Primary prevention of cardiovascular disease: A review of contemporary guidance and literature

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Abstract
Cardiovascular disease is a significant and ever-growing problem in the United Kingdom, accounting for nearly one-third of all deaths and leading to significant morbidity. It is also of particular and pressing interest as developing countries experience a change in lifestyle which introduces novel risk factors for cardiovascular disease, leading to a boom in cardiovascular disease risk throughout the developing world. The burden of cardiovascular disease can be ameliorated by careful risk reduction and, as such, primary prevention is an important priority for all developers of health policy. Strong consensus exists between international guidelines regarding the necessity of smoking cessation, weight optimisation and the importance of exercise, whilst guidelines vary slightly in their approach to hypertension and considerably regarding their approach to optimal lipid profile which remains a contentious issue. Previously fashionable ideas such as the polypill appear devoid of in-vivo efficacy, but there remain areas of future interest such as the benefit of serum urate reduction and utility of reduction of homocysteine levels.

Keywords
Primary prevention, cardiovascular disease, statins, exercise, diet, hypertension, smoking, alcohol, polypill, uric acid

Introduction
Cardiovascular disease (CVD) is an umbrella term for a number of linked pathologies, commonly defined as coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases and venous thromboembolism. Globally CVD accounts for 31% of mortality, the majority of this in the form of CHD and cerebrovascular accident.¹

In England CVD accounts for nearly 34% of all deaths, whilst the figure is approximately 40% in the European Union.² The rate of CVD worldwide is predicted to increase as the prevalence of risk factors for CVD rises in previously low-risk countries. Currently 80% of CVD mortality occurs in developing nations³ and CVD is expected to be the major cause of mortality in most developing nations by 2020, overtaking infectious disease.⁴ Not only is CVD a leading cause of mortality, but it is the leading cause of loss of disability-adjusted life years globally.³

The World Health Organisation (WHO) estimate that over 75% of premature CVD is preventable and risk factor amelioration can help reduce the growing CVD burden on both individuals and healthcare providers.⁵ Whilst age is a known risk factor for the development of CVD, autopsy evidence suggests that the process of developing CVD in later years is not inevitable,⁶ thus risk reduction is crucial.

The INTERHEART study elucidated the effect of CVD risk factors including dyslipidaemia, smoking, hypertension, diabetes, abdominal obesity, whilst it demonstrated the protective effects of consumption of fruits and vegetables, and regular physical activity. These risk factors were consistent throughout all populations and socioeconomic levels studied, helping to establish the viability of uniform approaches to CVD primary prevention worldwide.⁷

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In this review we look at the main components of primary prevention of CVD as discussed in current best practice guidelines in the United Kingdom, Europe and America and attempt to provide a summary of primary prevention guidelines in CVD for clinicians.

**Methods**

We looked specifically at the current National Institute for Health and Care Excellence (NICE) guidelines,8–10 European Society of Cardiology (ESC) guidelines,3,11,12 as well as guidelines from the American Heart Association (AHA) and American College of Cardiologists (ACC)13–15 or, in the case of hypertension, guidelines referred to by the ACC.16 We highlighted areas targeted by these guidelines and performed a review of current literature. A literature search was performed using the search terms ‘Primary prevention in Cardiovascular Disease’, then a combination of ‘diet’, ‘hypertension’, ‘lipids’, ‘exercise’, ‘smoking’, ‘alcohol’ ‘polypill’, ‘weight’, ‘blood glucose’ and the term ‘cardiovascular disease prevention’. Data, guidelines and their scientific underpinning were extracted from the above and compared.

**Discussion**

Here we discuss the main areas targeted for primary prevention of CVD, looking at current guidelines, the data which supports them and any variation in guideline recommendations.

**Lifestyle modifications**

**Exercise.** Exercise is universally recognised as having a positive impact on the majority of health outcomes and its effect on CVD is no different. Mortality and morbidity directly due to exercise remains minimal even up to very intense levels of exercise and in the overwhelming majority the benefits outweigh the risks.17

NICE recommend 150 minutes of moderate intensity aerobic activity per week, or 75 minutes of vigorous aerobic activity. This can be defined either subjectively or in terms of relative changes in metabolic rate. They also advise muscle strengthening activities on two or more days per week.8 NICE give only a consensus recommendation regarding the utility of exercise as primary prevention, however guidelines from the AHA and ESC give class 1A recommendations with almost identical prescriptions, referring to a solid and consensual body of evidence.11,13

The guidelines all state that any form of exercise provides CVD risk reduction, with those newly starting exercise achieving greatest benefit and any subsequent increases providing significant but diminishing returns. Persuading the population to exercise as suggested remains difficult despite the obvious benefits, but the evidence is clear that any increase in physical activity reduces risk of CVD.18

**Diet.** Diet is thought to play a significant role in CVD risk but the body of evidence regarding its use is not clear, nor are the guidelines overwhelmingly consensual.

The AHA recommend the Dietary Approaches to Stop Hypertension (DASH) diet which is low in sugars and saturated fats, high in vegetables, fruits and whole grains. This has been shown to as a method to lower blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) which are independent risk factors for CVD, but they do not attempt to show a direct reduction in CVD risk.13

NICE recommend reducing saturated fat intake, increasing monounsaturated fatty acids and five portions of fruit and vegetables per day. They also suggest a high fibre diet and two portions of fish per week. They do acknowledge that they lack evidence that these changes will impact directly on CVD risk, but rather that they have benefits on other areas of health. Notably, the majority of the studies referenced came from pre-1990s when dietary patterns were substantially different, and almost all their data were underpowered concerning CVD risk.19

The ESC recommends switching from saturated to polyunsaturated fatty acids, an increase in fibre, fruit, vegetable and fish intake as well as abstinence from alcohol and adherence to a Mediterranean type diet. These have all been shown to offer significant reductions in CVD risk.11

There is also clear evidence that industrially produced transfats are causally linked to CHD20 and these are specifically proscribed in ESC and NICE guidelines.

The disparity between the recommendations is multi-factorial. For example, NICE guidelines on fibre intake look only at randomised controlled trials (RCTs) from the 1980s cf. the ESC which refers to meta-analyses of data up to the 2010s.

Regarding the advice on saturated fats, the ESC guidelines use modelling data to extrapolate a CVD risk reduction from reduction in LDL-C rather than epidemiological evidence or RCTs, whilst AHA guidelines do not comment specifically on CVD risk. This is an area where NICE guidelines would benefit from an update of its evidence base and greater use of prospective or epidemiological data to justify its recommendations.

In summary, there does seem to be good evidence for recommending diets high in fibre, fruit and vegetable intake and low in simple sugars and salt. Adherence to a Mediterranean style diet also appears to be cardioprotective.
**Smoking.** Smoking has long been known as the major risk factor for CVD. European data indicate that smoking doubles the 10 year CVD mortality rate, whilst 30% of US CVD mortality is attributable to smoking. Not only is it deleterious but this effect is dose related with no safe lower limit seen. Passive smoking is similarly harmful as workplace exposure increases CVD risk by 30% and UK public health initiatives including smoking bans are associated with a significant fall in CVD events.

Stopping smoking is the single most cost-effective intervention in CVD prevention, and some benefits are seen within months of cessation. All guidelines recommend cessation, with short and long-term benefits seen irrespective of length or intensity of smoking habit.

Pharmacologically, the use of nicotine replacement therapy (NRT), bupropion (a norepinephrine dopamine reuptake inhibitor) and particularly varenicline (a partial nicotine receptor agonist) are universally recommended. The two former both improve abstinence rates by 50–70%, whilst varenicline doubles abstinence.

Medication choice should be patient led, with a particular note to side-effect profiles. NRT previously held warnings regarding its use in those with CVD but evidence suggests that the benefits of smoking cessation outweigh the risks. Also recommended is physician intervention as a cost-effective method of reducing smoking, notably effective in secondary prevention post myocardial infarction (MI).

E-Cigarettes are still controversial with regards to CVD risk. Whilst the reduction in toxic products within cigarette smoke is undoubtedly beneficial, animal models of nicotine exposure still display CVD effects with increased atherosclerotic plaques found in mice models.

Long-term data are awaited to determine the effect upon humans.

**Weight.** Having a body mass index (BMI) > 25 is a risk factor for CVD with lowest all-cause mortality seen at BMI 20–25 but, due to increased all-cause mortality with BMI < 20, reductions below this level are not routinely recommended. No guidelines recommend specific intervention regarding weight, but advise maintenance of a healthy weight for reduction of CVD risk. BMI is a good predictor of CVD risk, particularly at higher levels, but there is good evidence that, at all levels of BMI, visceral adiposity and liver fat are significant drivers of risk. This helps to explain the heterogeneity in the CVD risk profile seen in the overweight as it varies depending on the location of adipose deposition. There are moves to suggest that, alongside reduction in BMI, reduction in waist circumference as a proxy for reductions in visceral fat should become an important target for amelioration of CVD risk.

**Alcohol.** Alcohol consumption is a controversial subject given the known sequelae of regular and excess alcohol use. The difficulty exists as historically the evidence suggested a J-shaped curve when it comes to risk, where abstinence is associated with an increase in CVD compared to light drinkers, with low levels of alcohol consumption associated with a lower level of CHD. Besides the understood physiological effects of alcohol, interfering with platelet aggregation, evidence from the INTERHEART study would appear to substantiate these claims, showing reductions in risk for those with moderate and light use of alcohol.

A recent large mendelian analysis by Holmes et al. has, however, shown that within a genetic subset for alcohol dehydrogenase, reductions in alcohol intake are associated with reduction in CVD risk across the spectrum of alcohol intake. This would suggest that reductions in alcohol intake, even for moderate drinkers, are associated with a reduction in CVD risk. It is on this basis that the ESC guidelines recommend no safe level of alcohol intake. NICE guidelines were produced prior to this data being released and continue with advice on moderate intake, advising not more than four units per day for men and three for women, despite these being arbitrary figures. The ACC also advise moderation along the same lines, with one to two drinks per day for men, and one drink per day for women. As yet there does not seem to be a consensus of opinion regarding safe levels, but high levels are evidently deleterious.

**Medical treatment**

**Lipid-lowering therapy.** Interventions to ameliorate lipid levels have long been used in primary prevention and sub-fractions of serum lipids have been studied to differentiate their individual effects on CVD risk profile. LDL-C is the best understood atherogenic sub-fraction with a strong correlation between LDL-C levels and CVD risk: reducing LDL-C by 1.0 mmol/L causes a corresponding 20–25% risk reduction in CVD mortality and non-fatal MI. It has been hypothesised that raised high-density lipoprotein cholesterol (HDL-C) levels are cardioprotective but the causal link remains unproven. This controversy is borne out by the adverse CVD profile of HDL raising drugs such as torcetrapib, as well as recent mendelian randomisation analysis suggesting no intrinsic benefit from naturally higher levels of HDL-C.

Apolipoprotein B (ApoB) seems a similar predictor of CVD risk to LDL, whilst serum triglycerides lack the
strength of data of LDL but remain an independent risk factor for CVD.\textsuperscript{11}

3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, commonly referred to as statins, have been used since the 1980s to reduce LDL-C levels. Their side-effect and risk profile is well recognised, with a reported 5–10% experiencing significant side-effects, commonly in the form of myalgia, arthralgia and temporary gastrointestinal upset.\textsuperscript{34}

The AHA recommend statins for primary prevention in all patients with a serum LDL-C > 4.9 mmol/L regardless of risk profile,\textsuperscript{14} whilst the ESC recommend statins in high-risk patients or those with cholesterol levels raised to > 4.9 mmol/L.\textsuperscript{11} They are more circumspect about their general use, but do recommend them as ideal first-line monotherapy without suggesting dosing levels.

QRISK2 is a risk stratifying method which determines 10-year risk profile using multiple physiological and comorbidity data including serum cholesterol ratios. NICE guidelines advise atorvastatin 20 mg to be offered as primary prevention in patients < 85 years with a QRISK2 score of > 10\%. It also notes that patients > 85 years are likely to benefit from a similar CVD risk reduction despite a lack of confirmatory data. NICE does not use specific cholesterol levels nor ratios as individual markers of risk, though does suggest specialist referral if total lipid levels > 9 mmol/L or non-HDL > 7.5 mmol/L. Satisfactory lipid levels remain an area of controversy, with no guidelines defining a normal range.\textsuperscript{8}

Statins are one of the most commonly prescribed medications worldwide, thus the data behind their use is plentiful, with atorvastatin shown to significantly reduce LDL-C and be the most cost-effective throughout all risk profiles. NICE states that treatment remains cost effective for those with a QRISK2 < 10\%, but due to the reported side-effect profile NICE suggests 10% risk of CVD as a cut-off for statins as primary prevention.\textsuperscript{8}

The controversy regarding the above is twofold. Firstly, a 2013 paper by Abramson et al. claimed that their reanalysis of the data showed no reduction in mortality or morbidity in the low-risk population,\textsuperscript{35} thus causing iatrogenic harm in the form of intolerable side-effects – reported in 5–10\% of patients. Secondly, the corollary of this guideline would be the almost ubiquitous prescription of statins in otherwise well patients. A male aged 65 years would obtain a risk of 10\% despite optimal BMI, optimal cholesterol and no comorbidities, the same being true for a 70-year-old female.\textsuperscript{36} Given the current side-effect recommendations there is reluctance amongst the medical profession to engage in blanket therapy for a theoretical gain on a population-wide basis. Reanalysis from Collins et al., however, suggested that the side-effect profile is significantly misreported and therefore the risk–benefit ratio shifts back in favour of statins.\textsuperscript{37} Their analysis attributes a 1\% risk of diabetes, 1\% risk of muscle pain or weakness, 0.1\% risk of haemorrhagic stroke and 0.05\% risk of myopathy over five years of statin therapy – a significant reduction in side-effect rate.

Whilst controversy remains, the evidence is compelling for use in those with significant CVD risks and may be appropriate in more moderate risk profiles, but prescription requires careful tailoring to individual patients. A summary of guideline recommendations for LDL reduction can be seen in Table 1.

Non-statin therapies are also used, commonly in patients whose lipid profiles are not optimised by statin monotherapy. Commonly used drugs include bile acid sequestrants, fibrates and nicotinic acid, but these drugs are not recommended as monotherapy due to side-effects and a lack of reduction in CVD events.\textsuperscript{11} Further reductions in serum LDL can be achieved with combination therapies. No guideline recommends specific combinations but they do suggest combination with other lipid-lowering drugs in resistant cases or in those not tolerant of statins.

New therapies are forthcoming, with phase III data from proprotein convertase subtilisin–kexin type 9 (PCSK9) monoclonal antibodies such as alirocumab providing increasingly effective lipid-lowering therapies. They can be used either as monotherapies or as add-ons to statins with a significant impact on CVD events.\textsuperscript{38} Both alirocumab and evolocumab have recently been recommended by NICE for CVD prevention in those with primary hypercholesterolaemia,

| Table 1. Guidelines for LDL reduction. |
|-----------------------------------------|
| **Guideline**                          | **NICE\textsuperscript{8}** | **ACC\textsuperscript{14}** | **ESC\textsuperscript{12}** |
| Level at which to attempt LDL reduction | QRISK2 score > 10\% if < 85 yrs | >4.9 mmol/L irrespective of risk | >4.9 mmol/L if high risk of CVD |
| Recommended pharmacotherapy            | Atorvastatin 20 mg             | Statin – no preferred version | Statin – no preferred version |

LDL: low-density lipoprotein; CVD: cardiovascular disease.
mixed dyslipidaemia or in whom statins are not sufficient to control cholesterol. Their use is likely to become more widespread with further phase III and IV clinical trial data and eventual reduction in cost.

**Anti-hypertensive therapies.** Hypertension is an independent risk factor for the development of CVD. The effect of increasing BP > 115/75 mmHg is consistent and exponential, where each 20 mmHg increase in systolic blood pressure (SBP) or a 10 mmHg increase in diastolic BP doubles the risk of a cardiovascular event.

Previous meta-analyses have shown a reduction in CVD risk over a wider range of BPs suggesting that there is no lower limit to the benefit of BP reduction, and no obvious cut-off at which further reductions become harmful.

Contemporary meta-analyses indicate that the benefits of lowering BP from a baseline < 140 may be equivocal or even detrimental. Combining this evidence would suggest that BP reductions in hypertensives reduce mortality, but for normotensive or pre-hypertensive patients there is little evidence for early treatment.

Given that hypertension acts as an independent risk factor for CVD, and synergistically with other risk factors, it is the consensus opinion that the threshold for treatment of hypertension in those at risk of CVD should be lower.

Regarding timing of intervention and precise target ranges there is some variability between guidelines which can be seen broadly in Table 2.

The ESC and NICE guidelines note that the majority of data showed greatest benefit for those with BP > 160/100 mmHg, and whilst there may be benefit at lower levels the evidence was not yet considered strong enough to give direct recommendations.

Strong evidence suggests that the reduction in BP is more important than the individual drug class used, compounded by the fact that the majority of people with hypertension require more than one antihypertensive drug for optimal control.

The recommended pharmacotherapy can be seen in Table 3.

NICE justify the changes in treatment for Afro-Caribbean patients due to differences in plasma renin concentrations between ethnic groups and a tendency towards lower cardiac output with increased peripheral resistance in Afro-Caribbean hypertensives. The ACC recommended guidelines note that the ALLHAT trial

| Table 2. Guidelines for commencement of anti-hypertensives and target BP. |
|---------------------------------------------------------------|
| **Guideline** | **NICE**<sup>9</sup> | **ACC recommended guidelines**<sup>16</sup> | **ESC**<sup>12</sup> |
| Commencement of treatment – no comorbidities | >160/100 mmHg | >150/90 mmHg if ≥60 yrs | >160/100 mmHg – after lifestyle modification attempted |
| | | >140/90 mmHg if <60 yrs | |
| Target | <140/90 mmHg if <80 yrs | <150/90 mmHg if ≥60 yrs | <140/90 mmHg if <60 yrs |
| | <150/90 mmHg if >80 yrs | <140/90 mmHg if <60 yrs | SBP 140–150 mmHg if ≥ 60 yrs |
| Commencement of treatment if CKD/ DM/ risk of CVD | >140/90 mmHg | >140/90 mmHg | >140/90 mmHg |
| Target | <140/90 mmHg | <140/90 mmHg | <140/90 mmHg |

CKD: chronic kidney disease; DM: diabetes mellitus; CVD: cardiovascular disease.

| Table 3. Recommended anti-hypertensive therapy. |
|------------------------------------------------|
| **Guideline** | **NICE**<sup>9</sup> | **ACC recommended guidelines**<sup>16</sup> | **ESC**<sup>12</sup> |
| First line anti-hypertensive therapy | If <55 yrs – ACEi/ARB | ACEi/ARB, thiazide, CCBs | ACEi, thiazide, CCB, ARB, beta blocker |
| | If > 55 yrs/Afrocaribbean descent – CCB or thiazide | If black – thiazide or CCB |
| Additional notes | Use 2 drugs if goal BP not reached within one month |

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; BP: blood pressure.
showed improved outcomes in Afro-Caribbean patients treated with thiazides, whilst calcium channel blocker (CCBs) improved all outcomes other than heart failure.40

A small discrepancy exists with the ESC guidelines. Their use of beta blockers stems from a meta-analysis suggesting that the class cause an equal reduction in CVD mortality, though the ESC do acknowledge conflicting data which suggests inferiority and an increased side-effect profile.12

Whilst risk of CVD increases with BP, the majority of population events occur within the upper range of normal, therefore NICE public health guidelines10 suggest that a population-wide drop in BP would lead to a significant reduction in CVD events. As this group does not receive antihypertensive treatment, they recommend population measures to reduce salt intake. Salt intake is well associated with BP, with a strong causal link between increased intake and rise in BP. The reverse is also true: studies looking at reduction in salt intake show consistent reductions in BP, particularly in hypertensive individuals,59 and there is evidence of CVD event reduction.51 Given the above, all three guidelines recommend reduction in salt intake on an individual and population level regardless of BP.

Specific daily targets vary, largely due to the responsibilities of each organisation: AHA 2.4 g, ESC 5–6 g and NICE 6 g reducing to 3 g by 2025.50,11,13 NICE also has a greater public health remit than the ESC and AHA and recommends national-level interventions such as population education, pricing changes on higher-salt products, and national legislation if necessary to aid reduction in salt intake (NICE PH25). All agree, however, that lower salt intake leads to BP reduction and concomitant CVD risk reduction.52

**Blood glucose.** Glucose control is pertinent in the diabetic populations but is non-significantly associated with CVD risk in non-diabetics. On average diabetes mellitus (DM) risk of CVD, whilst those with impaired fasting glucose (IFG) are known to be at significant risk of CVD as well as progression to DM.53 In DM serum fasting glucose (IFG) are known to be at significant risk of CVD, whilst those with impaired glucose transporter 2 inhibitor class of oral hypoglycaemics such as empagliflozin have been shown to significantly reduce all-cause mortality by 32%, as well as CVD death by 28% and HF by 35% in comparison with standard care.56 It appears that these effects were not mediated by reduction in glucose, rather cardio-renal haemodynamic effects, but the substantial benefits demonstrated would recommend its early use in diabetic patients. Current guidelines need to be updated with further data on these medications.

**Anti-platelet therapy.** Anti-platelet therapy is a significant contributor to secondary prevention but should be avoided in primary prevention in those without comorbidities due to increased bleeding risk with no evidence of CVD risk reduction. In patients with DM the advice is conflicting: ESC guidelines maintain that the bleeding risk exceeds the benefits of aspirin therapy, whilst the American College of Chest Physicians recommend aspirin therapy in patients with DM and 10-year CVD event risk of ≥ 10%.57

**Further areas of research.** Other areas include the polypill, uric acid and homocysteine. The use of a polypill – a combination pill for CVD risk reduction – has impressive theoretical benefits, but meta-analyses on in-vivo data have not demonstrated significant improvement in CVD risk.58

Lowering serum uric acid levels may improve CVD risk, as it is known that both patients with gout or hyperuricaemia receiving urate-lowering therapies have improved CVD and all cause-mortality59,60; however more research is needed to clarify if these benefits translate to population-wide risk reduction. Homocysteine is a known atherogen, but lowering therapies have not demonstrated a reduced CVD.61

**Conclusion**

The objective of CVD prevention is to reduce the occurrence of major cardiovascular events thereby reducing premature disability and morbidity whilst prolonging survival and quality of life.

The American, European and British guidelines demonstrate numerous methods to reduce CVD risk profile with strong consensus regarding smoking and exercise, whilst the fine details may vary slightly for other factors. Pharmaceutical options have developed over the years whilst lifestyle advice remains largely unchanged.

Primary prevention continues to evolve and with greater availability of long-term data comes improved understanding of the means by which we can reduce CVD risk. It is an endeavour that must be continued if we are to reduce the burden of a preventable disease.

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