]

This classification recognises the associated increased risk of cardiovascular disease, death and accompanying complications. This is reflected in NICE guidance[15].

In patients with other risk factors, urinary protein estimation is one of the primary requirements in the diagnosis of CKD stages 1 and 2. Other significant risk factors include:

- ➔ Diabetes
- ➔ Hypertension
- ➔ CVD (ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease)
- ➔ Structural renal tract disease, renal calculi or prostatic hypertrophy
- ➔ Multisystem diseases with potential kidney involvement - e.g. systemic lupus erythematosus
- ➔ Family history of stage 5 CKD or hereditary kidney disease
- ➔ Opportunistic detection of haematuria or proteinuria

Identification and progression of CKD

CKD may be stable or progressive[16]. Progression of CKD is defined as an annual decline in eGFR of >5 mL/min/1.73m², or a 5-year decline of >10 mL/min/1.73m². The symptoms of CKD are usually non-specific and do not manifest until there is severe decline in kidney function, which further leads to irreversible kidney damage. Therefore, monitoring CKD is important to improve health outcomes and recommendations for screening range from yearly to six weekly (see Table 1).

A simple screening strategy targeting people with diabetes, hypertension, or age >55 years affords the highest detection rate for chronic kidney disease combined with a low "number needed to screen". However, for individuals over 55 years of age without additional risk factors, the prevalence of CKD with proteinuria is too low for screening to be cost-effective[18].

				Albuminuria stages, description and range (mg/g)				
				A1		A2	A3	
				Optimal and high-normal		High	Very high and nephrotic	
				< 10	10 -29	30 - 299	300 - 1999	≥ 2000
GFR stages, description and range ml/min per 1.73m²	G1	High and optimal	> 105					
			90 - 104					
	G2	Mild	75 - 89					
			60 - 74					
	G3a	Mild-moderate	45 - 59					
	G3b	Moderate - severe	30 - 44					
	G4	Severe	15 - 29					
	G5	Kidney failure	< 15					

Table 1. Composite Ranking for Relative Risk by GFR and Albuminuria[19]

It is important to routinely screen:

- ➔ patients from high risk groups (people with diabetes, hypertension, cardiovascular disease)
- ➔ those with structural kidney disease or multi-system diseases with potential for renal involvement

Management

In managing patients with CKD:

- ➔ Review existing medications and medication dose if necessary
- ➔ In individuals with CKD, aim for a target blood pressure of <140/90 mmHg, but for individuals with CKD and microalbuminuria a target blood pressure of <130/80 mmHg should be aimed for. There is good evidence that ACE-inhibitors and ARBs may benefit people with CKD with proteinuria, with greater benefit for individuals with higher SBP benefit[20]
- ➔ In patients with diabetes mellitus treat to target as per guidelines[20]
- ➔ Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are the drugs of choice in diabetic nephropathy. Recent high quality evidence indicates that cholesterol lowering agents in individuals with CKD reduces the risk of major atherosclerotic events and major vascular events by 17%1. Standard risk assessment tools should still be used when considering statin therapies[20-21]
- ➔ ACE-inhibitors and ARBs may benefit people with CKD with proteinuria. There is no evidence they are superior to other anti-hypertensive medications when similar levels of blood pressure reduction are achieved.[20] Anti-platelet therapy is indicated for secondary prevention of cardiovascular risk in people with CKD. Recent systematic review evidence indicates that anti-platelet therapy is associated with a reduced incidence of myocardial infarction, however the effects on mortality are currently uncertain.[20]
- ➔ In non-diabetic CKD there is limited evidence that statins reduce cardiovascular related mortality. It is therefore recommended that standard risk assessment tools are used when considering statin therapies[11]
- ➔ Anti-platelet therapy is indicated for secondary prevention of cardiovascular risk in people with CKD[22]
- ➔ Advice on lifestyle change should include smoking cessation and increasing physical activity
- ➔ Advice on healthy eating. Protein restriction (0.8 gm/kg per /day) in advanced kidney disease is generally recommended, however dietary restrictions in CKD should be balanced against the risk of malnutrition[23]
- ➔ Multifactorial intervention in diabetic nephropathy targeting lifestyle change, control of hyperglycaemia, hypertension, hypercholesterolaemia and use of ACE-inhibitors significantly improves cardiovascular mortality[24,25]

Prevention

The widespread introduction of eGFR reporting and incorporation of CKD domains into the revised Quality Outcomes Framework (QOF) of the General Medical Services (GMS) contract in the UK is beginning to drive early recognition of CKD in primary care[20]. A CKD register would theoretically enable appropriate investigation, advice, treatment and support with the aims of preserving kidney function and optimising CVD risk.

Key points

- ➔ CKD is defined as the presence of mildly impaired kidney function with evidence of kidney damage (proteinuria, haematuria or structural damage) or eGFR <60 mL/min/1.73m², on at least 2 occasions over ≥3 months
- ➔ Proteinuria is associated with cardiovascular disease and progression of kidney disease and its determination is of diagnostic and prognostic value in the management of CKD
- ➔ All patients with diabetes should be regularly monitored for the presence of CKD
- ➔ Cardiovascular risk factors should be identified and adequately controlled. Hypertension is a risk factor for CKD and target blood pressure is 130/80 mmHg
- ➔ Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are the agents of choice to reduce microalbuminuria/proteinuria
- ➔ High risk groups such as those with diabetes, hypertension and cardiovascular disease and those aged over 55 should be targeted for screening
- ➔ Screening tests may include albuminuria, eGFR and ACR

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SECTION 4: Hypertension

The risk of stroke, CHD, CKD and heart failure increases along with blood pressure (BP) and data from many RCTs provide compelling evidence that anti-hypertensive therapy is effective at reducing this risk. Such risk reduction is determined by the severity of hypertension and the co-existence of multiple vascular risk factors. For instance reduction in BP by an average of 12/6 mmHg can be expected to reduce stroke by 40% and CHD by 20%[1].

The benefits of treating hypertension also extend to the healthy aged population (>60 years) with moderate to severe systolic and / or diastolic hypertension[2]. An additional small scale reduction in BP below the standard target level may confer additional benefit in terms of reducing cardiovascular events in individuals with raised cardiovascular risk[3]. Findings from a recent meta-analysis suggest that primary prevention with BP lowering may be useful even in the absence of hypertension in those with raised cardiovascular risk[4].

In patients with T2DM and CKD, aggressive BP management aiming to achieve lower than standard BP targets is recommended[5]. In people with CKD with moderate to high proteinuria such a strategy may help to slow the decline of kidney function[6,7]. The benefits of a lower than standard BP target in preserving renal function is less clear in the absence of proteinuria[8].

In those with T2DM, BP reduction is associated with CVD risk reduction with no observable threshold. Furthermore, intensive BP control is known to reduce the risk of developing diabetic nephropathy and advanced renal failure[9-11].

Existing guidelines provide information on intervention thresholds, target BP cut-offs and recommendations for prescribing anti-hypertensive therapies[5,12-14]. The updated guidelines jointly released by NICE and the British Hypertension Society in 2011 are commonly used in England[14].

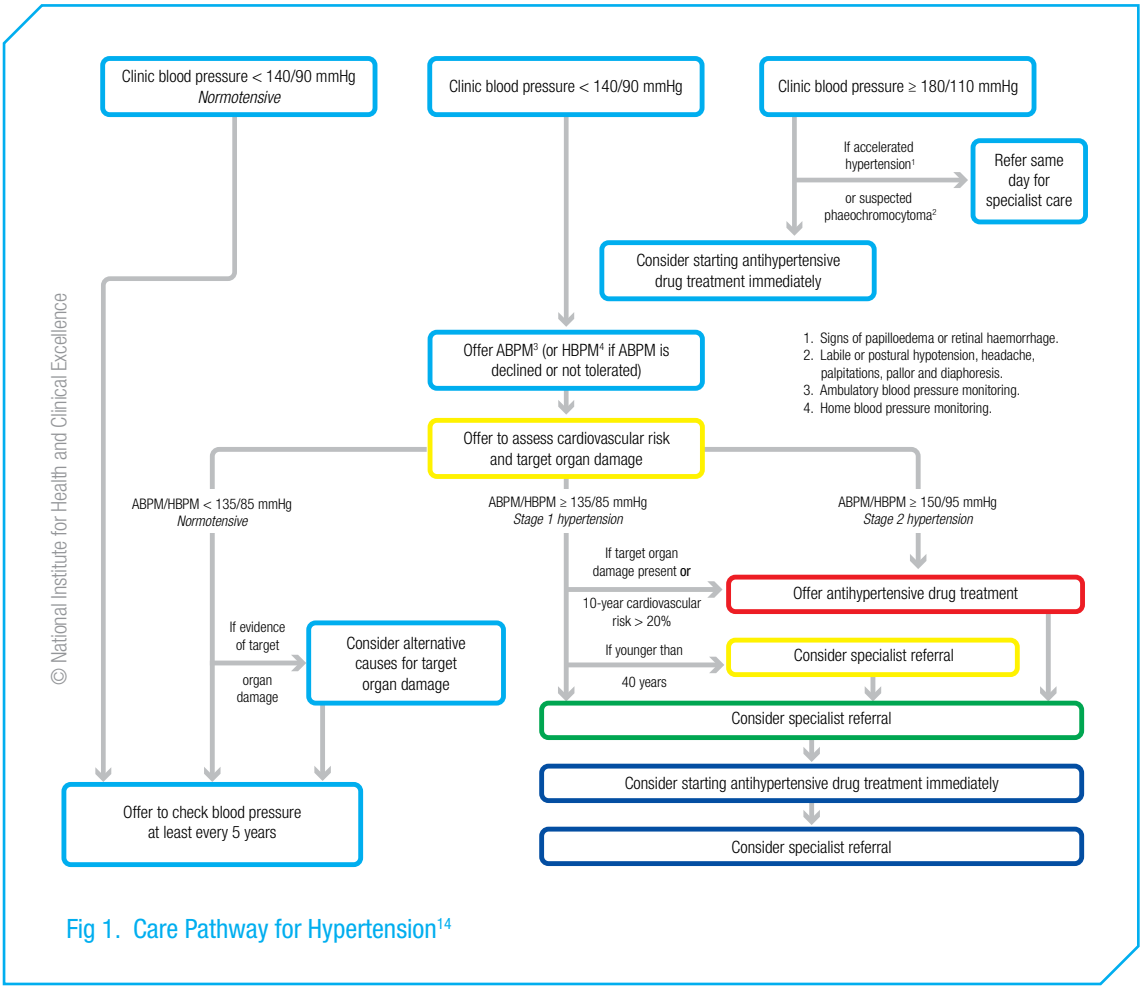

Fig 1. Care Pathway for Hypertension[14]

Interventions for Blood Pressure (BP)

Updated guidelines from NICE have, for the first time, advocated the use of 24–hour ambulatory BP monitoring (ABPM) as the preferred method for confirming the diagnosis of primary hypertension (Fig. 1, page. 31)[14]. Hypertension may be graded as follows with choice of treatment based upon the outcome of classification:

- ➔ stage 1 (ABPM/home BP monitoring (HBPM) >135/85)
- ➔ stage 2 (ABPM/HBPM >150/95)
- ➔ severe (clinic BP > 180/110)

All people with hypertension should undergo assessment for target organ damage and other cardiovascular risk factors in addition to receiving lifestyle advice to help reduce BP and CVD risk. According to the NICE guidance, those aged under 80 years with stage 1 hypertension and either of the following: target organ damage; T2DM; CKD; established CVD; 10 year cardiovascular risk >20% should be treated with anti-hypertensive therapy.

People of any age with stage 2 hypertension should be treated with anti-hypertensve therapies regardless of risk factors. People with severe hypertension should be started on anti-hypertensive therapies immediately and considered for an urgent same day referral to specialist care in the event of suspected accelerated hypertension or phaeochromocytoma. People aged <40 years with hypertension but without cardiovascular risk factors or target organ damage should be investigated in specialist care for secondary causes. Furthermore, patients should be offered education about the treatments of hypertension and reviewed annually for ongoing care[14].

Treatment targets

The guidelines from different societies and organisations acknowledge the benefits of intensive treatment to achieve lower than standard targets especially in high risk individuals with CKD, T2DM or established CVD[5,12-15]. Optimal and audit standards for blood pressure targets suggested by the JBS2 guidelines are outlined in Table 1. It should be noted the imminent JBS3 will be making a recommendation for a lifetime risk assessment, rather than a 10 year risk as outlined in the table. NICE guidelines advocate a similar target of clinic blood pressure below 140/90 in people aged under 80 years with treated hypertension. A more conservative target of BP below 150/90 mmHg is suggested for those over 80 years.

Choice of agents

The specific class of anti-hypertensive therapy is not as important as lowering BP-associated mortality and morbidity. The efficacy of the different classes of anti-hypertensive drug have been well-established in clinical studies[16-22].

In patients requiring two or three blood pressure lowering drugs, a step-wise approach is advocated for achieving target BP levels. ACE inhibitors, calcium channel blockers and thiazides diuretics are shown to be more effective as a first-line therapy in improving cardiovascular outcomes compared to other classes of drug[22].

Combining anti-hypertensive agents from different classes can have an additive effect offering superior BP control along with a better side effect profile compared to up-titrating the dose of a single agent[23]. The recent ESC guidelines have even recommended use of combination drug therapy using a low dose two-drug combination as an optional first-line therapy[13]. However, current practice in the UK has resulted in almost two-thirds of treated patients receiving mono-therapy and less than 10% receiving more than two drugs. This is reflected by the fact that less than half of patients with treated hypertension have their blood pressure optimally controlled[24]. The British Hypertension Society's ABCD algorithm published in the recent NICE guidelines informs practitioners of logical treatment options and combinations of drug therapy.

	Optimal[1,2] (mmHg)	Audit Standard used by JBS-2 (mmHg)[1]
Elevated BP >140/90 with a CVD risk 20% over 10 years and/or target organ damage	<140/85	<150/90
Elevated BP with diabetes or CKD or established atherosclerotic disease	<130/80	<140/80

Table. 1 Optimal and audit standard blood pressure targets

Key points

- ➔ Hypertension is a major risk factor for increased cardiovascular mortality and morbidity
- ➔ The risk can be effectively reduced by aggressive control of elevated BP
- ➔ Lower treatment thresholds and targets are advocated for people with higher baseline risk to achieve the desired cardiovascular benefits
- ➔ Adopting a stepwise approach to prescribing anti-hypertensive agents according to the existing guidelines is essential
- ➔ Combination therapy involving multiple anti-hypertensive agents is often beneficial in achieving effective BP control and minimising adverse drug effects

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SECTION 5: Cholesterol and Lipid Lowering

A consistent linear relationship between total or LDL-cholesterol concentration and CVD makes lipid measurement a standard feature of many risk assessments[1]. The total cholesterol/HDL ratio is commonly used in CVD risk equations despite LDL-cholesterol remaining the preferred target for lipid lowering therapies and the resultant cardiovascular benefits of LDL-cholesterol lowering being well established. A recent systematic review and meta-analysis of 58 RCTs of cholesterol-lowering agents concluded, that for one mmol/L reduction in LDL-cholesterol there was a reduction in coronary death and non-fatal myocardial infarction of 11% in the first year, 24% in the second year and 33% in the third to fifth year[2]. Statins remain the first line therapy to reduce LDL-cholesterol with highly significant benefits on cardiovascular endpoints across a range of settings within high risk populations. Conversely, there remains no independent evidence that increasing HDL-cholesterol concentration improves CHD outcomes and it is unclear whether lowering triglyceride levels in isolation with drugs such as fibrates improves CVD mortality[3-6].

The Benefits of Lowering Cholesterol for Cardiovascular Risk

Statins (HmGCoA reductase inhibitor) inhibit cholesterol synthesis in the liver, activating hepatocyte LDL-cholesterol receptors and increasing hepatic uptake of LDL-cholesterol from the circulation. The primary action of statins is to lower LDL-cholesterol with only small effects on HDL- cholesterol and triglyceride levels. Reductions in LDL-cholesterol are dose-dependent and log-linear, so that with each doubling of statin dose, LDL-cholesterol levels fall by approximately 6%[7].

In the cholesterol trialist's prospective meta-analysis, data from 90,056 participants from fourteen randomised statin trials were analysed. Reduction in LDL-cholesterol by one mmol/L with statin therapy reduced the overall 5-year incidence of major coronary events, coronary revascularisation and stroke by 20%. This was irrespective of pre-treatment cholesterol levels or other risk factors. There was a 12% reduction in all-cause mortality and 19% reduction in CHD mortality[8]. Statin therapy confers clear benefits, improving cardiovascular outcomes and survival across a broad range of patients with different levels of risks (including women, elderly people and those with diabetes)[9,10]. In the JUPITER trial, involving 17,800 patients with no history of CVD, a baseline LDL-cholesterol of <3.4 mmol/L and a CRP >2.0 mg/L, treatment with Rosuvastain 20mg daily for a mean period of 1.9 years significantly improved the risk of major cardiovascular events and deaths compared to placebo[10]. In a primary prevention meta-analysis involving 70,388 participants, statin therapy for primary prevention was found to significantly reduce all-cause mortality by 12% and major coronary events by 30%[9]. It is also cost-effective to initiate statins to individuals without evidence of CVD but with a ten-year risk of CVD ≥20% compared to providing standard diet and lifestyle measures[11,12].

Statin Therapy in High Risk Individuals without CVD[13]

- ➔ Lipid modification in high risk individuals without established CVD should be considered as a part of a multi-factorial approach
- ➔ For the primary prevention of CVD in primary care, a systematic strategy should be used targeting people aged 40-74 years with high CVD risk
- ➔ Risk equations should be used to assess this risk
- ➔ Those with a ≥20% 10-year CVD risk should be considered for statin therapy after lifestyle modification
- ➔ In people with near threshold CVD risk, other factors that may predispose to CVD and are not included in the risk score (for example family history of premature heart disease, severe obesity, low income and social deprivation) should be considered to inform treatment decisions. Similarly for people in whom an appropriate risk calculator is not available or appropriate (e.g. above 75 years old, high risk ethnic groups, underlying medical conditions or treatments) clinical judgement should be used to identify high risk individuals
- ➔ Before offering any pharmacotherapy for lipid modification, all other modifiable CVD risk factors should be identified and their management optimised if possible. This includes assessment and treatment of secondary causes of hyperlipidaemia and lifestyle advice (diet and physical activity) to reduce cholesterol levels

- ➔ Offer Simvastatin 40mg once daily (OD) (or drug of similar efficacy and acquisition cost) for adults over 40 years who have a ≥20% 10-year risk of developing CVD, based on risk equations and clinical judgement. If there are potential drug interactions or Simvastatin 40mg is contraindicated, offer a lower dose of Simvastatin or Pravastatin
- ➔ Do not routinely offer higher potency statins, anion exchange resins or fibrates
- ➔ Do not offer nicotinic acid or the combination of an anion exchange resin, fibrate or a fish oil supplement with a statin
- ➔ If statins are not tolerated then consider fibrates, anion exchange regimes or Ezetimibe
- ➔ In people treated with a statin for primary prevention of CVD, a target for total or LDL-cholesterol is not recommended and a repeat lipid measurement is unnecessary unless clinically indicated

Statin therapy for secondary prevention

Intensive LDL-cholesterol lowering using 'high-dose' statins compared to 'standard-dose' in the secondary prevention setting has been shown to have additional long-term benefits on CVD outcomes. In a meta-analysis involving a total of 27,548 participants, intensive treatment with 'high-dose' statins (Atorvastain 80mg, Simvastatin 80 mg or Rosuvastatin 40mg) achieved a lower LDL-cholesterol level (0.67 mmol/L) and resulted in an additional 16% reduction in CHD deaths compared to the group treated with 'standard-dose' statins[14]. The majority of guidelines therefore recommend aggressive lipid lowering and lower targets for LDL cholesterol in individuals with established CVD[13,15,16]. It is also cost-effective to treat all individuals with CVD, with a statin compared to providing standard diet and lifestyle measures[12,14, 17].

The long-term safety of this aggressive approach to lipid lowering is unclear. A "post hoc" analysis of a sub-group of 999 patients in the IDEAL study randomised to either 'high dose' Atorvastatin or 'standard dose' Simvastatin within 2 months of an acute coronary event, reported that high dose statin therapy was effective and well-tolerated over a five year study period[18]. Conversely in the SEARCH trial, involving 12,064 patients, myopathy occurred in 52 patients (0·9%) randomly assigned to simvastatin 80mg compared to just one patient (0·02%) randomly assigned Simvastatin 20mg[19]. Furthermore, an estimated 11 patients developed rhabdomyolysis, a potentially fatal complication, in the high dose group compared to none in the standard dose group. In May 2010, the Medicines Health and Regulatory Authority (MHRA) issued a drug safety alert highlighting an increased risk of myopathy associated with high dose Simvastatin (80mg)[20].

Therapy in Individuals with Established CVD[13]

- ➔ For secondary prevention, lipid lowering therapy should be offered as soon as possible
- ➔ Patients should be assessed and treated for secondary causes of hyperlipidaemia and other modifiable risk factors but this should not delay the initiation of statin therapy
- ➔ Treatment should be initiated with Simvastatin 40mg daily. If there are potential drug interactions, or Simvastatin 40mg is contraindicated, a lower dose or alternative preparation such as Pravastatin may be chosen
- ➔ In patients with acute coronary syndrome a high dose statin therapy should be commenced and the statin treatment should not be delayed until lipid levels are available
- ➔ Any decision to offer high dose statin should be based on various factors including informed patient preference after clear explanation of benefits and risks of treatment
- ➔ If statins are not tolerated for secondary prevention consider fibrates, nicotinic acid, anion exchange regimes or Ezetimibe

Cholesterol Targets for Therapy in Patients with Established Cardiovascular Disease (Secondary Prevention)

The Joint British Society (JBS) 2 guideline states "there are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL-cholesterol targets in relation to clinical events". Establishing a cholesterol target for therapy is therefore an extrapolation from the apparent benefits indicated by major trials of lipid lowering, while maintaining appropriate margins for safety[15].

A narrative systematic review, which examined the independent relationship between LDL-cholesterol and major cardiovascular outcomes in patients with LDL-cholesterol levels of <3.36 mmol/L, found no evidence to suggest that the degree to which LDL-cholesterol responds to statin therapy independently predicts the degree of cardiovascular risk reduction. Although the review indicated that there was compelling evidence for the risk effectiveness of statin therapy in lowering cholesterol in patients at high cardiovascular risk (regardless of their LDL-cholesterol values) it concluded that current clinical evidence does not demonstrate that lipid therapy should be titrated to achieve proposed LDL-cholesterol targets[21].

While patients with established symptomatic CVD should be considered for intensive therapy, the long-term safety and cost-effectiveness of such therapy is not yet established[14]. The ongoing large, IMPROVE IT trial involving 18,000 patients with acute coronary syndrome is testing the hypothesis that treating high risk patients to achieve a lower LDL-cholesterol target will translate into improved cardiovascular outcomes[22].

Several guidelines have recommended titration of lipid lowering therapy to achieve LDL-cholesterol levels <2.5 mmol/L for patients at high cardiovascular risk[15,21,23].

The guidance from the Department of Health in England and Wales recommends that patients with established CVD should receive statins and dietary advice to lower total serum cholesterol concentrations either to <5.0 mmol/L (LDL-cholesterol to below 3.0 mmol/L) or by 25% (30% for LDL-cholesterol), whichever is greater[24]. In the SIGN guidelines, the target for individuals at high cardiovascular risk is a total cholesterol of <5.0 mmol/L[17]. This level is consistent with the Quality and Outcomes Framework[25]. Reducing this target to 4.5 or 4.0 mmol/L would have major resource implications for NHS Scotland.

Pending further studies on mortality, safety and cost-effectiveness, the guideline development group suggests that current NHS Scotland targets are maintained as the minimum standard of care. The NICE guidance on Lipid Modification recommends, for secondary prevention, a target of total cholesterol of <4.0 mmol/L and a LDL-cholesterol of <2.0 mmol/L at individual level and an audit level of total cholesterol of 5.0 mmol/L[13].

Safety and ongoing monitoring of statin therapy

In the vast majority of cases statins are well-tolerated, safe and highly effective[8,24]. Mild aches and pains without an associated rise in muscle enzymes or an asymptomatic rise in transaminase levels of less than three times the upper limit of normal do not warrant medication withdrawal[24].

Significant hepatotoxicity (rise in transaminase levels more than 10 times the upper normal limit) and myositis (rise in total creatinine kinase levels more than ten times the upper normal limit) are rare and usually reversible. Adverse effects appear to be dose-dependent and are often related to the concomitant use of other drugs.

Key points relating to recent NICE guidelines on monitoring statin therapy are as follows[13]:

- ➔ Measure liver function within 3 months and at 12 months, but not again unless clinically indicated
- ➔ If drugs that interfere with statin metabolism are introduced for another illness, consider reducing the statin dose temporarily or permanently stopping it
- ➔ Advise people to seek medical advice if they develop muscle pain, tenderness or weakness
- ➔ Do not routinely monitor creatine kinase in people without adverse events, but consider it in people with muscle symptoms. Stop statins and seek specialist advice if unexplained peripheral neuropathy develops

Measuring Lipid Levels

LDL-cholesterol can be calculated indirectly by measuring total cholesterol, HDL-cholesterol and triglycerides from a fasting venous blood sample and applying the Friedewald equation[26]:

This method is not suitable for individuals with triglyceride levels >5 mmol/L. For greatest accuracy fasting samples are required as HDL-cholesterol and triglycerides levels vary between fasting and non-fasting states. HDL-cholesterol is reduced by between 5-10% in the non-fasting state and triglyceride levels are 20-30% higher. However, given the practical problems of routinely collecting fasting samples, non-fasting blood samples are generally collected for estimation of total and HDL-cholesterol[26].

It may be practical to start with a non-fasting sample for total cholesterol and HDL-cholesterol in terms of a comprehensive vascular assessment performed in the context of screening. Secondary causes of dyslipidaemia (diabetes, hypothyroidism) should be investigated and patients with suspected familial hyperlipidaemia should be considered for specialist referral (see Familial Hypercholesterolaemia below).

Management of Cholesterol in Special Groups

Diabetes

Subjects with diabetes are at higher risk of CVD and statin therapy is effective in both primary and secondary prevention of cardiovascular events[27]. Most diabetes guidelines in the UK recommend that for primary prevention, statin therapy should be considered in individuals aged

40 years or more while for those aged between 18 and 39 years such therapy should be considered in the presence of other risk factors such as[28]:

- Retinopathy
- Nephropathy
- Poor glycaemic control
- Elevated blood pressure
- Raised total cholesterol of ≥6.0 mmol/L
- Features of the Metabolic Syndrome
- Family history of premature CVD
- Active smoking

It is recommended that other factors including lifestyle, compliance and the likelihood of future pregnancy are discussed on an individual basis before statin therapy is considered in this group

Familial Hypercholesterolaemia

Familial hypercholesterolemia (FH) is an autosomal dominant condition causing significantly elevated blood cholesterol levels (usually > 8.0 mmol/L or higher). If untreated, FH can lead to greater than 50% risk of CHD in men by the age of 50 years and at least 30% in women by the age of 60 years. An aggressive approach in lipid lowering is warranted to reduce this risk[28].

Identification and management of Familial hypercholesterolemia[28]

- A diagnosis of FH should be considered in people with raised total cholesterol levels (usually > 7.5 mmol/L) especially if there is a personal or family history of premature CVD
- People with FH are already at a high risk of premature CVD and therefore CVD risk equations should not be used
- All patients, including children and young people with FH, should be offered a referral to a specialist with expertise in lipid management
- Further referral to a cardiologist should be considered for evaluation of CVD in people with symptoms of possible CVD or those with very high CVD risk (family history of premature CVD or presence of two or more other CVD risk factors)
- In adults with FH, treatment with high-dose statins should be considered to achieve a recommended reduction in LDL-cholesterol concentration of greater than 50% from baseline

Key points

- Hypercholesterolaemia is a strong risk factor for vascular disease
- A lipid assessment is incorporated into CVD risk assessment
- Statin therapy is highly effective at reducing CVD mortality in high risk groups
- High dose statins are increasingly used early in the management of acute coronary syndromes

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SECTION 6: Management of Specific Risk Factors

Smoking

Tobacco smoking markedly increases the risk of developing vascular disease. The exact elevation in risk is specific to the type of vascular disease; for example 7- and 2-fold increased risk for peripheral artery disease (PAD) and coronary artery disease (CAD) respectively[1]. This elevation in risk is also related to the amount of tobacco smoked as well as the duration of smoking (typically collectively defined by the unit 'pack-year'). The impact is greater still for patients with pre-existing hypertension or T2DM. Smoking cessation is followed by a rapid decline in risk of vascular disease[2].

There are a range of effective and evidence-based interventions available to assist in smoking cessation; these are broadly defined as either behavioural counselling or pharmacotherapies (including nicotine replacement therapies - NRT). Although the use of either of these are proven to increase the rate of long-term cessation maintenance, the use of both methods concurrently is recommended[3]. With respect to behavioural counselling, brief opportunistic advice is better than no advice but intensive counselling sessions, at higher frequency or for a greater duration, are more effective resulting in higher cessation rates[2-6].

NICE have published a range of guidance to tackle smoking in the community[7, 8]. All smokers should receive advice from a healthcare professional to stop smoking completely and the advice should be consistent, reiterated and reinforced by all healthcare professionals. Such advice should include a description of the vascular risks associated with smoking, assessing readiness to stop, information on the different ways of stopping, and agreeing a specific action plan with a follow-up arrangement.

Practical recommendations from NICE regarding brief intervention for smoking in healthcare and community care is illustrated in fig. 1 page.41[7]. Guidance is also available regarding the use of pharmacotherapy (NRT, Bupropion or Varenicline[8, 9]).

Management of Obesity

The risk of vascular disease rises as excess body weight (defined conventionally by BMI) rises. Greater risk is also associated with central adiposity which is measured by waist circumference[10]. BMI is a strong predictor of all-cause mortality in adults and risk is correlated with increasing BMI above 22.5kg/m^2, such risk is predominately attributed to vascular disease[11, 12].

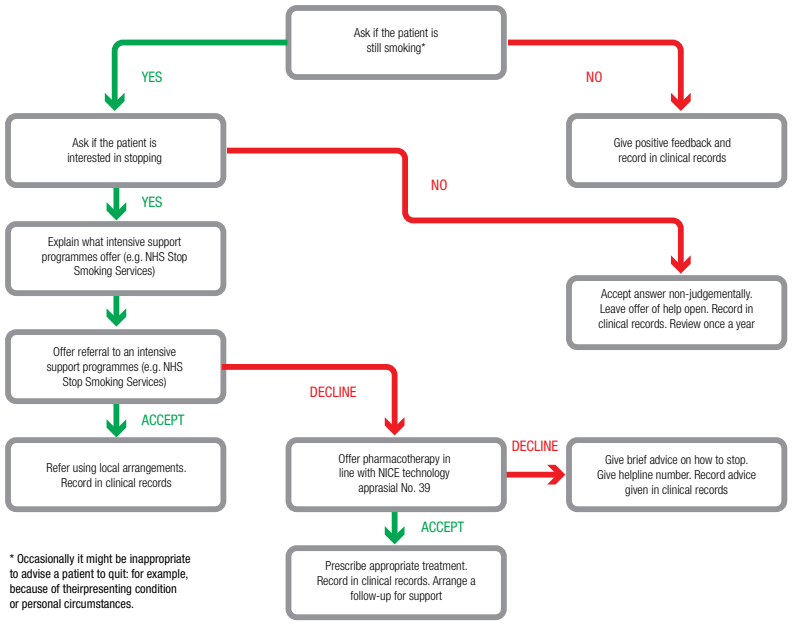

Fig 1. Brief intervention for smokers[7]

However, traditional categories do not apply to older adults where an optimum BMI of 25.0 to 30.0 kg/m2 has been shown to be associated with the lowest risk of mortality(13). A moderately obese individual (BMI 30.0 to 35.0 kg/m^2) has an average reduced life expectancy of three years and a morbidly obese individual (BMI 40.0 to 50.0 kg/m^2) by eight to ten years[11]. It is predicted that up to 23% of vascular deaths in middle aged people (aged 50 years) in the UK are attributed to obesity. A number of studies have shown that weight loss in the range of 5 to 10% results in clinically meaningful improvements in BP, lipid profile and glucose tolerance and if it can be maintained it is possible to extrapolate the reduction of the cardiac events that would be predicted by risk analysis[14-18].

Diet and exercise are the cornerstones of obesity treatment. Exercise is beneficial in weight reduction particularly when combined with diet and also improves cardiovascular risk irrespective of weight reduction. Behavioural and cognitive- behavioural therapies help to reduce additional weight when added to diet and exercise strategies[12].

Weight reduction strategies may be appropriate for those who are[19]:

- ➔ Overweight (BMI >25.0 kg/m2) with lower thresholds for those of South Asian (SA) origin (BMI> 23.0 kg/m^2)
- ➔ Obese (BMI > 30.0 kg/m^2) with lower thresholds for those of SA origin (27.5 kg/m^2)
- ➔ Increased abdominal fat as defined by a waist circumference of >94cm in men and 80cm in women (90 cm for SA men, 80cm in SA women)

Pharmacotherapy for the management of obesity

Weight loss with anti-obesity drugs is usually modest and weight regain is common after therapy is discontinued. Two major weight loss drugs were recently withdrawn as benefits of the drugs was not considered to outweigh their health risks[20,21]. Currently only Orlistat, a gastrointestinal lipase inhibitor, is licensed in Europe for this purpose[21]. In a Cochrane review Orlistat was found to achieve a modest weight loss of 2.9 kg and offer additional benefits of improved cholesterol levels and reduced risk of developing diabetes[22]. No major systematic toxicities are known with Orlistat use but studies assessing long-term cardiovascular outcomes are lacking. Furthermore, the treatment effects of this therapy can be quite uncomfortable: common side effects include steatorrhea and faecal incontinence leading to premature discontinuation. Anti-obesity medication should only be prescribed as a part of an overall plan of obesity management and after dietary, exercise and behavioural approaches have been attempted[21,23].

Bariatric surgery for Obesity

Surgical interventions for obesity are now becoming standard practice. The most frequently used surgical approaches are adjustable gastric banding, gastric bypass and sleeve gastrectomy[24].

NICE has recommended bariatric surgery as a first-line therapy for adults with BMI of more than 50 kg/m^2. For lower BMI (> 40.0 kg/m2 or 35.0 kg/m^2 to 40.0 kg/m^2 in presence of other co-morbidities such as T2DM and hypertension) bariatric surgery is recommended when other non-surgical measures have been unsuccessful[25]. It is increasingly recognised that bariatric surgery affords sustained long-term reduction in body weight with concomitant reductions in cardiovascular risk[24]. Furthermore, improved glycaemic control or in some instances complete resolution of T2DM following bariatric surgery is well-documented. A recent systematic review found 82% of morbidly obese patients with T2DM had resolution of the clinical and laboratory manifestations of diabetes in the first 2 years after surgery, with 62% remaining free of diabetes for more than 2 years after surgery[26]. In a HTA review, surgery was found to be most cost-effective in people with BMI > 40.0 kg/m2 followed by those with BMI between 30.0 kg/m^2 to 40.0 kg/m^2 and T2DM at baseline[26].

Dietary advice for prevention of vascular disease

Diet is a major modifiable risk factor for the prevention of vascular disease. The government states around 70,000 fewer premature deaths in the UK could be achieved if nutritional guidelines were met in full[27].

Dietary Fat

Diets high in fat are conducive to obesity as fat provides more calories per gram than other nutrients. Saturated fatty acids (SFA) have consistently been shown to raise LDL-cholesterol levels and reducing SFA intake is recommended for the prevention of CVD[28]. Exchanging SFA for polyunsaturated fatty acids (PUFA) or monounsaturated fatty acids (MUFA) appears to be beneficial for vascular health. A recent meta-analysis demonstrated the benefit of replacing SFA with PUFA on clinical CHD events[29]. This supports an earlier Cochrane review which concluded vascular risk could be lowered by reducing total fat or by replacing SFA with USFA[30]. The accumulated evidence supports the recommendation that SFA should be less than 10% of total energy intake, with total fat intake being 30% or less and the intake of dietary cholesterol should be less than 300mg per day.

Omega-3 Fatty Acids

Omega-3 Fatty Acids are thought to have beneficial anti-inflammatory and anti-atherogenic properties. They are found in fish oils and therefore diets with a high fish intake are hypothesised to have cardio-protective benefits. A meta-analysis of cohort studies found inverse associations between fish consumption and CHD mortality rates. The results suggested that eating fish once a week may reduce death from CHD by 15%. The association was most apparent in studies with follow up periods of 12 years or greater[31]. The current recommendation is to eat two portions of fish per week, one of which should be an oily fish (e.g. Mackerel or Salmon). Fish intake may also help to reduce intake of SFA by replacing red meat in the diet. Trials of omega-3 supplements have resulted in conflicting and inconsistent results. One review found the association of reduced vascular events was heavily influenced by those at highest risk[32]. Collectively, the data is too inconclusive to recommend stopping or taking omega-3 supplements and further research is required in this area[28,33].

Trans Fatty Acids (TFA)

Epidemiological studies have consistently shown an increased risk of CVD with greater consumption of TFA; in addition RCTs have shown that TFA have adverse effects on blood lipids[34]. WHO currently recommends that TFA do not make up more than 1% of total energy intake[35]. TFA in the human diet are rare in their natural form, existing in low levels in ruminant meat and milk products and have no apparent health effects. The majority of TFA in the diet come from industrially produced trans fatty acids (IPTFA) found in baked goods, deep fried food, packaged snacks and margarine. A 12-step manifesto for better public health from the UK Faculty of Public Health and Royal Society for Public Health propose banning IPTFAs due to their proven detrimental effects to health, thus eliminating them from individuals' diets by 2011[36].

Fruit and Vegetables

Inadequate consumption of fruit and vegetables remains a problem worldwide. In the UK only 25% of men and 28% of women report meeting the 5 a day guideline[37].
A report from 1997 demonstrated a link between low fruit and vegetable intake and increased risk of CHD and stroke[27].
More recent studies have consistently added data which support the evidence that fruit and vegetables play a protective role in the prevention of stroke and CHD[38-40]. A study investigating the role of fruit and vegetable intake and risk of ischaemic stroke found a particularly strong protective association for cruciferous and green leafy vegetables[41]. In addition, a recent review also found a significant benefit of green leafy vegetables for the prevention of T2DM[42].
The greatest reductions in risk of CVD have been demonstrated when individuals have consumed five or more portions of fruit and vegetables per day and thus support the current recommendations to consume at least 5 portions per day[39,41]. One portion is equal to 80g, which can be fresh, frozen, tinned or canned. 150ml of fruit juice also counts as one portion.
The following websites give advice on meeting the 5 a day recommendations, portions, planning meals and healthy food swaps.

- ➔ http://www.eatwell.gov.uk
- ➔ http://www.nhs.uk/livewell/goodfood/pages/goodfoodhome.aspx

Plant Sterols/Stanols (PS)

Plant sterols and stanols are found naturally in plant foods such as fruit, vegetables, nuts, cereals and legumes; they can also be incorporated into foods such as milk, yoghurt, margarine and bread[43]. A meta-analysis of RCTs to investigate the ability of PS to lower CVD risk showed that PS significantly lowered LDL-cholesterol compared to placebo. However, the magnitude of cholesterol lowering effects varies between individuals and appears to be linked to baseline levels. The study also showed the effect of PS on LDL-cholesterol was influenced by frequency and time of intake[44]. Similar results were also seen in a review of PS in diabetic individuals. PS significantly reduced total- and LDL-cholesterol but had no effect on triglyceride levels and only showed a trend towards increasing HDL-cholesterol[45]. A Cochrane review which examined cholesterol lowering treatments in both children and adults with familial hypercholesterolaemia found that a significant benefit was obtained with PS as compared to other cholesterol lowering diets[46].

Antioxidant Supplements

Observational studies have demonstrated high dietary intakes of antioxidants vitamin C and vitamin E are associated with reduced risk of CVD[47,48]. However clinical trials have failed to show consistent health benefits. Indeed evidence from RCTs and meta analyses have demonstrated that supplementation with some antioxidants, particularly vitamin A and E, is in fact associated with an increased risk of mortality and some cancers[49,50].

Salt

Reduced salt intake has been demonstrated as an important dietary factor for prevention of disease[51]. A recent meta-analysis examined habitual levels of salt intake and incidence of stroke or total CVD. Higher salt intakes were significantly associated with both stroke and CVD[52]. A dose-response analysis provided evidence of a significant direct association between salt intake and incidence stroke, on a population level; for every 50 mmol/day increase in sodium there was a 6% increase in the incidence of stroke. A similar trend was seen for overall CVD but results were not significant[52]. Another study used the CHD policy model to calculate the benefits of dietary salt reduction and found that 1g per day reduction in salt intake would be more cost-effective than medications to lower blood pressure in those with hypertension[53]. UK guidelines suggest that adults should have a maximum of 6g of salt per day, however the WHO suggest a target of 5g per day[28].

Alcohol

Guidelines for alcohol intake are based on numerous studies that show a 'J' or 'U'shaped curve for alcohol intake and CVD mortality[54]. An observational study of alcohol consumption in otherwise healthy men found that the lowest risk of myocardial infection was seen in those who consumed 5-30g per day, equivalent to one to three units. However, high doses of alcohol are harmful to the heart, problems include cardiomyopathy, arrhythmias and hypertension[55].

Therefore current recommendations state that alcohol should be limited to 3-4 units per day for men, and 2-3 units per day for women and people should avoid binge drinking. Binge drinking is defined as drinking sufficient alcohol to achieve a blood-alcohol concentration of ≥0.08%, usually >4 or >3 drinks on a single occasion for men and women respectively. Recent UK government guidelines also suggest drinkers should have at least 2 alcohol-free days per week[56].

Processed Meat

There are currently no guidelines for the consumption of red or processed meat, however evidence is growing that demonstrates a link to CVD with increased intake. A meta-analysis showed that both risk of CHD and T2DM were significantly associated with processed meat consumption. For each increase in 50g serving, risk of CHD and T2DM increased by 42% and 19% respectively. It has also been shown that processed meat is significantly associated with incidence T2DM. However, red meat on its own was not associated with either CHD or T2DM[57,58].

Processed meat contains more calories per 50g, more energy from fat, less energy from protein and less iron as compared to red meat. It also contains approximately 4 times the amount of sodium than red meat[57].

Wholegrains

The Scientific Advisory Committee on Nutrition state that a high fibre diet is associated with lower body weight and waist circumference. However studies on fibre, wholegrains and CVD are inconclusive and inconsistent, making firm conclusions and recommendations difficult. Further research into the area is therefore required[59].

Promoting Physical Activity

Health benefits of physical activity

Physical inactivity is recognised as a major contributing factor to the increasing chronic disease burden observed nationally and internationally; WHO estimate that it is now the fourth leading cause of premature mortality globally, higher than both obesity and dietary factors[60]. It has been estimated by the Department of Health that those classified as physically active, have a 30% reduced risk of all-cause mortality and up to a 50% reduced risk of developing chronic disease[61].

Physical inactivity has been identified as contributing to over 20 diseases and chronic conditions, with the strongest effects being observed for vascular disease, musculoskeletal disorders and colon cancer. Importantly the health benefits of physical activity work through adiposity dependent and independent pathways, meaning the health benefits of physical activity can be observed in the absence of weight loss. Therefore physical activity should be promoted for its own sake, rather than the end-point of weight loss[62].

In particular, it has been estimated that physical inactivity is the most common cause of mortality from CHD, the leading cause of premature death[63]. Physical inactivity is also generally involved in the pathogenesis of T2DM[64].

Recommendations

General physical activity recommendations for adults have typically specified engaging in at least 150 minutes per week of moderate-to-vigorous intensity physical activity. This weekly target has traditionally been packaged as needing to achieve least 30 minutes on at least five days a week in bouts of at least 10 minutes in length. However, recent updated recommendations have started to emphasise and prioritise the weekly (150

minutes) rather than daily (30 minutes) target, allowing more flexibility throughout the week in how the recommendations are accumulated[61,65]. It should be emphasised that this is a minimum recommendation and higher levels lead to greater health benefits in a dose-response manner. This minimum target needs to be increased to at least 60 minutes per day to avoid obesity and help maintain weight loss. It is also beneficial for adults to undertake regular resistance training in addition to aerobic activity[65].

Walking is the most prevalent, and the preferred choice of, physical activity undertaken in the general population. Pedometers (step counters) are increasingly popular with the general population and have been shown to be highly effective in the promotion of physical activity as they allow for the creation of simple and personalised goals and the ability to accurately self-monitor behaviour[66].

Although the recommendation of 10,000 steps per day has gained some traction among the general population, this is lacking in empirical evidence and is likely to be viewed as unattainable and de-motivating for the majority of the population who are sedentary. Instead, step per day categories have been proposed to help individuals judge their current activity levels and provide simple goals[67]. For example, sedentary individuals should aim to increase their physical activity by 2000 steps per day, conducted at moderate intensity. This roughly equates to an additional 150 minutes of physical activity per week.

Prevalence of inactivity

Across England, Scotland and Wales it has been estimated that 60-65% of males and 70-80% of women fail to meet the minimum physical activity recommendations for heath[68-70]. This figure rises to over 95% for both men and women when objective methods of measuring physical activity are used, suggesting that physical inactivity is a near universal condition on a population level[68].

Costs of inactivity and potential saving of increased activity

The direct cost to the NHS of physical inactivity has been estimated at over £1billion[71]. However, a further £6.5 billion is estimated to be wasted through indirect costs resulting from lost productivity and premature mortality in those of working age in England alone[61].

In Wales the total cost of physical inactivity is around £0.5 billion annually - equivalent to £200 per person[69]. In Scotland around 2,500 people die prematurely due to physical inactivity per year[70]. These figures are in-line with those from WHO which estimate that 2.5% of national health care costs are incurred through physical inactivity[72].

In England, shifting the proportion of individuals achieving the physical activity recommendations by just 5% could theoretically result in a cost saving of £300 million per year[62]; the equivalent figure for Northern Ireland is £131 million. Similarly in Scotland, £85 million could be saved if inactivity levels were reduced by 1% per year for 5 years[70].

National policy

The promotion of physical activity is a key policy aim in England, Wales, Scotland and Northern Ireland; three specific physical activity recommendations have been published from NICE[73-75]. In England, the Department of Health has developed a physical activity care pathway[76], including professional guidance and a patient pack, in order to provide the resources necessary to help PCTs meet NICE guidance recommending that health care professionals should identify individuals who are insufficiently active and provide brief physical activity counselling.

Key points

- ➔ There are various modifiable lifestyle risk factors centrally involved in the causation of chronic disease, these include smoking, diet, physical activity and weight loss.
- ➔ Increasing physical activity to 150mins/week is paramount for the effective prevention of vascular disease
- ➔ Recommended dietary habits should include daily or weekly portions of fruits and vegetable, oily fish and to reduce foods with high levels of salt, fat or drinking excess alcohol.

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